DRUG:	BHV-3000 (rimegepant)
STUDY NUMBER(S):	BHV3000-310
PROTOCOL(S) TITLE:	BHV3000-310: Phase 3: Double-Blind, Randomized, Placebo Controlled, Safety and Efficacy Trial of BHV-3000 (rimegepant) 75 mg for the Acute Treatment of Migraine
SPONSOR:	BioShin Limited
ORIGINAL PROTOCOL DATE:	Jan 2, 2020
VERSION NUMBER:	V 2.3
VERSION DATE:	May 25, 2021

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: BHV3000-310: Phase 3: Double-Blind, Randomized, Placebo Controlled, Safety and Efficacy Trial of BHV-3000 (rimegepant) 75 mg for the Acute Treatment of Migraine

Study No: BHV3000-310

Original Protocol Date: Jan 2, 2020

Protocol Version No: V 2.3

Protocol Version Date: May 25, 2021

This study protocol was subject to critical review and has been approved by the appropriate protocol review committee of the sponsor. The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the investigational product.
- The moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and principles of GCP as described in 21 CFR parts 50, 54, 56 and 312 and according to applicable local requirements.

The Investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

SIGNATURE PAGE

Name and Title	**Signature Approval**	**Date**
Author/Protocol Writer: PPD I confirm, QC completed for required elements	PPD	May 31, 2021
Biostatistics: PPD	PPD	
Medical Lead: PPD, MD Senior Clinician		
Regulatory Affairs: PPD	PPD	June 2, 2021
Clinical Operations: PPD	PPD	

SIGNATURE PAGE

Name and Title	**Signature Approval**	**Date**
Author/Protocol Writer: PPD I confirm, QC completed for required elements		
Biostatistics: PPD		
Medical Lead: PPD MD Senior PPD	PPD	June 1, 2021
Regulatory Affairs: PPD		
Clinical Operations: PPD		

SUMMARY OF CHANGES

Version Number	Change	Summary	Date
V 1.0			Jan 2, 2020
V 2.0	2. Study Objectives	Study Objectives were updated	Apr 26, 2020
	3. Study Endpoints	Study Endpoints were updated	
	5. Exclusion criteria	Exclusion criterion 5.3.6d was revised	
	9. Statistics	Statistics section has been updated	
		Minor typographical errors/inconsistencies identified during review have been corrected	
V 2.1	15.4 Appendix IV – Power Calculations	Added Appendix IV and a reference to Appendix IV in section 9.2 Sample Size	June 11, 2020
V 2.2	4.4 COVID-19 Contingencies	COVID-19 Contingencies were added	Apr 8,2021
	6.2.4 Laboratory Assessments	Use of local laboratory is permitted in exceptional circumstances with prior Sponsor approval	
	8.1.2 Collection and reporting SAEs	PPD information for SAE reporting is added	
	15.1 Appendix I	Medical Monitor name is updated	
	Sponsor name change	Sponsor name is changed from Biohaven Asia Pacific Ltd to BioShin Limited	
		Minor typographical errors/inconsistencies identified during review have been corrected	
V 2.3	9.4.4 Missing data	One typeographical error has been corrected	May 25,2021
	10.1 Good Clinical Practice	Update Biohaven to BioShin Limited for serious breach reporting	

BHV-3000-310

BHV3000-310: Phase 3: Double-Blind, Randomized, Placebo Controlled, Safety and Efficacy Trial of BHV-3000 (rimegepant) 75 mg for the Acute Treatment of Migraine

Confidentiality and Investigator Statement

The information contained in this protocol and all other information relevant to BHV-3000 (rimegepant) are the confidential and proprietary information of BioShin Limited, and except as may be required by federal, state or local laws or regulation, may not be disclosed to others without prior written permission of BioShin Limited.

I have read the protocol, including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with local regulations, Good Clinical Practices and International Conference on Harmonization guidelines, and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by BioShin Limited or specified designees. I will discuss the material with them to ensure that they are fully informed about Biohaven and the study.

Principal Investigator Name (printed)	Signature
Date	Site Number

STUDY SUMMARY (SYNOPSIS)

Title:	BHV3000-310: Phase 3: Double-Blind, Randomized, Placebo Controlled, Safety and Efficacy Trial of BHV-3000 (rimegepant) 75 mg for the Acute Treatment of Migraine
Rationale:	Rimegepant is being developed for the treatment of migraine, with a specific focus on acute treatment. Effectiveness against migraine has been demonstrated in 4 large placebo-controlled trials: Phase 2b double-blind, randomized, placebo-controlled, dose-ranging study where rimegepant at 75 mg showed efficacy on all four traditional endpoints: pain, nausea, photophobia and phonophobia; and in three Phase 3, placebo controlled, clinical studies, rimegepant as a single 75 mg dose (tablet) was well tolerated in adult subjects with moderate to severe migraine, and demonstrated a safety profile similar to placebo (N = 1,771 rimegepant-treated subjects, and N = 1,782 placebo-treated subjects). The data from this regional study will allow characterization of the relative safety and efficacy of 75 mg of rimegepant versus placebo in the treatment of moderate or severe migraine in Asian patients (Chinese and Korean subjects). The co-primary endpoints to be measured are freedom from pain and freedom from most bothersome symptom (nausea, photophobia or phonophobia) at 2 hours after dosing in patients who have a moderate or severe migraine attack during the study period. Information regarding time to onset of action, the duration of action, and the sustainability of pain freedom and other secondary endpoints will also be obtained.
Target Population:	The study will recruit male and female subjects 18 years of age and older with at least a one-year history of migraines (with or without aura), consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd edition beta version [1], including an age of onset prior to 50, migraine attacks that last about 4 - 72 hours, not more than 8 attacks of moderate or severe intensity per month within the last 3 months and not less than 2 attacks per month.
Number of Subjects:	Approximately 1,800 subjects will be screened to randomize approximately 1,430 subjects (approximately 715 per arm). The subjects will be randomized in a 1:1 ratio to the rimegepant or placebo treatment groups. The randomization will be stratified by the use of prophylactic migraine medications (yes or no) and country (China or Korea). If roughly 85% of the 715 subjects randomized to each treatment arm have a migraine in the allotted time period, there will be approximately 600 treated subjects per group. 600 treated subjects provides 95% power to detect a difference between rimegepant and placebo on the subject's self-reported most bothersome symptom. Also, 600 subjects provides 95% power to detect a difference in freedom from pain at 2 hours. Having at 95% power on each co-primary endpoint provides roughly 90% power to detect a difference on both endpoints jointly.

Study Design	This is a double-blind, randomized, regional, multicenter, outpatient evaluation of the safety and efficacy of rimegepant as compared to placebo in the treatment of moderate or severe migraine. The study drug will be rimegepant presented in a 75 mg Orally Disintegrating Tablet (ODT) or matching placebo. The study will randomize approximately 1,430 subjects. The subjects will be randomized in a 1:1 ratio to the rimegepant or placebo treatment groups. The randomization will be stratified by the use of prophylactic migraine medications (yes or no) and country (Korea or China). A subject whose usual migraine attack results in headache pain of moderate or severe intensity and who is otherwise found acceptable for entry into this trial based on inclusion and exclusion criteria will first participate in the screening phase (3 – 28 day period). Subjects on prophylactic migraine medication are permitted to remain on therapy provided they have been on a stable dose for at least 3 months prior to study entry. After randomization, the subject will be dispensed a single dose of the double-blind study medication that will be taken at the time a migraine attack reaches moderate or severe pain intensity (described below) on the numeric rating scale (NRS) as indicated in the electronic diary (eDiary). The subject will be instructed to take their study medication, as an outpatient, when (if) they have a migraine headache which reaches moderate or severe pain intensity and only after they have identified their most bothersome migraine-associated symptom (phonophobia, photophobia or nausea) in the eDiary. The subject will complete an eDiary for forty-eight hours after taking study medication. The subject will telephone the study center immediately if a severe or serious adverse event occurs. Subjects will record efficacy data in their eDiary. This includes the following: onset time of headache, intensity of the headache prior to ***and*** at time of taking study medication. Subject should not dose with study medication until headache reaches moderate to severe intensity. Headache severity will be recorded using a four-point numeric rating scale (no pain, mild pain, moderate pain, severe pain) at the onset of the migraine and after dosing at time points of 15, 30, 45, 60, and 90 minutes and 2, 3, 4, 6, 8, 24 and 48 hours. The presence or absence of associated symptoms (nausea, photophobia, phonophobia) and ratings of functional disability (four-point scale: normal, mildly impaired, severely impaired, requires bedrest) will be recorded at the same time points as the headache severity ratings. Subjects who experience reduction of headache pain to a mild intensity or pain free intensity level will be considered to have achieved pain relief. The subject who does not experience relief of their migraine headache at the end of two hours after dosing with study medication (and after the two hour assessments have been

	completed on the eDiary) will be permitted to use the following rescue medications: aspirin, ibuprofen, acetaminophen up to 1000mg/day (this includes Excedrin Migraine), naprosyn (or any other type of non- steroidal anti-inflammatory (NSAID)), antiemetics (e.g., metoclopramide or promethazine), or baclofen. These are the only medications allowed for rescue treatment after 2 hours post dose of study medication. If at the end of 48-hours after dosing with study medication (but before the End of Treatment Visit) subjects are in need of migraine relief, they may take their prescribed standard of care medications, including triptans if not contraindicated, provided all of the assessments have been completed on the eDiary. Exclusionary rescue medication such as opioids, ergotamines, butalbital compounds, and muscle relaxants (except baclofen as a rescue medication, see above) are not allowed on this study. Similarly, if the migraine is relieved by study medication at 2 hours after dosing but then recurs to a moderate or severe intensity level between two and forty-eight hours, the subject will be permitted to take the same rescue therapy as outlined above. In all circumstances, the subject will always continue to complete his or her eDiary for up to forty-eight hours after consuming the study medication. During the 45 days the subject is participating in the study, if the subject has a nonqualifying migraine (mild migraine) or a migraine that they do not treat with study medication, the subject is permitted to use only the following medications: aspirin, ibuprofen, naprosyn (or any other type of non- steroidal anti-inflammatory (NSAID)), antiemetics (e.g., metoclopramide or promethazine), or baclofen. Subjects will return to the study site within 7 days (+2) of study treatment for review of the eDiary, assessment of medication compliance, and monitoring of tolerability and safety (including vital signs, laboratory tests, and electrocardiography). If a subject has NOT experienced a migraine headache of sufficient severity within 45 days after randomization, they still are required to complete all EOT visit procedures. All subjects must return unused study medication and eDiary to the study center.

STUDY SCHEMATIC

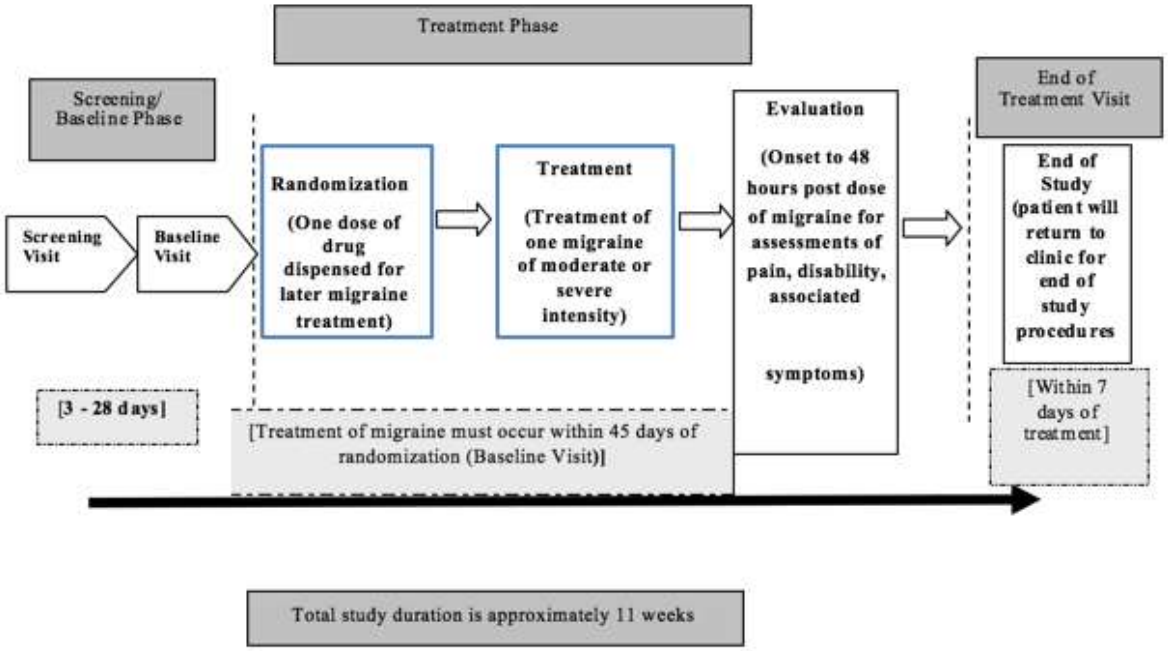


TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

ACS	Acute Coronary Syndrome
ADHD	Attention Deficit Hyperactivity Disorder
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BID	Twice Daily
BHV	Biohaven
BP	Blood Pressure
BUN	Blood Urea Nitrogen
C_{max}	Maximum Plasma Concentration
C_{min}	Minimum Concentration
CGRP	Calcitonin gene-related peptide
CNS	Central Nervous System
CONMED	Concomitant Medication
CRC	Cognitive Research Corporation
CRL	Clinical Reference Laboratory
CRO	Clinical Research Organizations
CV	Coefficient of Variation
DILI	Drug induced liver injury
DSMC	Data and Safety Monitoring Committee
DSM V	Diagnostic and Statistical manual of mental Disorders Fifth edition
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report forms
EDC	Electronic Data Capture
eDiary	Electronic Diary
EE	Ethinyl Estradiol
eGFR	Glomerular Filtration Rate
EOT	End of Treatment
ePRO	Electronic Patient Reported Outcome
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice

GLP	Good Laboratory Practice
HIV	Human Immunodeficiency Virus
HR	Heart Rate
HRT	Hormone Replacement Therapy
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IHS	International Headache Society
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
Iv	Intravenous
IWRS	Interactive Web Response System
LDH	Lactate Dehydrogenase
LDL	Low-density lipoprotein
LOCF	Last Observation Carried Forward
kg	Kilogram
kBq	Kilobecquerel
MBS	Most bothersome Symptom
MBq	Megabecquerel
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat
mg	Milligram
MI	Myocardial Infarction
Min	Minute
msecs	Milliseconds
MTD	Maximum tolerated dose
NSAIDs	Non-Steroidal Anti-Inflammatories
NRS	Numeric Rating Scale
OC	Oral Contraceptive
PCI	Percutaneous Coronary Intervention
PCP	Phencyclidine
PK	Pharmacokinetic
PVG	Pharmacovigilance

QD	Once Daily
QTc	Interval between Q-wave and T-wave in the cardiac cycle
SAE	Serious Adverse Event
TBL	Total Bilirubin
TIA	Transient Ischemic Attack
ULN	Upper Limit of Normal
USPI	US Prescribing Information
WBC	White Blood Cell
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

1 INTRODUCTION AND RATIONALE

1.1 Therapeutic Area Background

Migraine is a common and debilitating neurological disorder that affects approximately 8-9% of the adult population in China [2]. Migraine causes very significant socioeconomic costs to Chinese society. It is characterized by moderate-to-severe episodic unilateral pulsating headaches that last for 4 to 72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea and/or photophobia and phonophobia.

BHV-3000 (rimegepant, /rih-MEJ-eh-pant/) is a calcitonin gene-related peptide (CGRP) receptor antagonist in development for the acute treatment of migraine. The CGRP receptor is located within pain-signaling pathways, intracranial arteries and mast cells and its activation is thought to play a causal role in migraine pathophysiology. For example, research and clinical studies have shown: serum levels of CGRP are elevated during migraine attacks, infusion of intravenous CGRP produces persistent pain in migraine sufferers and non-migraine sufferers, and treatment with anti-migraine drugs normalize CGRP levels. Additionally, multiple clinical studies show that small molecule CGRP receptor antagonists, which inhibit the binding of endogenous CGRP to CGRP receptors, are effective in aborting migraine attacks. Treatment with a CGRP receptor antagonist is believed to relieve migraine through the possible mechanisms of 1) blocking neurogenic inflammation, 2) decreasing artery dilation, and 3) inhibiting pain transmission. This new approach to the treatment of migraine avoids the cardiovascular effects produced by active vasoconstriction associated with the current standard triptan therapy (non-selective 5-HT1B/1D agonists (e.g., sumatriptan [Imitrex™]).

1.2 Product Development Background

Details of the clinical and preclinical studies are provided in the most current investigator brochure. A summary of the relevant data is presented below.

1.2.1 Non-clinical Pharmacology

1.2.1.1 Nonclinical Pharmacokinetics and Pharmacodynamics

A series of in vitro and in vivo pharmacokinetic (PK) and metabolism studies were conducted with rimegepant in rats, dogs, and monkeys. In addition, rimegepant was compared with two different triptans to assess the potential to constrict coronary vessels. While sumatriptan and zolmitriptan exhibited progressive constriction of human coronary vessels at increasing concentrations, rimegepant did not induce any changes in the baseline tension in human coronary vessels even at very high (10 uM) concentrations. Rimegepant was tested using the identical protocols in dog coronary artery (when viable human tissues were not available) and no vessel constriction was observed, in contrast to the triptans which again showed progressive concentration-dependent constriction. These data provide direct evidence that rimegepant acts without the undesirable effect of active vasoconstriction associated with treatment by triptans. Please refer to the most current version of the Investigator Brochure for further details.

1.2.1.2 Nonclinical Toxicology

The nonclinical toxicity of rimegepant was comprehensively evaluated in a series of single- and repeat-dose oral toxicity, developmental and reproductive toxicity, carcinogenicity, genetic toxicity, phototoxicity, and safety pharmacology studies. Rimegepant is not genotoxic or phototoxic, has a low potential for off-target receptor interactions or adverse effects on the cardiovascular, respiratory, and central nervous (CNS) systems, and is not a selective developmental toxicant or carcinogenic. Please refer to the most current version of the Investigator Brochure for further details.

1.2.2 Clinical Experience

Currently, 22 clinical studies have been completed in healthy volunteers and subjects with migraine that inform PK, metabolic interactions, safety, tolerability and efficacy. Approximately 6,000 unique subjects have participated in Phase 1 studies in healthy subjects or Phase 2 and 3 studies in subjects with migraine; of these, over 3,000 unique subjects have received the rimegepant clinical dose of 75 mg. The clinical pharmacology of rimegepant has been well characterized in a comprehensive program based on 18 Phase 1 studies, including 4 studies that examined the biopharmaceutics of rimegepant. In three completed Phase 3, placebo-controlled, clinical studies, rimegepant as a single 75 mg dose (tablet or ODT) was well tolerated in adult subjects with moderate to severe migraine, and demonstrated a safety profile similar to placebo (N = 1,771 rimegepant-treated subjects, and N = 1,782 placebo-treated subjects). In total, the current data suggests a favorable benefit-risk profile for rimegepant in the acute treatment of migraine attacks.

1.2.2.1 Bioequivalence of Rimegepant ODT and Tablet Formulations

The rimegepant 75 mg ODT and tablet formulations provide bioequivalent exposures and thus support equivalent PK performance upon administration with respect to C_{max} and AUC, as shown in studies BHV110 and 113 [3, 4]. Demonstration of bioequivalence in this manner mutually bridges the existing clinical safety and efficacy data across the tablet and ODT formulations. Additionally, the rate of absorption is faster with the ODT administered sublingually than with the tablet administered orally, with an earlier T_{max} of 1.5 versus 1.9 hours, respectively ($p < 0.003$).

1.2.2.2 Single Ascending Dose (CN17001)

Following single-dose (25 mg to 1500 mg) oral administration of rimegepant capsules to healthy male and female subjects under fasted conditions, rimegepant was rapidly absorbed with a range of Tmax from 0.75 - 4 hours post dose with a trend of delayed median Tmax with increasing doses. Plasma rimegepant pharmacokinetic profiles were biphasic with a terminal elimination half-life of approximately 8-12 hours. The pharmacokinetics of rimegepant appeared to increase in exposure from 25 - 900 mg dose range, and was less than dose proportional at 1500 mg suggesting that increase in dose did not increase the absorption. Therefore dose limiting absorption occurred at 1500 mg due to the low aqueous solubility of rimegepant. No formal dose proportionality assessment has been conducted. The variability (coefficient of variation) in the PK estimates were high and ranged from 49 - 85% however the variability at the higher doses (600 - 900 mg) was lower and ranged from 23 - 49% [5].

1.2.2.3 Multiple Ascending Dose (CN17001)

Following multiple dosing of 75, 150, 300 and 600 mg daily dose over a 14-day period, the accumulation index for Cmax and AUC ranged from ~1.2 - 1.6, consistent with the predictions based on single dose data. In general, the exposures obtained from the multiple day study appeared to be slightly higher than single dose data, but were within the variability of the drug. The exposure increased with increasing doses from 75 mg to 300 mg dose. Cmin concentrations in general reached a plateau after 48 hours post dosing. A variability of 37 - 54% was observed in the PK estimates throughout the different doses studied [5].

1.2.2.4 Intrinsic Factor Evaluation (Specific Populations)

Intrinsic factors of age and renal and hepatic impairment were explored in dedicated studies BHV106, 107 and 108 [6-8]. In addition, the effects of intrinsic factors of gender, age, weight, race, and renal and hepatic function were defined through population PK modeling. As there were no meaningful alterations in exposures across these covariates, dosing frequency recommendations are not required. Please refer to the most current version of the Investigator Brochure for further details.

1.2.2.5 Extrinsic Factor Pharmacokinetics (Drug-Drug Interaction)

1.2.2.5.1 Effect of Co-administered Drugs on Rimegepant

CYP3A4 Inhibitors

Strong CYP3A4 inhibitors, such as itraconazole, cause an increase in rimegepant exposure with less prominent increases in C_{max} (study BHV103) [9]. Population PK modeling demonstrates patients taking a strong CYP3A4 inhibitor should not concurrently administer rimegepant 75 mg more frequently than once every 3 days to allow for rimegepant washout and prevent accumulation.

No dose regimen adjustment is required when rimegepant is co-administered with weak to moderate CYP3A4 inhibitors, based on a dedicated fluconazole DDI study (BHV105) [10] and population PK modeling.

CYP3A Inducers

In the presence of rifampin, a strong CYP3A inducer, clinically meaningful reductions in rimegepant AUC to 20% of reference were observed (study BHV104) [11]. Concomitant use of CYP3A inducers co-administered with rimegepant was allowed in Phase 3 clinical studies BHV3000-301 and BHV3000-302, but the total clinical experience with such agents is limited. Given the effect of strong inducers on rimegepant PK, the concomitant use of rimegepant with strong CYP3A inducers is not recommended.

Topiramate (a weak CYP3A inducer), was an allowable concomitant medication in Phase 3 studies and subjects who were taking concomitant topiramate (approximately 7% of subjects) showed no decrement in efficacy compared to subjects who were not taking concomitant topiramate. Rimegepant may be co-administered with weak CYP3A inducers.

It should be recognized that rimegepant co-administered with moderate CYP3A inducers may result in reduced rimegepant exposures and consequently, reduced efficacy; however, clinical experience is limited. This potential for reduced exposure of rimegepant should be considered if co-administration of a moderate inducer is required.

Sumatriptan

In a dedicated DDI study (BHV114) [12], co-administration of sumatriptan with rimegepant did not meaningfully change the PK of rimegepant or of sumatriptan. Co-administration of sumatriptan with rimegepant does not cause an elevation in mean arterial blood pressure or of systolic or diastolic blood pressure greater than seen with sumatriptan alone. Rimegepant may be co-administered with a triptan without dose frequency modification.

1.2.2.5.2 Effect of Rimegepant on Co-administered Drugs

Although in vitro studies suggested that rimegepant may be an inhibitor of CYP3A4 and therefore increase concentrations of CYP3A4 substrates, co-administration of midazolam, a sensitive CYP3A4 substrate, with multiple doses of rimegepant 150 mg showed that rimegepant caused only weak inhibition (< 2-fold) of CYP3A4 metabolism of midazolam (CN170007) [13]. Further, co-administration of an oral contraceptive with rimegepant at a single dose of 600 mg or multiple doses of 450 mg confirmed that rimegepant is capable of only weak inhibition of CYP3A4 (1.2-fold elevation in victim PK exposures) (CN170002) [14]. This limited elevation in sensitive substrate exposure indicates that rimegepant, even at multiples of the 75 mg clinical dose, is not a meaningful perpetrator of PK interactions with CYP3A4 substrates. Rimegepant may be administered with an oral contraceptive without dose frequency adjustment.

Whereas rimegepant is metabolized through a separate route (CYP3A4) than triptans (MAO-A) and each exerts their effects through different mechanisms of action, no clinically meaningful PK DDIs were anticipated; however, owing to their potential concomitant use in the intended clinical population, a clinical DDI study was conducted (BHV114) [12]. A lack of interaction was confirmed in this study, wherein co-administration of multiple daily doses of rimegepant 75 mg with sumatriptan did not meaningfully change the PK of sumatriptan. Co-administration of sumatriptan with rimegepant did not cause an elevation in mean arterial blood pressure or of

systolic or diastolic blood pressure greater than seen with sumatriptan alone. Co-administration of rimegepant with a triptan is allowed without dose frequency modification.

1.2.2.6 QT Evaluation

The effect of rimegepant on the QTc interval was evaluated in a randomized, placebo-and positive-controlled, partially double-blind, single-dose, crossover study. Rimegepant C_{max} concentrations in subjects given a single dose of 300 mg was 5.6-times higher than with the maximum recommended human dose (MRHD). There was no clinically relevant prolongation of the QTc interval. Concentration QT analysis projects no clinically relevant prolongation of the QTc interval at rimegepant C_{max} concentrations up to 10.8 times higher than the MRHD (BHV109) [15].

1.2.2.7 Pharmacokinetics in Migraine Subjects (CN170004)

Study CN170004 was a phase 1, open-label, randomized, single sequence study with two dose groups to compare the PK of rimegepant in migraine subjects during an acute migraine attack and during a non-migraine period [16]. The primary objective of this open-label study was to assess the single dose PK profile of rimegepant, 300 mg and 600 mg doses, in migraine subjects with and without a migraine attack. The 48 treated subjects included 30 (62.5%) females and 18 (37.5%) males with a mean age of 36.7 years (range 22 to 52 years). 48 subjects were dosed in this study.

Rimegepant was rapidly absorbed during both the migraine and non-migraine attack where median peak concentrations were achieved by 2 to 3 hours for the 300 and 600 mg dose. For the 300 mg group, mean C_{max} ranged from 5099 ng/mL [54% CV] in the migraine state to 2939 ng/mL [58.6% CV] in the non-migraine state and mean AUC_{0-24} ranged from 27,355 ng*h/mL [46% CV] to 18,189 ng*h/mL [56% CV], respectively. For the 600 mg group, mean C_{max} ranged from 8,697 ng/mL [54%% CV] in the migraine state to 7540 ng/mL [44% CV] in the non-migraine state and mean AUC_{0-24} ranged from 65,264 ng*h/mL [40% CV] to 55,609 ng*h/mL [43% CV], respectively. The values are comparable to what was observed in healthy volunteers in the SAD phase of Study CN170001 for the 300 mg dose and generally less than that observed with the 600 mg dose, where suprapropportional exposure trends emerged.

Overall, exposures in the migraine state tended to be modestly higher than the non-migraine state. For example, the geometric mean concentration at 30 min following migraine was lower than non-migraine state and the geometric mean concentration at 2 hours post-dose in migraine was higher than non-migraine states. For subjects receiving 300 mg of rimegepant, the ratio for C_{max} (90% confidence intervals, CI) for the non-migraine period compared to the migraine period was 0.58 (0.45, 0.73). For subjects receiving 600 mg, the C_{max} ratio was 0.79 (0.61, 1.02). For subjects receiving 300 mg of rimegepant, the ratio for AUC_{0-24} of the non-migraine period compared to the migraine period was 0.66 (0.51, 0.86). For subjects receiving 600 mg the AUC ratio was 0.79 (0.60, 1.03). Due to nature of the study design, potential period effects cannot be excluded (i.e., Period 1 was always the migraine state and Period 2, non-migraine state) as the magnitude of the trends were modest.

1.2.3 Clinical Efficacy

1.2.3.1 Dose-ranging Trial of Rimegepant for Acute Migraine (CN170003)

Study CN170003 [17] was a double-blind, randomized, placebo-controlled, dose-ranging trial of rimegepant for the acute treatment of migraine. The primary objective was to evaluate the efficacy of rimegepant compared with placebo in the acute treatment of migraine as measured by pain freedom (head pain intensity level reported as "no pain") at 2 hours post-dose using a four point rating scale (no pain, mild pain, moderate pain, severe pain) while identifying an optimal dose to support the Phase 3 clinical trials. Subjects were randomized to receive placebo, sumatriptan 100 mg or rimegepant (10 mg, 25 mg, 75 mg, 150 mg, 300 mg, or 600 mg). Randomization made use of an adaptive design, whereby one quarter of subjects were assigned placebo and one-eighth were assigned sumatriptan; the remainder were assigned to one of six rimegepant groups based on a Bayesian analysis of the observed response rates. Subjects were instructed to treat one migraine of moderate or severe pain intensity and then return to the clinic within 7 days.

A total of 885 subjects were randomized and 812 completed the study.

A broad and durable efficacy profile for rimegepant was demonstrated to be fully present at 75 mg [18]. This dose was selected as the optimal dose to support Phase 3 clinical trials, given that larger doses showed a similar efficacy profile and there was negligible benefit identified with larger doses, consistent with previously published migraine studies characterizing the dose-response profiles of acute treatments for migraine [19].

Rimegepant at 75 mg showed statistically significant efficacy across all four traditional endpoints at 2 hours (pain, nausea, photophobia and phonophobia) which was durable and persisted through 24 hr. At 2 hours following a single oral dose of 75 mg, subjects who previously were experiencing moderate-to-severe migraine pain had no-pain (31.4% $p < 0.0018$) or mild-to-no-pain (72.1% = < 0.0007) as compared to placebo (15.2% and 51.2%, respectively).

In conclusion, Study CN170003 [17] demonstrated that rimegepant is superior to placebo in the acute treatment of migraines. The selection of 75 mg rimegepant as the Phase 3 dose is based on reliably demonstrated efficacy on the key primary outcome measure, Pain Freedom at 2 hours (31.4% vs 15.3% placebo; $p = 0.0018$).

1.2.3.2 Phase 2/3 Studies in Acute Migraine

Three phase 3 studies have been completed, BHV301, 302 and BHV303 (N = 1,771 rimegepant-treated subjects, and N = 1,782 placebo-treated subjects) [20-22]. In all three Phase 3 studies, statistically significant efficacy was demonstrated on the co-primary endpoints of freedom from pain, and freedom from most bothersome symptom (MBS) at 2 hours post-dose. Also in all three studies, significant results were achieved on photophobia freedom, phonophobia freedom and pain relief at 2 hours post-dose.

In addition to the completed phase 3 studies, there is one additional concluded Phase 2/3 trials conducted with rimegepant 75 mg for the acute treatment of migraine. BHV201 study is a Phase 2/3, 52-week, multiple dose, open-label, safety study that is designed to enroll approximately 2000 subjects. As of a database lock date of 13-Jun-2019, 1,798 subjects have been treated. An interim CSR for concluded study BHV3000-201 has been prepared.

1.2.4 Clinical Adverse Event Profile

Rimegepant appears to be generally safe and well tolerated in humans when given as single oral doses up to the maximum dose of 1500 mg and multiple oral doses up to the maximum daily dose of 600 mg for 14 days. The concluded BHV201 study is a Phase 2/3, 52-week, open-label, safety study with rimegepant 75 mg that is designed to enroll approximately 2000 subjects to receive rimegepant up to once daily. Please refer to the current version of Investigators Brochure for a summary of the clinical safety profile.

The primary identified AE of interest is potential change in liver function tests. Investigators must carefully monitor routine liver function tests (ALT, AST, total bilirubin, and ALP) and potentially liver related symptoms and signs. Clinicians should also monitor changes in hematology and other laboratory measures. Please refer to the current Investigators Brochure for further information regarding the clinical safety profile of rimegepant.

1.3 Study Rationale

Migraine is a chronic and debilitating disorder characterized by recurrent attacks lasting four to 72 hours with multiple symptoms, including typically one-sided, pulsating headaches of moderate or severe pain intensity that are associated with nausea or vomiting, and/or sensitivity to sound (phonophobia) and sensitivity to light (photophobia). The World Health Organization's (WHO) Global Burden of Disease Study ranks migraine as the third most prevalent disease worldwide [23] and the Global Burden of Disease Survey 2010 rates migraine as the seventh highest specific cause of disability worldwide. Migraine affects approximately 9% of the adult population in China [2], comprising approximately 80 million adults. Approximately 90% of Chinese migraineurs suffer from between one to fourteen headache days per month, and approximately 10% have more than fourteen per month [24]. Approximately 24% of individuals Chinese migraineurs miss more than twenty days of work over a three month period as a result of migraine [2]. The total indirect cost to Chinese society from lost productivity is estimated to be about USD$40 billion [2]. Comorbid conditions associated with migraine include depression, anxiety and cardiovascular disease [25] .

While there are multiple classes of medications for the acute treatment of migraine, considerable unmet need remains, as evidenced by migraines being the seventh leading cause of disability

worldwide [23]. In part, this burden is attributed to limitations of current standard-of-care pharmacotherapies, which are contraindicated for use in migraine sufferers with known cardiovascular disease as well as many others with multiple cardiovascular risk factors. The Prescribing Information for triptans includes warnings and precautions for migraine subjects with risk factors for cardiovascular disease and states that high risk subjects, including those with increased age, diabetes, hypertension, smoking, obesity or a strong family history of coronary artery disease, should be evaluated prior to receiving the first dose of a triptan. Triptans are contraindicated in subjects with a history of ischemic heart disease, coronary artery vasospasm, history of stroke, peripheral vascular disease or uncontrolled hypertension. Even in subjects who have a negative cardiovascular evaluation, product labeling for triptans recommends that consideration be given to administration of the first dose in a medically-supervised setting and performing an electrocardiogram immediately following administration. Additionally, periodic cardiovascular evaluation should be considered for long-term users of triptans who have cardiovascular risk factors.

There have been no new class of medicine approved in China for the acute treatment of migraine since the triptans first became available in the 1990s. Traditional Chinese Medicines (TCM) are often used by patients with migraine, but data suggests that efficacy is poor, and patients are unsatisfied with TCM options compared to Western Medicines [26].

Thus, there remains a significant unmet medical need for a novel migraine-specific medication that does not increase the risk of cardiovascular liability.

Biohaven is developing a small molecule CGRP receptor antagonist, rimegepant, for the acute treatment of migraine that will address such cardiovascular limitations. Clinical and nonclinical studies show that rimegepant is not associated with adverse vasoconstrictive properties that are thought to cause the serious cardiovascular adverse events of the triptan class and does not share a mechanism with other agents of cardiovascular concern such as Non-Steroidal Anti-Inflammatories (NSAIDs) and ergotamine derivatives. A completed Phase 2 trial [17] demonstrated the efficacy of rimegepant in the acute treatment of migraine, with and without aura, at doses of 75 mg and above Overall, the Phase 2b dose-ranging study demonstrated that rimegepant 75 mg was the lowest effective dose with no incremental efficacy benefit observed at 150 mg, 300 mg, or 600 mg doses. The choice of the rimegepant 75 mg dose as fully efficacious compared to placebo was confirmed in 3 subsequent Phase 3 pivotal studies, where significant efficacy results were achieved across a broad range of endpoints in each study [Rimegepant IB].

BHV3000-303, BHV3000-302, and BHV3000-301 were Phase 3, single-dose, double-blind, randomized, outpatient studies evaluating the safety and efficacy of rimegepant 75 mg orally dissolving tablet (ODT; BHV3000-3003) or rimegepant 75 mg tablet (BHV3000-302 and BHV3000-301) as compared to placebo in the treatment of subjects experiencing a migraine attack with moderate or severe intensity in a broad patient population.

In BHV3000-303, 1,466 subjects were randomized in a 1:1 ratio for the 1,375 subjects administered rimegepant 75 mg ODT (682 subjects) or matching placebo (693 subjects).

Efficacy endpoints were analyzed using the modified-intention-to-treat (mITT) population including 669 rimegepant-treated subjects and 682 placebo-treated subjects.

In BHV3000-302, 1,186 subjects were randomized in a 1:1 ratio for the 1,083 subjects

administered rimegepant 75 mg tablet (543 subjects) or matching placebo (540 subjects). Efficacy endpoints were analyzed using the mITT population including 537 rimegepant treated subjects and 535 placebo-treated subjects.

In BHV3000-301, 1,162 subjects were randomized in a 1:1 ratio for the 1,095 subjects administered rimegepant 75 mg tablet (546 subjects) or matching placebo (549 subjects). Efficacy endpoints were analyzed using the mITT population including 543 rimegepant treated subjects and 541 placebo-treated subjects.

In all 3 studies, the therapeutic benefit of rimegepant was seen for primary end points and across a wide range of secondary endpoints.

The randomized controlled study proposed herein will provide data on the efficacy and safety of rimegepant for the acute treatment of migraine in Chinese and Korean subjects and bridge to the existing complete clinical package for rimegepant 75mg for the acute treatment of migraine. As such, this study serves the broader objectives of the rimegepant clinical development program: to demonstrate the safety, tolerability, and efficacy of rimegepant in the acute treatment of migraine with or without aura in adults.

1.3.1 Study Design Rationale

This is a double-blind, randomized, multicenter, outpatient evaluation of the safety and efficacy of rimegepant as compared to placebo in the treatment of moderate or severe migraine. The study is designed provide data in Chinese and Korean subjects that will bridge to the existing comprehensive clinical trial data available for rimegepant 75mg dose in the treatment of migraine. As noted above, there is a complete clinical data set available for the rimegepant 75mg in the treatment of migraine that has been submitted to the US FDA with an expected PDUFA data in the first quarter of 2020. Study BHV3000-310 will demonstrate that rimegepant 75mg for the acute treatment of migraine has a safety and efficacy profile in Chinese and Korean subjects with migraine that is consistent with the profile observed in the clinical program to date.

The study drug will be rimegepant formulated in a 75 mg ODT tablet or a matching placebo. The subjects will be instructed to take their study medication, as an outpatient, when (if) they have a migraine headache which reaches moderate or severe intensity.

The study will randomize approximately 1430 subjects. The subjects will be randomized in a 1:1 ratio to the rimegepant or placebo treatment groups. The randomization will be stratified by the use of prophylactic migraine medications (yes or no) and country (China or Korea).

This study design is utilized to confirm the efficacy and safety profiles observed in the Phase 2b and three completed phase 3 studies with rimegepant. Incorporation of placebo and use of appropriate rescue medications will permit enrollment of subjects with a broad range of comorbidities, including cardiovascular conditions, representative of the potential treatment population.

1.3.2 Dose Selection Rationale

Study CN170003 was a double-blind, randomized, placebo-controlled, dose-ranging trial of rimegepant for the acute treatment of migraine [18]. The primary objective was to evaluate the efficacy of rimegepant compared with placebo in the acute treatment of migraine as measured by pain freedom (head pain intensity level reported as “no pain”) at 2 hours post-dose using a four point rating scale (no pain, mild pain, moderate pain, severe pain) while identifying an optimal dose to support the Phase 3 clinical trials. Subjects were randomized to receive placebo, sumatriptan 100 mg or rimegepant (10, 25, 75, 150, 300, or 600 mg). Randomization made use of an adaptive design, whereby one quarter of subjects were assigned placebo and one-eighth were assigned sumatriptan; the remainder were assigned to one of the six rimegepant groups based on a Bayesian analysis of the observed response rates. Subjects were instructed to treat one migraine of moderate or severe pain intensity and return to the clinic within 7 days.

A total of 885 subjects were randomized and 812 completed the study. Key entry criteria were very similar to those chosen for this clinical trial.

A comprehensive and durable efficacy profile for rimegepant was demonstrated to be fully present at 75 mg but not at lower doses (i.e., 10 mg or 25 mg). This dose was selected as the optimal dose to support Phase 3 clinical trials, given that larger doses (150 mg, 300 mg, 600 mg) showed a similar efficacy profile and there was no pattern of added benefit in dosing higher, consistent with

previously published migraine studies [19]. rimegepant at 75 mg showed statistically significant broad efficacy across all four traditional endpoints at 2 hours (pain, nausea, photophobia and phonophobia) which was durable and persisted through 24 hr. At 2 hours following a single oral dose of 75 mg, subjects who previously were experiencing moderate-to-severe migraine pain had no-pain (31.4% p = 0.0018) or mild-to-no-pain (72.1%) as compared to placebo (15.3% and 51.2%, respectively). For the 75 mg dose at 2 hours, subjects also showed significant freedom from nausea (67.4%, p = 0.0074) freedom from phonophobia (52.3%, p = 0.0001) and freedom from photophobia (41.9%, p = 0.0023) vs. placebo (51.2%, 28.1% and 24.1%, respectively). The lasting nature of these beneficial anti-migraine effects were evidenced by a comparatively similar efficacy profile in the 2-24 hour measures, where rimegepant at 75 mg produced significant 2-24 hour sustained pain freedom (27.9%, p < 0.0001) and 2-24 hour sustained pain relief (69.8%, p < 0.0001) vs. placebo (7.4% and 42.4%, respectively).

1.3.3 Other Rationale related to the compound/study

Prior to initiation of this study, two Phase 1 crossover studies were conducted in healthy volunteers to assess the pharmacokinetic comparability of a single dose of the orally disintegrating tablet (ODT) of rimegepant with the previously studied rimegepant tablet.

1.4 Research Hypothesis

Rimegepant will have efficacy superior to placebo in the treatment of acute migraine with a favorable safety profile suitable for use by a broad subject population.

2 STUDY OBJECTIVES

2.1 Primary

To evaluate the efficacy of rimegepant compared with placebo in the acute treatment of migraine as measured by the co-primary endpoints of **pain freedom** and **freedom from the most bothersome symptom** (MBS), associated with migraine, at two hours post dose.

2.2 Secondary

2.2.1 Key Secondary Objectives

1. To compare rimegepant to placebo on pain relief at 2 hours post-dose
2. To compare rimegepant to placebo on the ability to function normally at 2 hours post-dose as reported on the Functional Disability scale
3. To compare rimegepant to placebo on the Use of Rescue Medications through 24 hours post-dose
4. To compare rimegepant to placebo on sustained pain freedom from 2 to 24 hours post-dose
5. To compare rimegepant to placebo on sustained pain freedom from 2 to 48 hours post-dose

2.2.2 Other Secondary Objectives

1. To compare rimegepant to placebo on pain freedom at 15, 30, 45, 60 and 90 minutes post-dose
2. To compare rimegepant to placebo on freedom from Most Bothersome Symptom at 15, 30, 45, 60 and 90 minutes post-dose
3. To compare rimegepant to placebo for the incidence of pain relapse from 2 to 48 hours post-dose

2.3 Exploratory Objectives

1. To compare rimegepant to placebo on pain relief at all post-dose timepoints.
2. To compare rimegepant to placebo on pain freedom at all post-dose timepoints.
3. To compare rimegepant to placebo on freedom from MBS at all post-dose timepoints.

4. To compare rimegepant to placebo on freedom from functional disability at all post-dose timepoints.

5. To compare rimegepant to placebo on freedom from phonophobia at all post-dose time points

6. To compare rimegepant to placebo on freedom from photophobia at all post-dose time points

7. To compare rimegepant to placebo on freedom from nausea at all post-dose time points

8. To compare rimegepant to placebo on sustained pain relief from 2 to 48 hours post-dose

9. To compare rimegepant to placebo on sustained pain relief from 2 to 48 hours post-dose

10. To compare rimegepant to placebo on freedom from Most Bothersome Symptom from 2 to 24 hours post-dose

11. To compare rimegepant to placebo on freedom from Most Bothersome Symptom from 2 to 48 hours post-dose

12. To compare rimegepant to placebo on the ability to function normally from 2 to 24 hours post-dose as reported on the Functional Disability scale

13. To compare rimegepant to placebo on the ability to function normally from 2 to 48 hours post-dose as reported on the Functional Disability scale

3 STUDY ENDPOINTS

3.1 Primary

Pain freedom at 2 hours will be assessed using the number of evaluable subjects that report no pain at two hours post-dose. Pain will be measured on a 4 point Likert scale (0=none, 1=mild, 2=moderate, 3=severe).

Freedom from the most bothersome symptom (MBS) at 2 hours will be assessed using the number of evaluable subjects that report the absence of their MBS at 2 hours post-dose. The MBS (nausea, phonophobia or photophobia) will measured using a binary scale (0=absent, 1=present).

3.2 Secondary

3.2.1 Key Secondary Endpoints

1. Pain Relief at 2 hours post-dose, will be assessed using the number of subjects that report a pain level of moderate or severe at baseline and then report a pain level of none or mild at two hours post-dose.

2. The proportion of subjects able to function normally, at 2 hours post-dose, will be assessed using the number of subjects that self-report as "normal" on the Functional Disability scale in the subset of subjects that report any level of disability just prior to taking study medication.

3. The use of rescue medication will be assessed using the number of subjects that take rescue medication within 24 after administration of study medication (rimegepant or placebo).

4. Sustained pain freedom, from 2 to 24 hours, will be assessed using the number of subjects that do not experience any headache pain through the time period of interest.

5. Sustained pain freedom, from 2 to 48 hours, will be assessed using the number of subjects that do not experience any headache pain through the time period of interest.

3.2.2 Other Secondary Endpoints

1. Pain freedom at 15, 30, 45, 60 and 90 minutes will be assessed using the number of subjects that report a pain level of moderate or severe just before taking study medication and then report a pain level of none at the timepoint of interest.

2. Freedom from the most bothersome symptom (MBS) at 15, 30, 45, 60 and 90 minutes will be assessed using the number of subjects that report the absence of their MBS at the time point of interest.

3. Pain relapse will be assessed using the number of subjects that are pain free at 2 hours post-dose and then have a migraine of any pain severity (response of: 2 or 3 on the 4 point scale) within 48 hours after administration of study medication.

3.3 Exploratory Endpoints

The exploratory endpoints will be described in the Statistical Analysis Plan (SAP).

3.4 Measures of Interest

Safety and Other assessments:

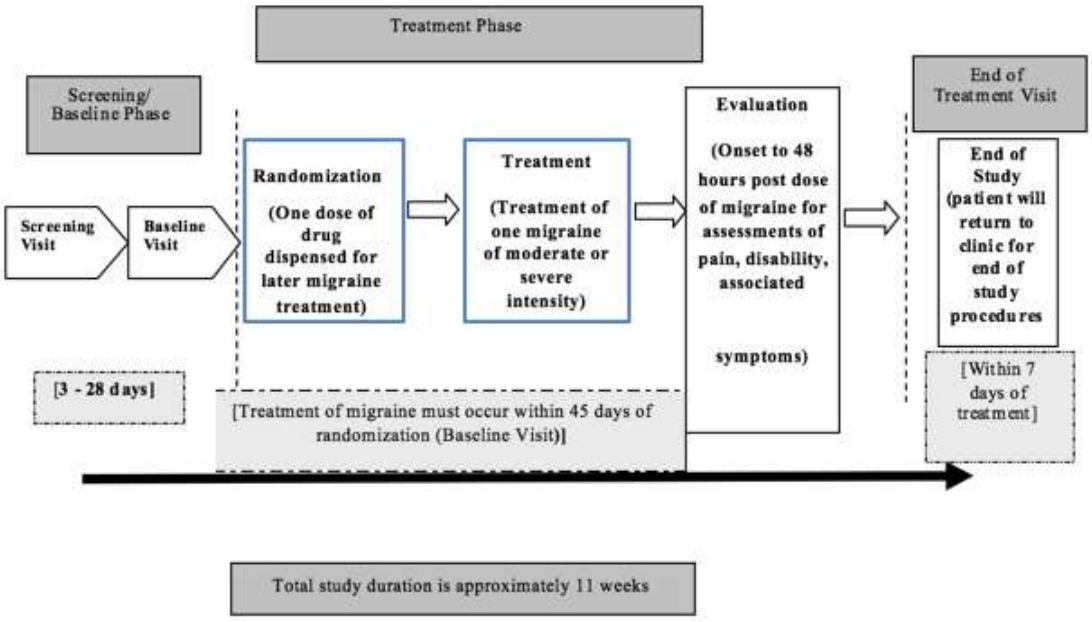
- Adverse Events
- ECG assessments
- Vital Sign and Physical Measurements
- Routine Laboratory Tests
- Assessment of Migraine Pain and Symptoms
- Functional Disability Scale

4 STUDY PLAN

4.1 Study Design and Duration

This is a double-blind, randomized, multicenter, outpatient evaluation of the safety and efficacy of rimegepant as compared to placebo in the treatment of moderate or severe migraine. Subjects will be dispensed one dose of study medication consisting of a rimegepant 75 mg tablet or a matching placebo. The total duration of the study will be approximately 11 weeks. This includes a 3-28 day Screening Period, an Acute Phase that can last up to 45 days or until the subject has a migraine that reaches moderate or severe intensity, followed by an End of Treatment Visit 7 days after the administration of the study medication.

4.2 Study Schematic



4.3 Schedule of Assessments

Table 1: Schedule of Assessments

Procedure	Screening Visit (3-28 days)[1]	Baseline Visit (Randomization)[1]	Onset of moderate or severe migraine[2]	During Treatment 15, 30, 45, 60 and 90 minutes Post-Dose	During Treatment 2, 3, 4, 6, 8 hours Post-Dose	During Treatment 24 hours Post-Dose	During Treatment 48 hours Post- Dose	End of Treatment Visit (within 7 days of migraine)[14]
Eligibility Assessments								
Informed Consent	X							
Inclusion/Exclusion Criteria	X	X						
Medical History	X							
Prophylactic Migraine Medication/ Concomitant Medication[3]	X	X						X
Assessment of Migraine History (Signs and symptoms) paper source[13]	X							

Procedure	Screening Visit (3-28 days)[1]	Baseline Visit (Randomization)[1]	Onset of moderate or severe migraine[2]	During Treatment 15, 30, 45, 60 and 90 minutes Post-Dose	During Treatment 2, 3, 4, 6, 8 hours Post-Dose	During Treatment 24 hours Post-Dose	During Treatment 48 hours Post- Dose	End of Treatment Visit (within 7 days of migraine)[14]
Safety Assessments								
Physical Examination	X							X
Vital Signs/Physical Measurements[4]	X	X						X
Clinical Safety Laboratory Testing[5]	X							X
Urine drug screen for drugs of abuse	X							X
ECG	X							X
Pregnancy Test[6]	X	X	X					X
Adverse Event and Serious Adverse Event Assessment[7]	X	X	X	X	X	X	X	X
Clinical Drug Supplies/Study Supplies								
Randomize[8]		X						
Dispense Study Medication		X						
Administer 1 dose of study medication[9]			X					
Return unused study medication								X
eDiary returned/reviewed for completeness[10]								X

Procedure	Screening Visit (3-28 days)[1]	Baseline Visit (Randomization)[1]	Onset of moderate or severe migraine[2]	During Treatment 15, 30, 45, 60 and 90 minutes Post-Dose	During Treatment 2, 3, 4, 6, 8 hours Post-Dose	During Treatment 24 hours Post-Dose	During Treatment 48 hours Post- Dose	End of Treatment Visit (within 7 days of migraine)[14]
Efficacy Assessments[11]								
Assessment of migraine pain[12]			X	X	X	X	X	
Assessment of Migraine Symptoms (photophobia, phonophobia, and nausea - eDiary)[12]			X	X	X	X	X	
Functional Disability Scale[12]			X	X	X	X	X	

[1] **Screening Phase** will be 3 - 28 days. The **Baseline Visit** may be scheduled but should only occur ***after*** all screening procedures are complete, subject meets inclusion/exclusion criteria, and lab test results have been received by the site.

[2] Subjects will use eDiary to answer questions about their migraine symptoms upon experiencing a moderate/severe migraine headache. The subject will administer pre- dispensed study drug if 1) the headache remains moderate or severe; 2) the subject has completed all required migraine assessment questions in the eDiary, including their current most bothersome migraine symptom, and 3) the subject has not already taken prohibited medications (see protocol section 5.4).

[3] Subjects should keep track of their concomitant medications throughout the study and report them to the study personnel at the End of Treatment Visit. Any medication taken for recurrent headache should be documented. Use of concomitant medications after randomization, including rescue medications, will be recorded by the subject on a paper diary and reported to the site.

[4] Height will only be captured at the Screening Visit. Weight, body temperature, respiratory rate, blood pressure and heart rate will be collected at all time points where indicated. Sitting arterial systolic and diastolic blood pressure and pulse rate will be measured.

[5] **Screening Visit**: All screening visit laboratory test results must be received prior to Baseline (randomization) Visit.

[6] A serum pregnancy test will be completed at Screening and End of Treatment Visits as part of the standard laboratory tests (if appropriate). Confirmatory urine pregnancy test for WOCBP should be completed on site at Baseline Visit and any subsequent visits for confirmation at the Investigator's discretion.

[7] SAEs are reported from the time of informed consent and non-serious AEs are reported from baseline. All ongoing non-serious AEs and SAEs will be followed to resolution or until investigator deems there will be no further status change. SAEs that occur during the treatment period should be reported to site according to local regulatory requirements. Non-serious AEs that occur during the treatment period should be reported to the site at the EOT.

[8] Subjects will be randomized in the IWRS system at the Baseline Visit (Randomization Day 01).

[9] Subjects should be instructed that the dose should be taken once the migraine attack reaches moderate or severe pain and after the subject has completed all required migraine assessments in the eDiary. The eDiary will prompt the subject to take study medication.

[10] Site staff to review and confirm entries with subjects and confirm all data points are transferred to the system and reset eDiary for future subject use, PRIOR to the subject leaving the clinic.

[11] ± Windows for timeframe around efficacy assessments (15, 30, 45, 60, 90 min, 2, 3, 4, 6, 8, 24 and 48 hours) will be automated and captured in the eDiary.

[12] These scales will be captured in the eDiary. Subjects will also be asked about their most bothersome symptom at the time of reporting and treating a qualifying migraine.

[13] Paper source document will be used to capture Migraine History. Subjects will also be asked about their typical most bothersome symptom when having a migraine.

[14]Subjects should return to the site for their EOT visit within 7 (+2) days from their migraine occurring.

4.3.1 Screening Phase (3-28 days)

It is estimated that approximately 1,800 subjects will be screened to allow approximately 1,430 subjects to be randomized at the Baseline visit. All subjects who are screened into the study will be entered into the IWRS system. After obtaining informed consent, subjects will undergo all screening procedures as detailed in Table 1. After signing the informed consent and completing all screening procedures on Day 1, subjects will return between Day 3-28 days from signing informed consent to be randomized at the Baseline visit if they meet all eligibility criteria.

Subjects in this study may be screened only once. Rescreening is not permitted.

4.3.2 Acute (Randomization) Phase (45 days)

If the subject meets all eligibility criteria they will be randomized at the Baseline Visit via the IWRS. The subjects will be provided with an eDiary. The study personnel will instruct the subject on the proper use of the eDiary and ensure proper understanding and use of the tool, prior to the subject leaving the office.

After randomization via the IWRS, the subject will be dispensed a single dose of the double-blind study medication to take home for up to 45 days. This study medication is to be taken when a migraine attack reaches moderate or severe intensity on the numeric rating scale (NRS) as indicated in the eDiary. The subject will be instructed to take their study medication, as an outpatient, when (if) they have a migraine headache which reaches moderate or severe intensity **after they answer eDiary questions about their current pain and symptoms and identify their currently most bothersome, migraine associated, symptom (phonophobia, photophobia or nausea)**. The subject will complete an eDiary for forty-eight hours after taking study medication to record efficacy and other quality of life measures.

Subjects in this study may be randomized only once. Under no circumstances may a subject be re-randomized.

4.3.2.1 eDiary Data Collection

Subjects will record efficacy measures in their eDiary. This includes the following: onset time of headache, intensity of the headache prior to and at time of taking study medication. The subjects should not dose with study medication until the headache reaches moderate or severe intensity. Headache severity will be recorded using a four-point numeric rating scale (no pain, mild pain, moderate pain, severe pain) at the onset of the migraine and after dosing at time points of 15, 30, 45, 60, and 90 minutes and 2, 3, 4, 6, 8, 24 and 48 hours. The presence or absence of associated symptoms (nausea, photophobia, phonophobia) and ratings of functional disability (four-point scale: normal, mildly impaired, severely impaired, requires bedrest) will be recorded at the same time points as the headache severity ratings. Subjects will also identify their currently most bothersome symptom before taking study medication. Subjects will record the date and time study therapy was taken in their eDiary. Subjects who have headache pain reduced to a mild intensity or pain free intensity level will be considered to have achieved pain relief.

After dosing with study medication, all other headache medication is prohibited during the 2 hours post dose. However, a subject who does not experience relief of their migraine headache at the end of two hours after dosing with study medication (and after the two hour assessments have been completed on the eDiary) will be permitted to use the following rescue medication: aspirin, ibuprofen, acetaminophen up to 1000mg/day (this includes Excedrin Migraine) naproxen (or any other type of nonsteroidal anti-inflammatory (NSAID)), antiemetics (e.g., metoclopramide or promethazine), or baclofen. **These are the only medications allowed for rescue treatment after 2 hours post dose of study medication.** However, if needed, after 48-hours of administering the one dose of study medication (and before returning for the End of Treatment Visit) subject may take their prescribed standard of care medications for treatment of migraine, including triptans if not contraindicated, **provided all of the assessments have been completed on the eDiary**. Exclusionary rescue medication such as, opioids, ergotamines, butalbital compounds, and muscle relaxants (except baclofen as a rescue medication, see above) are not allowed on this study. Similarly, if the migraine is relieved by study medication at 2 hours after dosing but then recurs to a moderate or severe intensity level between two and forty-eight hours, the subject will be permitted to take the same rescue therapy as outlined above.

Subjects should be encouraged to treat the first qualifying (moderate to severe) migraine that occurs during the treatment phase. If subjects are unable to treat their first qualifying migraine due to scheduling, etc. the same medication restrictions would still apply (i.e.) aspirin, ibuprofen, acetaminophen up to 1000mg/day (this includes Excedrin Migraine) naproxen (or any other type of nonsteroidal anti-inflammatory (NSAID)), antiemetics (e.g., metoclopramide, promethazine, or baclofen).

Similarly, for treatment of non-qualifying migraines (i.e. mild migraines, or other headaches) that occur during the randomization period before a qualifying migraine is reported, subject will only be permitted to use the medications listed above. Triptans and acetaminophen (over 1000mg/day) are prohibited after randomization except as rescue medication as described in Section 5.4.1. In all circumstances, the subject will continue to complete his or her eDiary for up to forty-eight hours after consuming the study medication.

4.3.3 Extension Phase

Not Applicable

4.3.4 End of Treatment (7 days after Treatment)

Subjects will return to the study site within 7 days of study treatment (+2 days) for review of the eDiary assessment of medication compliance, and monitoring of tolerability and safety (including vital signs, laboratory tests, and electrocardiography). If a subject has NOT experienced a migraine headache of sufficient severity within 45 days after randomization, they still are required to complete all EOT visit procedures. All subjects must return unused study medication, paper diary and eDiary to the study center.

4.4 COVID-19 Contingencies

If a subject is unable to visit the study site due to restrictions as a result of the COVID-19 pandemic, remote visits may be allowed on a case by case basis, however the investigator should first contact the sponsor medical monitor (or designee) to discuss the most appropriate course of action. If the remote visit requires laboratory tests, a local laboratory may be used for tests instead of the central laboratory and results obtained and reviewed by the investigator. With prior sponsor approval, shipping of study drug directly to the subject via overnight tracked and certified courier may also be allowed.

4.5 Post Study Therapy

At the end of the study the investigator should advise the subject regarding appropriate standard of care to treat their migraine.

5 POPULATION

Individuals entered in this trial will be subjects who suffer from migraines. The treatment setting for these subjects may include clinics, institutions or private office practices. Subjects may be recruited through a variety of sources, including referral from physicians and other health care professionals.

5.1 Number of Subjects

It is anticipated that approximately 1,800 subjects will need to be screened in order to randomize approximately 1,430 subjects. The subjects will be randomized in a 1:1 ratio to the rimegepant or placebo treatment groups. It is anticipated that enrollment will occur at approximately 80 sites in China and Korea over a period of approximately 18 months during this trial.

5.2 Inclusion Criteria

1. Signed Written Informed Consent

    a. Written informed consent must be obtained from the subject in accordance with requirements of the study center's institutional review board (IRB) or ethics committee, prior to the initiation of any protocol-required procedures.

2. Target Population

    Subjects has at least a 1 year history of headaches consistent with a diagnosis of migraine (with or without aura) according to the International Classification of Headache Disorders, 3rd Edition, beta version [1], including the following:

    a. Migraine attacks present for more than 1 year with the age of onset prior to 50 years of age

    b. Migraine attacks, on average, lasting about 4 - 72 hours if untreated

    c. Not more than 8 attacks of moderate or severe intensity per month within last 3 months

    d. Subjects must be able to distinguish migraine attacks from tension/cluster headaches

    e. Consistent migraine headaches of at least 2 migraine headache attacks of moderate or severe intensity in each of the 3 months prior to the Screening Visit and maintains this requirement during the Screening Period

    f. Less than 15 days with headache (migraine or non-migraine) per month in each of the 3 months prior to the Screening Visit and maintains this requirement during the Screening Period

    g. Subjects on prophylactic migraine medication are permitted to remain on therapy if they have been on a stable dose for at least 3 months prior to screening visit, and the dose is not expected to change during the course of the study

h. Subjects with contraindications for use of triptans may be included provided they meet all other study entry criteria

3. Age and Reproductive Status

a. Male and Female subjects ≥ 18 years and older

b. Women of childbearing potential (WOCBP) with male partners and men with women partners of childbearing potential must be using two acceptable methods of contraception to avoid pregnancy throughout the study in such a manner that the risk of pregnancy is minimized. See Section 5.5 for the definition of WOCBP. Males with vasectomy are considered surgically sterile provided the procedure occurred greater than 6 months prior to the screening visit

c. No clinically significant abnormality identified on the medical or laboratory evaluation. A subject with a clinical abnormality or laboratory parameters outside the reference range may be included only if the investigator considers that the finding is not clinically significant and will not introduce additional risk factors and will not interfere with the study procedures

d. At the Baseline Visit prior to dispensing Investigational Study Medication, WOCBP must have a negative urine pregnancy test

e. Women must not be breastfeeding

5.3 Exclusion Criteria

1. Disease Target Exclusion

a. Subjects has a history of migraine with brainstem aura; or hemiplegic migraine

2. Medical History and Concurrent Diseases

a. Subjects history of HIV disease

b. Subject history with current evidence of uncontrolled, unstable or recently diagnosed cardiovascular disease, such as ischemic heart disease, coronary artery vasospasm, and cerebral ischemia. subjects with Myocardial Infarction (MI), Acute Coronary Syndrome (ACS), Percutaneous Coronary Intervention (PCI), cardiac surgery, stroke or transient ischemic attack (TIA) during the 6 months prior to screening

c. Uncontrolled hypertension (high blood pressure), or uncontrolled diabetes (however subjects can be included who have stable hypertension and/or diabetes for at least 3 months prior to being enrolled)

d. Subject has a current diagnosis of major depression, other pain syndromes, psychiatric conditions (e.g., schizophrenia), dementia, or significant neurological disorders (other than migraine) that, in the Investigator's opinion, might interfere with study assessments

e. Subject has a history of gastric, or small intestinal surgery (including Gastric Bypass, Gastric Banding, Gastric Sleeve, Gastric Balloon, etc.), or has a disease that causes malabsorption

f. The subject has a history or current evidence of any significant and/or unstable medical conditions (e.g., history of congenital heart disease or arrhythmia, known suspected infection, hepatitis B or C, or cancer) that, in the investigator's opinion, would expose them to undue risk of a significant adverse event (AE) or interfere with assessments of safety or efficacy during the course of the trial

g. History of, treatment for, or evidence of, alcohol or drug abuse within the past 12 months or subjects who have met DSM-V criteria [27] for any significant substance use disorder within the past 12 months from the date of the screening visit

h. Subjects should be excluded if they have a positive drug screen for drugs of abuse that in the investigator's judgment is medically significant, in that it would impact the safety of the subject or the interpretation of the study results. In addition:

i. Detectable levels of cocaine, amphetamine, and phencyclidine (PCP) in the drug screen are exclusionary. Subjects who are positive for amphetamines, and who are on a prescribed amphetamine medication for an approved indication (e.g. ADHD) will be allowed into the study at the Investigator's discretion. This determination by the Investigator must be well documented in the subject's source medical records. The stimulant dose must be stable from 3 months prior to baseline until the end of treatment visit occurs.

j. Hematologic or solid malignancy diagnosis within 5 years prior to screening. Subjects with a history of localized basal cell or squamous cell skin cancer are eligible for the study if they are cancer-free prior to the screening visit in this study.

3. Allergies and Adverse Drug Reactions

   a. History of drug or other allergy which, in the opinion of the principal investigator, makes the subject unsuitable for participation in the study.

4. Sex and Reproductive Status

   a. Females of child-bearing potential who are unwilling or unable to use an acceptable contraceptive method or abstinence to avoid pregnancy for the entire study period and for 56 days after the study.

   b. Women who are pregnant or breastfeeding. Women with a positive pregnancy test on enrollment or prior to study drug administration.

5. ECG and Laboratory Test Findings

a. Estimated glomerular filtration rate (eGFR) according to the re-expressed abbreviated (four-variable) Modification of Diet in Renal Disease (MDRD) Study equation ≤ 40 ml/min/1.73m^2

b. Corrected QT interval > 470 msec (QTc by method of Frederica), at Screening

c. Left Bundle Branch block

d. Right Bundle Branch Block with a QRS duration ≥ 150 msec.

e. Intraventricular Conduction Defect with a QRS duration ≥ 150 msec.

f. Serum bilirubin (Total, Direct or Indirect) > 1 x ULN (Only abnormal values of between 1-1.5x ULN may be repeated once for confirmation during the screening period)

g. Neutrophil count ≤ 1000/μL (or equivalent).

h. AST (SGOT) or ALT (SGPT) > 1 x ULN (Only abnormal values of between 1-1.5x ULN may be repeated once for confirmation during the screening period)

6. Other Exclusion Criteria

a. Prisoners or subjects who are involuntarily incarcerated

b. Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness

c. Participation in clinical trial with non-biological investigational agents or investigational interventional treatments within the 30 days prior to Baseline Visit

d. Subjects who have previously participated in any study of rimegepant or other experimental CGRP-antagonist study (either small molecule or biologic), or have been prescribed CGRP-antibodies within the last 6 months

e. Participation in clinical trial with biological investigational agents within the 90 days prior to Baseline visit

f. Participation in any other investigational clinical trial while participating in this clinical trial

7. Please see 5.4 for Prohibited medications and 5.4.1 for allowable Rescue Medications

5.4 Prohibited Concomitant Medication

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

1. St. John's Wort should not be taken 14 days prior to randomization and throughout the study.

2. TCMs should not be taken 14 days prior to randomization and throughout the study.

3. Barbiturate-containing products (e.g. Fioricet, Fiorinal, butalbital, phenobarbital) should not be taken 14 days prior to randomization and throughout the study.

4. Modafinil (PROVIGIL®) should not be taken 14 days prior to randomization and throughout the study.

5. Butterbur root or extracts should not be taken 14 days prior to randomization and throughout the study.

6. History of use of ergotamine medications on greater than/equal 10 days per month on a regular basis for greater than/equal 3 months.

7. History of non-narcotic analgesic intake on greater than/equal 15 days per month for greater than/equal 3 month (e.g. acetaminophen, NSAIDs, gabapentin etc.) ***for other pain indications.*** (Please refer to Section 5.4.1 for rescue medication).

8. Use of narcotic medication, such as opioids (e.g. morphine, codeine, oxycodone and hydrocodone) for at least 2 days prior to randomization.

9. Use of all acetaminophen or acetaminophen containing products must be discontinued at least 2 days prior to randomization (acetaminophen $\leq$ 1000mg/day is allowed as rescue medication, see Section 5.4.1). During the screening phase (3-28 days) use of acetaminophen or acetaminophen containing products at daily dosing levels of greater than 1000mg/day is prohibited.

10. Use of marijuana is prohibited during the study.

11. Muscle relaxants (baclofen is allowed as rescue medication, see Section 5.4.1).

12. Concomitant use of strong CYP3A4 inhibitors with rimegepant is prohibited during the study. If use of a strong CYP3A4 inhibitor is required, such as use of HIV Protease Inhibitors, Hepatitis C protease inhibitors, certain azole antifungals, or clarithromycin, dosing with rimegepant should be stopped and should not start again until 14 days after the last dose of the strong CYP3A4 inhibitor. Please see Appendix 3, Section 15.3.

13. Concomitant use of strong CYP3A4 inducers with rimegepant is prohibited during the study. If use of a strong CYP3A4 inducer is required, such as use of carbamazepine, phenytoin, or rifampin, dosing with rimegepant should be stopped and should not start again until 14 days after the last dose of the strong CYP3A4 inducer. Please see Appendix 3, Section 15.3..

Subjects on prophylactic migraine medication are permitted to remain on therapy provided they have been on a stable dose for at least 3 months prior to study entry.

Low dose aspirin (e.g. 81 mg or less) for documented cardiovascular prophylaxis is allowed.

5.4.1 Rescue Medications

After dosing with study medication, <u>all other headache medication</u> is prohibited during the 2 hours post dose. However, a subject who does not experience relief of their migraine headache at the end of two hours after dosing with study medication (***and after the two hour assessments have been completed on the eDiary***), will be permitted to use the following rescue medication: ***aspirin, ibuprofen, acetaminophen up to 1000mg/day (this includes Excedrin Migraine) naprosyn (or any other type of non- steroidal anti-inflammatory (NSAID)), antiemetics (e.g., metoclopramide or promethazine), or baclofen. These are the only medications allowed for rescue treatment after 2 hours post dose of study medication.***

However, if needed, after 48-hours of administering the one dose of study medication (and before coming in for the End of Treatment Visit) subject may take their prescribed standard of care medications for treatment of migraine (including triptans if not contraindicated, provided all of the assessments have been completed on the eDiary. Similarly, if the migraine is relieved by study medication at 2 hours after dosing but then recurs to a moderate or severe intensity level between two and forty-eight hours, the subject will be permitted to take the same rescue therapy as outlined above. In all circumstances, the subject will always continue to complete his or her eDiary entries through the 48-hour assessment after consuming the study medication. Use of concomitant medication after randomization, including rescue medication, will be recorded by the subject on a paper diary (Concomitant, Adverse Event and Rescue Medication Log) and reported to the site. The site will record medications that were taken within 14 days of dosing with study medication (or until the End of Treatment Visit).

During the 45 days the subject is participating in the study, if the subject has a nonqualifying migraine (mild migraine) or a migraine that they do not treat with study medication, the subject is permitted to use only the following medications: aspirin, ibuprofen, naprosyn (or any other type of non- steroidal anti-inflammatory (NSAID)), antiemetics (e.g., metoclopramide or promethazine), or baclofen.

After completing all assessments (through 48 hours and before End of Treatment Visit) in their eDiary, if subjects experience a migraine they are allowed to take their prescribed standard of care medication (including triptans if not contraindicated and acetaminophen up to 1000mg/day, this includes Excedrin Migraine).

5.5 Women of Childbearing Potential

Women of childbearing potential (WOCBP) include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Post menopause is defined as:

1. Amenorrhea greater than or equal to 12 consecutive months without another cause and a documented serum follicle stimulating hormone (FSH) level > 35mIU/mL or

2. Woman with irregular menstrual periods and a documented serum follicle stimulating hormone (FSH) level > 35mIU/mL or

NOTE: FSH level testing is not required for women greater than or equal to 62 years old with amenorrhea of greater than or equal to one year

3. Woman on hormone replacement therapy (HRT)

Women of childbearing potential (WOCBP) with male partners and men with women partners of childbearing potential must be using two acceptable methods of contraception to avoid pregnancy throughout the study and for up to 56 days after the last dose of investigational product in such a manner that risk of pregnancy is minimized. It is required that all WOCBP use two methods of contraception for the duration of the study (i.e. beginning before treatment with the 1 dose of study medication to 56 days after dosing). The two methods should include one barrier method (i.e. condom with spermicidal gel, intrauterine devices, cervical cap etc.) and one other method. The other method could include oral contraceptives or another barrier method (note, an Intra Uterine Device is considered one method).

Women who suspect that they have become or may have become pregnant despite using proper birth control methods, should not take Investigational Study Drug and subject should immediately contact Study Investigator.

5.6 Other Restrictions and Precautions (if applicable)

Not Applicable

5.7 Deviation from Inclusion/Exclusion Criteria

Any significant event that does not comply with the inclusion exclusion criteria, study conduct, or study procedures will be documented as a deviation. Deviations will be documented and reported through the clinical monitoring of the trial. Clinically significant deviations will be reported to the IRB/EC at the frequency required by your IRB/EC. There will be no protocol exceptions granted by the Sponsor for Inclusion/Exclusion criteria.

6 STUDY CONDUCT AND DESCRIPTION OF STUDY PROCEDURES

6.1 Study Materials

The following study materials will be provided at the study start:

- Investigator File/Regulatory Binder
- Pharmacy Binder
- Drug Accountability Logs
- Paper AE, Concomitant and Rescue Medication Logs (take home for subjects)
- Investigator Brochure
- Interactive Web-based Response System (IWRS)
- Electronic Case Report Form (eCRF) instructions
- Electronic Diary (eDiary): 1 device will be given to each randomized subject
- Instructions for the eDiary and training materials for subjects
- Laboratory Kits and Laboratory Manual
- Serious Adverse Event (SAE) forms
- Pregnancy Report Forms

All sites will use an Electronic Data Capture (EDC) tool to submit study data to Sponsors CRO. Electronic Case Report Forms (eCRFs) will be prepared for all data collection fields including Serious Adverse Events (SAE) Reporting. SAE data (including responses to queries) will be submitted to the CRO using eCRFs. Any assessments completed by the subject in the eDiary will be transferred from the device to vendor and/or sponsor. No additional source documents are required for the scales and assessments (See Section 6.3) which are completed by the subject in the eDiary.

Safety laboratory, plasma, serum and instructions for all specimens collected will be provided by a designated central laboratory.

6.2 Safety Assessments

6.2.1 Vital Signs and Physical Measurements (Height and Weight)

Body weight and height will be recorded at the scheduled visits as outlined in Table 1.

6.2.2 Electrocardiogram (ECG)

A standard 12-lead ECG will be recorded during the Screening Phase and at the scheduled visits as outlined in Table 1.

6.2.3 Physical Exam

Subjects will undergo a routine physical examination during the Screening Phase and at the scheduled visits as outlined in Table 1.

6.2.4 Laboratory Assessments

6.2.4.1 Safety Laboratory Testing

Blood and urine samples will be obtained as outlined in Table 1 for clinical laboratory evaluations. A central laboratory vendor will be utilized for this study and a laboratory manual will be provided to each site. **If possible, subjects should be fasting for a minimum of 8 hours prior to all blood draws.** However, if a subject is not fasting at a given visit, the blood draw should still be performed, and the non-fasting status should be documented.

Hematology: Hemoglobin, hematocrit, red blood cell count, white blood cell count (WBC) with differential, and platelets.

Blood chemistry/electrolyte: 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, CK. End of Treatment Visit – elevations in CK (>1.5xULN) may have further CK fractionation tests performed through the central lab.

Lipid panel: Cholesterol, LDL, HDL, triglycerides (Screening Only).

Estimated glomerular filtration rate: eGFR using the estimated MDRD formula will be calculated and reported by the central lab at each visit that clinical laboratory tests are collected as outlined in Table 1.

Urinalysis: pH, specific gravity, ketones, nitrites, urobilinogen, leukocyte esterase, protein, glucose and blood. If blood, protein or leukocytes are positive, reflex to microscopic examination.

Urine Drug Screen: For drugs of abuse.

For applicable subjects only:

Hepatitis screen: to confirm subjects meet Exclusion Criteria 5.3 2.f, Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (HBcAb) and HCV antibodies may be performed at the Investigator's discretion.

HIV screen: to confirm subjects meet Exclusion Criteria 5.3 2.a, HIV seropositivity may be performed at the Investigator's discretion.

FSH: to confirm female subjects other than those defined in section 5.5 are post menopausal, FSH may be performed at the Investigator's discretion.

In exceptional circumstances, subjects may be asked to return to the hospital for additional laboratory tests between visits. If blood or urine samples need to be collected for retesting, or in the case of restrictions e.g. due to COVID-19, the investigator may request approval from the Sponsor to use a local laboratory instead of the central labboratory.

6.2.4.2 Pregnancy Testing

Pregnancy tests will be conducted (serum or urine,), if appropriate prior to randomization, and as outlined in Table 1.

6.3 Efficacy Assessments

6.3.1 Pain

Subjects are given an eDiary to record their migraine pain score, on a 4-point numeric rating [no pain, mild pain, moderate pain, severe pain] at the time points indicated in Table 1.

6.3.2 Nausea, Phonophobia and Photophobia

The migraine associated symptoms of photophobia, phonophobia and nausea are measured on a two point scale (present or absent), using the eDiary, at the time points listed in Table 1. If a subject reports the presence of a symptom, the subject is then asked to rate the severity of the symptom on a four point scale (none, mild, moderate or serve). All assessments are done using the eDiary.

The subjects are also asked to identify their most bothersome symptom on the eDiary (nausea, phonophobia or photophobia) at the onset of the migraine to be treated. The most bothersome symptom must be identified before the subject takes study medication.

6.3.3 Rescue Medication

The subject's use of rescue medication is recorded by the subject in a paper diary.

6.3.4 Functional Disability

Impact of treatment on functional disability will be assessed using a single-question scale. Subjects rate the level of disability they perceive as a result of their migraine in performing normal actions. This is done in the eDiary, at the times indicated in Table 1, using a 4 point numeric rating scale: Normal Function, Mild Impairment, Severe Impairment, Required Bedrest.

6.4 Early Discontinuation from the Study

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator or sponsor, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study by BioShin Limited.
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness

All subjects who discontinue should comply with protocol specified End of Treatment procedures as outlined in Table 1. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

7 STUDY DRUG MANAGEMENT

7.1 Description of Study Drug

7.1.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as follows:

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

The rimegepant and the matching placebo appear identical visually, via touch, smell and taste.

7.1.2 Non-investigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

In this protocol, non-investigational product(s) is/are: Not applicable for this study.

7.1.3 Packaging, Shipment and Storage

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the sponsor. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor immediately.

7.2 Dose and Administration

7.2.1 Method of Assigning Subject Identification

At the time of enrollment, immediately after written informed consent is obtained and before performing any study-related procedures, each subject will be assigned a unique sequential 4-digit subject number beginning with 0001, 0002, 0003, etc. for identification throughout the study through an IWRS. This subject number must not be reused for any other subject in the study. The physician/coordinator must contact the IWRS to enroll each subject into a centralized database at the time of signing consent.

After completion of all screening evaluations all eligible subjects will be randomized in a 1:1 ratio to the rimegepant or placebo treatment groups. **The randomization will be stratified by the use of prophylactic**

migraine medications (yes or no) and country (China or Korea). It is important for you to correctly enter subjects who are using prophylactic migraine medication in the IWRS system. Once a patient is stratified in the IWRS, this cannot be changed and will be considered a deviation.

Randomization schedules will be generated and kept by the IWRS vendor in a secure network folder with access limited to only unblinded team members. Each subject who is qualified for treatment will be randomized via the IWRS randomization option. Subjects will maintain their subject number assigned at screening throughout the trial. The IWRS will provide the double-blind treatment assignments.

The randomization will trigger a bottle number for the randomized treatment type. The drug will be dispensed at the time of randomization.

7.2.2 Selection and Timing of Dose and Administration

Study medication (one 75 mg orally disintegrating tablet or matching placebo) will be packaged in a bottle. There are no dose adjustments in this study and subjects will receive one dose to treat one migraine headache of moderate or severe intensity within 45 days of randomization (Baseline Visit). Subjects will be dispensed the study medication at randomization (Baseline Visit) and will take one dose at the time of moderate or severe migraine headache onset ***ONLY after answering questions regarding their migraine symptoms in the eDiary*** device. The tablet should be placed under the tongue until fully dissolved then swallowed. Subjects should be instructed to use dry hands when handling the study medication.

7.2.3 Dose Modifications

There will be no dose adjustments in this study.

7.3 Blinding and Unblinding

Blinding is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual subject, in which knowledge of the investigational product is critical to the subject's management, the blind for that subject may be broken by the treating physician.

Before breaking the blind of an individual subject's treatment, the investigator should have determined that the information is necessary, (i.e., that it will alter the subject's immediate management). In many cases, particularly when the emergency is clearly not investigational product related, the problem may be properly managed by assuming that the subject is receiving active product without the need for unblinding.

In cases of accidental unblinding, contact the Medical Monitor and ensure every attempt to preserve the blind is made.

7.4 Treatment Compliance

Responsible study personnel will dispense the study drug. Accountability and compliance verification should be documented in the subject's study records.

Subjects have to be counseled on the importance of taking the study drug as directed when a migraine occurs and reaches moderate or severe intensity. If the subject does not have a migraine or take their study medication within 45 days of the Baseline Visit, they should return to the clinic for their End of Study Visit and return their study medication.

7.5 Destruction and Return of Study Drug

If the study drug (those supplied by the sponsor or sourced by the investigator) are to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for the disposal, procedures for proper disposal have been established according to the applicable regulations, guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused study drugs can only be destroyed after being inspected and reconciled by the responsible Biohaven Study monitor or the sponsor's designee unless this is against institutional policy.

All unused and/or partially used study drug may be destroyed on site providing the site has an applicable standard operating procedure on file.

8 ADVERSE EVENTS

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a subject or clinical investigation subject administered an investigational (medicinal) product 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 for example) symptom, or disease temporally associated with the use of the investigational product, whether or not considered related to the investigational product.

Adverse events can be spontaneously reported or elicited during an open-ended questioning, examination, or evaluation of a subject. In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.

Subjects should be instructed to notify the Investigator when a Serious Adverse Event occurs.

There are two types of adverse events, Serious Adverse Events (SAE) and Non-Serious Adverse Events (AEs).

8.1 SERIOUS ADVERSE EVENT

8.1.1 Definition of Serious Adverse Event (SAE)

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

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

Definition of Terms

Life threatening: An AE is life threatening if the subject was at immediate risk of death from the event as it occurred; i.e., it does not include a reaction that if it had occurred in a more severe form might have caused death. For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug induced hepatitis can be fatal.

Hospitalization: AEs requiring hospitalization should be considered SAEs. Hospitalization for elective surgery or routine clinical procedures that are not the result of AE (e.g., elective surgery for a pre-existing condition that has not worsened) need not be considered AEs or SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'non-serious' according to the usual criteria.

In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

The following hospitalizations are not considered SAEs in BHV clinical studies (but may be considered non-serious AEs):

1. A visit to the emergency room or other hospital department <24 hours that does not result in an admission (unless considered “important medical event” or event that is life threatening);

2. Elective surgery, planned prior to signing consent;

3. Admissions as per protocol for a planned medical/surgical procedure;

4. Routine health assessment requiring admission (i.e., routine colonoscopy);

5. Admission encountered for another life circumstance that carries no bearing on health and requires no medical intervention (i.e., lack of housing, care-giver respite, family circumstances).

Disability/incapacitating: An AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.

8.1.2 Collection and Reporting Serious Adverse Events

Following the subject’s written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specific procedures. All SAEs must be collected that occur during the screening period and throughout the course of the study up to and including the End of Treatment Visit. The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specific procedures.

All SAEs should be followed to resolution or stabilization.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

If the investigator believes that an SAE is not related to the study drug, but is potentially related to the conditions of the study (such as a withdrawal of previous therapy or a complication related to study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, overdose (see section 8.1.3), potential drug induced liver injury (see section 8.1.5) and pregnancies (see section 8.1.4) must be reported within 24 hours of the Investigator becoming aware of the event. For this study we will be capturing SAEs through electronic data capture (EDC) and on the SAE form.

The Investigator is responsible for reporting all SAEs and all Other Important Medical Events to the Pharmacovigilance CRO within 24 hours of learning of the event. The Pharmacovigilance CRO will then immediately notify the Biohaven Medical Monitor of the event. The Investigator is responsible for submitting all applicable events to the Independent Review Board (IRB) as per the IRB's reporting requirements. Additionally, the Investigator, or designated staff, is responsible for entering the SAE information in the Electronic Data Capture (EDC) system (i.e.: event term, start stop dates, causality, severity).

Any serious adverse event must be reported immediately or no later than 24 hours after awareness of the event to the Pharmacovigilance CRO. A written description of any serious adverse event, using the Pharmacovigilance CRO SAE report form, must be sent to Pharmacovigilance CRO **wilsafety@ppd.com** within 24 hours after awareness of the event.

If a form is unable to be submitted within 24 hours, the SAE may be reported by telephone via the Safety Hotline Number:

+1-800-201-8725

If only limited information is initially available, follow-up reports are required. If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours of the Investigator becoming aware of the updated information using the same procedure used for the transmission of the initial SAE and the same event term should be used.

The minimum information required for an initial SAE report is:

Sender of report (Site number, Investigator name)

Subject identification (subject number)

Protocol number

SAE term (if an SAE is being reported)

8.1.3 Overdose

An overdose is defined as the accidental or intentional administration of any dose of the product that is considered excessive and medically important as determined by the investigator. All occurrences of overdose (suspected or confirmed and irrespective of whether or not it involved rimegepant or placebo) must be communicated to Biohaven or a specified designee within 24 hours and be fully documented as an SAE. Details of any signs or symptoms and their management should be recorded including details of any antidote(s) administered.

8.1.4 Pregnancy

If following the baseline visit, it is subsequently discovered that a study subject, or the female partner of a male study subject, is pregnant or may have been pregnant at the time of the investigational product exposure, including during at least 6 half-lives after the product administration, the investigational product will be permanently discontinued in an appropriate manner (i.e., dose tapering if necessary for subject's safety). Protocol-required procedures for the study discontinued and the follow-up must be performed on the subject unless contraindicated by the pregnancy (i.e., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

Sites should instruct subjects to contact the Investigator immediately if they become pregnant during the course of the study. The Investigator must immediately notify the Biohaven Medical Monitor (or designee) of the event and complete and forward the Pregnancy Report Form to the Pharmacovigilance CRO immediately via telephone within 24 hours and in accordance with SAE reporting procedures as described in Section 8.1.2.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable offspring information must be reported on a Pregnancy Report Form.

Any pregnancy that occurs in a female partner of a male study subject should be reported to the sponsor. Information on this pregnancy will be collected on the Pregnancy Report Form, as appropriate.

8.1.5 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of the initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs as per Section 8.1.2.

Potential drug induced liver injury is defined as:

1. Aminotransferases (AT) (ALT or AST) elevation > 3 times the upper limit of normal (ULN)

AND

2. Total bilirubin (TBL) > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

AND

3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

If any potential DILI is identified and meets the criteria above, the Biohaven Medical Monitor (or designee) should immediately be contacted for further instructions on appropriate follow up requirements.

8.2 Non-serious Adverse Events

A ***non-serious adverse event*** is an AE not classified as serious.

8.2.1 Collection and Reporting of Non-Serious Adverse Events

The collection of non-serious AE information should begin at the Baseline visit. Non-serious AE information should also be collected from any observational period intended to establish a baseline status for a subject.

Non-serious adverse events should be followed until conclusion or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug or those that are present at the end of study treatment.

8.2.2 Laboratory Test Abnormalities

The following laboratory test abnormalities should be captured on the non-serious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

1. Any laboratory test result that is clinically significant or meets the definition of an SAE;

2. Any laboratory abnormality that required the subject to have the study drug discontinued or interrupted;

3. Any laboratory abnormality that required the subject to receive specific corrective therapy.

9 STATISTICS

9.1 General Procedures

Categorical variables are tabulated with counts and percentages. Continuous variables are summarized with univariate statistics (e.g., n, mean, standard error, median, minimum and maximum).

For the calculation of descriptive statistics of observed data, subjects must have an initial value (e.g. baseline value) to be evaluable for endpoints based on values and changes from the initial value over time.

Tabulations of the following endpoints present the number of unique subjects with an event: protocol deviations; interruptions of study therapy; non-study medications; adverse events; and laboratory abnormalities. Thus, for these endpoints, multiple occurrences of the same event are counted only once per subject.

For the assessments of most endpoints, if a subject uses rescue medication before the endpoint data have been fully collected then the subject will be considered a failure on that endpoint. Full details will be provided in the statistical analysis plan.

9.2 Sample Size

If roughly 85% of the 715 subjects randomized to each treatment arm have a migraine in the allotted time period, there will be approximately 600 treated subjects per group.

Based on data from studies BHV3000-301 and BHV3000-302, 600 treated subjects provides 95% power to detect a difference between rimegepant and placebo on the subject's self-reported most bothersome symptom. Also, 600 subjects provides 95% power to detect a difference in freedom from pain at 2 hours. Having at 95% power on each co-primary endpoint provides roughly 90% power to detect a difference on both endpoints jointly.

For additional details, please see 15.4 Appendix IV – Power Calculations.

9.3 Populations for Analysis

- Enrolled subjects: Subjects who sign an informed consent form and are assigned a subject identification number.

- Randomized subjects: Enrolled subjects who receive a randomization treatment assignment from the IWRS (rimegepant or placebo).

- Treated subjects: Enrolled subjects who take study therapy (rimegepant or placebo).

- Modified Intent to Treat (mITT) subjects: randomized subjects that take study therapy, have a migraine of moderate or severe intensity at the time of treatment, and provide at least one post-treatment, efficacy data point.

No separate per protocol analysis set is defined for this study. There will not be any per protocol analysis conducted for this study.

9.4 Statistical Methods

9.4.1 Primary Endpoint(s)

BHV-3000 (rimegepant) is tested for superiority to placebo, at an alpha=0.05 level, on both the co-primary endpoints of pain freedom at 2 hours post-dose and freedom the most bothersome symptom at 2 hours post-dose.

Both endpoints are evaluated using Cochran-Mantel Haenszel methodology to estimate the common risk difference, and are stratified by the use of prophylactic migraine medication (yes or no) and country (China or Korea). These tests are conducted using the mITT subjects, with missing data at two hours imputed to be failure (i.e., Non-Completers = Failure; NC=F). Subjects that use rescue medication prior to reporting their co-primary endpoints will be classified as failures. Sensitivity analyses are described in the Statistical Analysis Plan (SAP).

9.4.2 Secondary Endpoint(s)

If the primary endpoint tests are both significant, then the key secondary endpoints are evaluated using the Hochberg procedure, conducted at alpha=0.05.

Like the co-primary endpoints, all of the key secondary endpoints are all binary endpoints. Hence the key secondary endpoints will be analyzed in the same manner as the primary endpoint. In particular they will be analyzed using Cochran-Mantel methodology to estimate the common risk difference, and are stratified by the use of prophylactic migraine medication (yes or no) and country (China or Korea).

9.4.3 Control of multiplicity

As discussed above, the co-primary endpoints are both tested at alpha=0.05. No correction for multiplicity is needed, since both co-primary endpoints must be positive for the study to be positive. The secondary endpoints are protected by a gate-keeper procedure. If both of the co-primary endpoints are significant, only then will the key secondary endpoints be tested for significance. Within the family of key secondary endpoints, multiplicity is controlled using the Hochberg procedure.

9.4.4 Missing Data

As discussed above, missing data for the co-primary endpoints is handled using a composite variable strategy, with missing data imputed to be failure (NC=F). In addition, subjects taking rescue medications prior to reporting their co-primary endpoints will be classified as failure.

The first two key secondary endpoints, pain relief at 2 hours post-dose and the ability to function normally at 2 hours post-dose, are binary endpoints and identical in structure to the co-primary endpoints. Hence, these two key secondary endpoints will be handled with the same composite variable strategy as is applied to the coprimary endpoints.

The third key secondary endpoint, use of rescue medications through 24 hours post-dose will be handled in a similar manner, with NC=F. However, since the use of rescue medications is the endpoint of interest, this is not treated as an intercurrent event.

The fourth and fifth key secondary endpoints, sustained pain freedom from 2 to 24 hours post dose, and from 2 to 48 hours post-dose, are with handled with a similar composite variable strategy. Subjects that use rescue medications before reporting the last data for an endpoint, either at 24 or 48 hours, will be classified as failures. Since subjects will need to sleep over periods as long as 24 or 48 hours, the requirement that non-completers be classified as failures is relaxed slightly. For these variables, subjects with more than 1 missing data point, other than at the critical 2, 24 or 48 hour data points, are classified as failures. For example, for sustained pain freedom from 2 to 24 hours, the subjects are expected to provide data at 2, 3, 4, 6, 8, and 24 hours. The data at 2 and 24 hour time points must be present or the subject is classified as a failure. However, any single data point may be missing at 3, 4, 6 or 8 hours without penalty. For sustained pain freedom from 2 to 48 hours, the data at 2, 24, and 48 hours are required to be present.

9.4.5 Analysis of Safety

The investigators determine the intensity of AEs and the relationship of AEs to study therapy. The investigators' terms are coded and grouped by system organ class using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) available. AEs are presented by system organ class and preferred term, ordered by the overall frequency of events. If a subject had an adverse event with different intensities over time, then only the greatest intensity is reported.

Treatment Emergent AEs are tabulated in all treated subjects. SAEs occurring in subjects enrolled but not treated are listed. Deaths are listed for enrolled subjects without regard to onset.

The frequencies of the following safety events are summarized by treatment regimen, and overall, for treated subjects: SAEs; all AEs, non-serious AEs, AEs by intensity; and AEs by relatedness.

Graphical and tabular displays of liver function test results are provided.

Further safety analyses will be described in the statistical analysis plan.

9.4.6 Demographic and Baseline Characteristics

Tabulations of demographic and baseline characteristics are made for: subjects randomized but not treated; subjects randomized and treated; and overall. A separate set of tabulations are made for subjects enrolled but not randomized.

9.5 Interim Analysis

There is a final analysis after the last subject has his/her last visit. No interim analyses are anticipated.

10 ETHICS AND RESPONSIBILITIES

10.1 Good Clinical Practice

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), Good Laboratory Practice (GLP) and all applicable regulations, including the Federal Food, Drug and Cosmetic Act, U.S. applicable Code of Federal Regulations (title 21), any IEC requirements relative to clinical studies. The study will also be conducted in compliance with the recommendations laid down in the most recent version of the Declaration of Helsinki, with the exception that registration of such Phase 1 trials in a publicly accessible database is not mandatory.

This study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All serious breaches must be reported to BioShin Limited (or designee) immediately. A Serious breach is a breach of the conditions and principles of GCP in connection with the study or protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s).

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

10.2 Data and Safety Monitoring Committee

This study will not make use of a Data and Safety Monitoring Committee (DSMC). The study medication rimegepant has been found to be well tolerated in previous clinical studies. Safety will be closely monitored via the sites and procedures for unblinding in cases of emergency will be followed.

10.3 Institutional Review Board/Independent Ethics Committee

The Investigators agree to provide the IEC with all appropriate documents, including a copy of the protocol/amendments, ICFs, advertising text (if any), Investigator's brochure and any other written information provided to study subjects. The trial will not begin until the Investigators have obtained the IEC favorable written approvals for the above-mentioned study documents. A properly executed written ICF shall be read, signed, and dated by each subject prior to entering the trial or prior to performing any study procedure. The original signed and dated ICF will be kept at the Investigator site and a copy will be given to the subject.

In the event that the protocol is amended, the revised protocol must be approved by the IEC prior to its implementation, unless the changes involve only logistical or administrative aspects of the trial. If a revised ICF is introduced during the study, each subject's further consent must be

obtained. The new version of the ICF must be approved by the IEC, prior to subsequently obtaining each subject's consent.

The Principal investigator and the Sponsor's representative must sign the protocol and its amendments (if any) before initiating the study.

It is the Sponsor's responsibility to submit the protocol and its amendments (if any), and the ICFs to regulatory authorities when necessary.

10.4 Informed Consent

Investigators must ensure that subjects, or, in those situations where consent cannot be given by subjects, their legally acceptable representatives, are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

Biohaven (or designee) will provide the investigator with an appropriate (i.e., Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Before the potential subject has undergone any study-related screening procedures, the nature of the study and the potential risks associated with it will be explained to the subject, and the subject will be given an opportunity to ask questions to his or her satisfaction. After the questions are answered, but before proceeding further, the subject must read and sign a written informed consent form. This signed informed consent form will be reviewed and approved by an IRB/IEC, revisions to the protocol and informed consent form will be reviewed and approved by the IRB/IEC, a copy retained in the Study Master File, and the date and time the subject signed the form will be entered in his or her CRF. The subject will be provided with a copy of his or her signed and dated informed consent form.

If informed consent is initially given by a subject's legal guardian or legally acceptable representative, and the subject subsequently becomes capable of making and communicating their informed consent during the study, then the consent must additionally be obtained from the subject.

The informed consent form must also include a statement that Biohaven and its representatives and regulatory authorities may have direct access to subject records.

The rights, safety, and well-being of study subjects are the most important considerations and should prevail over interests of science and society.

10.5 Case Report Forms

An Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation of each study subject. Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

Electronic CRFs will be prepared for all data collections fields when EDC is being used.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The Investigator must retain a copy of the CRFs including records of changes and corrections. If EDC is being used, signatures will be obtained electronically and a copy of the electronic CRFs will be provided (or the data from the CRFs) for future reference.

10.6 Records Management and Retention

In accordance with the principles of GCP and GLP, the study may be inspected by regulatory authorities, the Sponsor and CRO. The Sponsor is entitled to access information about the status of the study and to review the original documents of the study.

The Investigator must retain all study records and source documents for the maximum required by the applicable regulations and guidelines, or institution procedures or for the period of time specified by the sponsor, whichever is longer. The Investigator must contact the Sponsor prior to destroying any records associated with this study.

Biohaven will notify the Investigators when the study files for this study are no longer needed.

If the Investigator withdraws from the study (i.e., retirement, relocation), the records shall be transferred to a mutually agreed upon designee. Notice of such transfer will be given in writing to Biohaven.

It is the responsibility of the Investigator to ensure that the current disposition record of investigational product (those supplied by the sponsor) is maintained at each study site where the study drug is inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

1. amount of study drug received and placed in storage area
2. label ID number or batch number or Kit number as specified for the protocol
3. amount dispensed to and returned from each subject
4. amount transferred to another area or site for dispensing or storage if applicable
5. amount of drug lost or wasted
6. amount destroyed at the site if applicable
7. amount returned to sponsor, if applicable
8. retain sampled for bioavailability/bioequivalence, if applicable
9. record of dates and initials of personnel responsible for IM dispensing and accountability

10.7 Source Documentation

An Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent for all subjects on study.

If source documents are created to support the collection of study information, this must be retained with the other pertinent medical record for each subject for verification of data points. Unless otherwise instructed by the Sponsor or designee to enter data directly on the eCRF.

10.8 Study Files and Record Retention

The CRO will maintain adequate study records after completion or termination of study. After that period, the Sponsor will be contacted to determine whether the study records will be forwarded to the Sponsor, destroyed or kept at CRO or at another facility for a longer period of time at the Sponsor's expense.

11 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Biohaven. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the IRB/IEC is notified within 5 days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the investigator must await approval before implementing the changes. Biohaven will submit protocol amendments to the appropriate regulatory authorities for approval.

If in the judgment of the IRB/IEC, the investigator, and/or Biohaven, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the subject and/or has an impact on the subject's involvement as a study participant, the currently approved written informed consent form will require similar modification. In such cases, informed consent will be renewed for subjects enrolled in the study before continued participation.

12 STUDY REPORT AND PUBLICATIONS

Biohaven is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements.

The publication policy of Biohaven is discussed in the investigator's Clinical Research Agreement.

13 STUDY DISCONTINUATION

Both Biohaven and the Principal Investigator reserve the right to terminate the study at the investigator’s site at any time. Should this be necessary, Biohaven or a specified designee will inform the appropriate regulatory authorities of the termination of the study if needed and the reasons for its termination, and the Principal Investigator will inform the IRB/IEC of the same. In terminating the study, Biohaven and the Principal Investigator will assure that adequate consideration is given to the protection of the subjects’ interests.

14 CONFIDENTIALITY

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from Biohaven. However, authorized regulatory officials, IRB/IEC personnel, Biohaven and its authorized representatives are allowed full access to the records.

Identification of subjects and eCRFs shall be by initials, subject numbers only. Only if required by law, the subject's full name may be made known to an authorized regulatory agency or other authorized official.

15 APPENDICES

15.1 APPENDIX I – Names of Study Personnel

Sponsor:	BioShin Limited Refer to study reference manual for contact information
Sponsor Medical Monitor: CRO Medical Monitor:	PPD MD PPD PPD MD PPD
Clinical Research Organizations:	Tigermed Refer to study reference manual for contact information
Central Laboratory:	Covance Lab Refer to manual for contact information
eDiary	ERT Refer to manual for contact information
Pharmacovigilance Vendor	PPD Refer to manual for contact information

15.2 APPENDIX II – Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI: Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975, 35th WMA General Assembly, Venice, Italy, October 1983, 41st WMA General Assembly, Hong Kong, September 1989, 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my subject will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the subject's interest when providing medical care which might have the effect of weakening the physical and mental condition of the subject."

Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects.

In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best-proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

Research investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

Appropriate caution must be exercised in the conduct of research, which may affect the environment, and the welfare of animals used for research must be respected.

The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the Sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any SAEs. The researcher should also submit to the committee, for review, information regarding funding, Sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a subject of the research, even though the subject has given consent.

Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

The subjects must be volunteers and informed participants in the research project.

The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the subject's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the subjects who are research subjects.

The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

At the conclusion of the study, every subject entered into the study should be assured of access to the best-proven prophylactic, diagnostic and therapeutic methods identified by the study.

The physician should fully inform the subject which aspects of the care are related to the research. The refusal of a subject to participate in a study must never interfere with the subject-physician relationship.

In the treatment of a subject, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the subject, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

15.3 APPENDIX III – Strong CYP3A4 Inhibitors and Inducers (Not all inclusive)

The following medications and medication combinations are some of the strong inhibitors of CYP3A4. This list should not be considered all-inclusive. As described in the study protocol, concomitant use of strong CYP3A inhibitors is prohibited. Individual drug labels should be reviewed for specific information on propensity to inhibit CYP3A4 for a specific compound.

Strong CYP3A inhibitors
Boceprevir, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir and ritonavir, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole, clarithromycin, nefazodone, nelfinavir

The following medications and supplements are some of the strong inducers of CYP3A4. The list should not be considered all-inclusive. As described in the study protocol, concomitant use of strong CYP3A inducers is prohibited. Individual product labels should be reviewed for specific information on propensity to induce CYP3A4 for a specific compound.

Strong CYP3A inducers
Carbamazepine, phenytoin, rifampin, St. John's Wort

Resources:

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-2

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-3

Hachad H, Ragueneau-Majlessi I, Levy RH. A useful tool for drug interaction evaluation: the University of Washington Metabolism and Transport Drug Interaction Database. Hum Genomics. 2010 Oct;5(1):61-72

University of Washington Metabolism and Transport Drug Interaction Database accessible at https://www.druginteractioninfo.org/

15.4 APPENDIX IV – Power Calculations

Executive Summary

To date, the sponsor has conducted three pivotal trials for the acute treatment of migraine with rimegepant [20, 21, 22]. All three studies were statistically significant, and all were conducted with roughly 600 evaluable subjects per treatment arm. The sponsor is proposing conducing a fourth acute study, BHV3000-310 using 600 evaluable subjects per treatment arm.

The data from 3 previous studies for the treatment of migraine are summarized. The previous data are used to generate a range of plausible values for the placebo rate and treatment effect that might be seen in the BHV3000-310 study. These values are used as the basis for power calculations which show that a sample size of 600 evaluable subjects per arm provides adequate power over most of the plausible values.

Background

Three previous studies examined the efficacy of rimegepant in the acute treatment of migraine. Studies BHV3000-301 and BHV3000-302 were conducted using a standard, immediate release tablet. Study BHV3000-303 was conducted using an orally disintegrating tablet (ODT).

All three of the previous studies had close to 600 evaluable subjects per arm. Studies BHV3000-301 and BHV3000-302 were conducted with roughly 540 evaluable subjects per arm. Study BHV3000-303 was conducted with roughly 680 subjects per arm.

All three of the previous studies had significant results for both of their coprimary endpoints of freedom from pain at two hours post dose, and freedom from Most Bothersome Symptom (MBS) at 2 hours post dose. The response rates for these 3 studies, for pain freedom and MBS freedom, are presented in Table 1 and 2, respectively. The tables also show number of responders, sample size per arm and p-values.

From Table 1, it can be seen that the placebo response rates for pain freedom at two hours post-dose range from 10.9% to 14.2%. The therapeutic gains (difference between rimegepant and placebo response rates) range from 4.9% to 10.4%. The p-values for all three studies ranged from <0.0001 to 0.0298.

Table 1: Response Rates and Therapeutic Gains for Pain Freedom at 2 Hours Post-Dose

	BHV3000-301	BHV3000-302	BHV3000-303
Rimegepant Group	19.2% (104/543)	19.6% (105/537)	21.2% (142/669)
Placebo Group	14.2% (77/541)	12.0% (64/535)	10.9% (74/682)
Therapeutic Gain	4.9%	7.6%	10.4%
p-value	0.0298	0.0006	< 0.0001

From Table 2, it can be seen that the placebo response rates for MBS freedom at two hours post-dose range from 25.2% to 27.7%. The therapeutic gains range from 8.3% to 12.4%. The p-values ranged from < 0.0001 to 0.0016.

Table 2: Response Rates and Therapeutic Gains for MBS Freedom at 2 Hours Post-Dose			
	BHV3000-301	BHV3000-302	BHV3000-303
Rimegepant Group	36.6% (199/543)	37.6% (202/537)	35.1% (235/669)
Placebo Group	27.7% (150/541)	25.2% (135/535)	26.8% (183/682)
Therapeutic Gain	8.9%	12.4%	8.3%
p-value	0.0016	<0.0001	0.0009

Outline of Power Calculations

Based on the 3 studies described above, a range of plausible response rates and therapeutic gains were chosen as the basis for a series of power calculations. These values are shown in Table 3. It can be seen from the table that the ranges of placebo rates and therapeutic gains selected for the power analyses roughly span the ranges observed in the 3 previous studies.

Table 3: Response Rates and Therapeutic Gains Selected for Power Analyses		
	Pain Freedom	MBS Freedom
Placebo Rates	11%, 12%, 13%, 14%	25%, 26%, 27%, 28%
Therapeutic Gains	5%, 6%, 7%, 8%, 9%, 10%	8%, 9%, 10%, 11%, 12%, 13%

To conduct the power analyses all values of the placebo rates were paired with all values of the therapeutic gains. For example, for pain freedom, there are 4 values for the placebo rates and 6 values for the therapeutic gains, so power analyses were conducted for 4 x 6 = 24 pairs of values. Similarly, for MBS freedom, power analyses were conducted at 4 x 6 = 24 pairs of values.

The power calculations were conducted using the Pearson Chi-Square test, a two-sided alpha of 0.05, and all of the pairs of placebo rates and therapeutic gains described above. The target sample size for BHV3000-310 is 600 evaluable subjects per treatment arm. Hence, all of the calculations were conducted at that sample size. The calculations were executed using SAS PROC POWER, with the TWOSAMPLE FREQ and TEST=pchi options.

Power Calculations for Pain Freedom

The results of the power calculations for pain freedom presented in Table 4. These results have been sorted in descending order by the calculated power. From the table, it can be seen that the power for testing pain freedom at 2 hours post dose is higher than 95% as long as the therapeutic gain is at least 8%. The power is greater than 89% as long as the therapeutic gain is at least 7%.

The lowest power shown in the table is 64%, which corresponds to a true placebo rate in the population of interest of 14% and a therapeutic gain of 5% in that population. However, if the data observed in study 3000-310 were to have these rates, then the difference between placebo 14% success (84/600 subjects) and rimegepant 19% success (114/600 subjects) would be statistically significant. A simple chi-square test would have chi-square=5.444, p=0.0196.

Table 4: Power for Pain Freedom		
Placebo Rate	Therapeutic Gain	Power
11%	10%	99.7%
12%	10%	99.6%
13%	10%	99.5%
14%	10%	99.3%
11%	9%	99.1%
12%	9%	98.8%
13%	9%	98.5%
14%	9%	98.1%
11%	8%	97.3%
12%	8%	96.6%
13%	8%	95.9%
14%	8%	95.1%
11%	7%	93.2%
12%	7%	91.9%
13%	7%	90.5%
14%	7%	89.2%
11%	6%	85.1%
12%	6%	83.0%
13%	6%	81.0%
14%	6%	79.1%
11%	5%	71.8%
12%	5%	69.2%
13%	5%	66.8%
14%	5%	64.6%

Power Calculations for MBS Freedom

The results of the power calculations for MBS freedom are presented in Table 5. These results have been sorted in descending order by the calculated power.

Table 5 shows that the power for testing MBS freedom at 2 hours post-dose is greater than 95% as long as the therapeutic gain is at least 10%, and the power is greater than 90% when the therapeutic gain is at least 9%. The power is greater than 80% for all scenarios considered.

Table 5: Power for MBS Freedom		
Placebo Rate	Therapeutic Gain	Power
25%	13%	99.8%
26%	13%	99.8%
27%	13%	99.8%
28%	13%	99.7%
25%	12%	99.5%
26%	12%	99.4%
27%	12%	99.3%
28%	12%	99.3%
25%	11%	98.6%
26%	11%	98.4%
27%	11%	98.3%
28%	11%	98.2%
25%	10%	96.6%
26%	10%	96.4%
27%	10%	96.1%
28%	10%	95.8%
25%	9%	92.9%
26%	9%	92.4%
27%	9%	92.0%
28%	9%	91.5%
25%	8%	86.4%
26%	8%	85.7%
27%	8%	85.1%
28%	8%	84.5%

Power for Pain Freedom and MBS Jointly

If we assume the two coprimary endpoints are findependent, then the power for success on both endpoints is equal to the product of the power for pain freedom multiplied by the power for MBS freedom.

If both primary endpoints have a power of at least 0.95, then the power for success on both endpoints would be 0.95 x 0.95 = 0.9025. Hence, study BHV3000-310 will have 90% power when the therapeutic gain for pain freedom is 8% or more, and the therapeutic gain for MBS freedom is 10% or more.

If both primary endpoints have a power of at least 0.90, then the power for success on both endpoints would be 0.90 x 0.90 = 0.81. Hence, study BHV3000-310 will have 80% power when the therapeutic gain for pain freedom is 7% or more, and the therapeutic gain for MBS freedom is 9% or more.

Conclusions

The sponsor plans to conduct study BHV3000-310 with 600 evaluable subjects per arm.

The choice of 600 subjects per arm is supported by 3 previous studies that used rimegepant for the treatment of migraine. All 3 studies produced significant results with sample sizes close to 600 subjects per arm. BHV3000-301 and BHV3000-302 were conducted with roughly 540 evaluable subjects per arm. Study BHV3000-303 was conducted with roughly 680 subjects per arm. All three of these studies achieved statistical significance.

The choice of 600 subjects per arm is also supported by the power calculations presented in this memo. Assuming the placebo rate in study BHV3000-310 is no higher than the maximum rate observed in the three previous studies, then BHV3000-310 will have more than 90% power to show that both primary endpoints are significant when the therapeutic gain for pain freedom is 8% or more, and the therapeutic gain for MBS freedom is 10% or more. BHV3000-310 will have at least 80% power when the therapeutic gain for pain freedom is 7% or more, and the therapeutic gain for MBS freedom is 9% or more.

16 REFERENCES

1. IHS, *International Classificaton of Headache Disorders, 3rd edition beta version*. 2016.
2. Yu, S., et al., *The prevalence and burden of primary headaches in China: a population-based door-to-door survey.* Headache, 2012. **52**(4): p. 582-91.
3. BHV3000-110-CSR, *A Phase 1, Study to Evaluate the Bioequivalence Between Two Tablet Formulations of Rimegepant and to Evaluate the Relative Bioavailability of a Sublingual Orally Disintegrating Tablet of Rimegepant in Healthy Adult Subjects Under Fasting Conditions. Biohaven Pharmaceuticals, Inc; 2018.*
4. BHV3000-113-CSR, *A Phase 1 Study to Evaluate the Bioequivalence Between Two Tablet Formulations of Rimegepant and to Evaluate the Food-effect on an Orally Dissolving Tablet of Rimegepant in Healthy Adult Subjects. Biohaven Pharmaceuticals, Inc; 2019.*
5. CN170001-CSR, *Placebo-controlled, randomized, single and multiple-dose study to evaluate the safety, tolerability, and pharmacokinetics of BMS-927711 in healthy subjects. Bristol-Myers Squibb Pharmaceutical Research Institute; 2012.*
6. BHV3000-106-CSR, *A Phase 1, Open-label, Single-dose, Parallel-group Study to Evaluate the Effects of Renal Impairment on the Pharmacokinetics of Rimegepant. Biohaven Pharmaceuticals, Inc; 2018.*
7. BHV3000-107-CSR, *A Phase 1, Open-label, Single-dose, Parallel-group Study to Evaluate the Effects of Hepatic Impairment on the Pharmacokinetics of Rimegepant. Biohaven Pharmaceuticals, Inc; 2018.*
8. BHV3000-108-CSR, *A Phase 1, Open-label, Parallel-group, Single-dose Study to Compare the Pharmacokinetics of Rimegepant in Non-elderly versus Elderly Male and Female Subjects. Biohaven Pharmaceuticals, Inc; 2018.*
9. BHV3000-103-CSR, *A Phase 1, Open-label, One-arm, Fixed-sequence Study to Evaluate the Effects of Multiple-dose Administration of Itraconazole on the Single-dose Pharmacokinetics of Rimegepant in Healthy Adult Subjects. Biohaven Pharmaceuticals, Inc 2018.*
10. BHV3000-105-CSR, *A Phase 1, Open-label, One-arm, Fixed-sequence Study to Evaluate the Effects of Multiple-dose Administration of Fluconazole on the Single-dose Pharmacokinetics of Rimegepant in Healthy Adult Subjects. Biohaven Pharmaceuticals, Inc 2018.*
11. BHV3000-104-CSR, *A Phase 1, Open-label, One-arm, Fixed-sequence Study to Evaluate the Effects of Multiple-dose Administration of Rifampin on the Single-dose Pharmacokinetics of Rimegepant in Healthy Adult Subjects. Biohaven Pharmaceuticals, Inc; 2018.*
12. BHV3000-114-CSR, *A Phase 1 Randomized, Partially-blind, Placebo-controlled Study to Evaluate the Effects of Rimegepant and Concomitant Sumatriptan on Blood Pressure in Healthy Adult Subjects. Biohaven Pharmaceuticals, Inc; 2019.*
13. CN170007, *DDI with Midazolam (CYP3A4 substrate) to study the changes of midazoloam pharmacokinetics with or without BMS-92771*. Bristol-Myers Squibb Company.
14. CN170002, *Effect of BMS-927711 on the Pharmacokinetics of a Combined Oral Contraceptive Containing Ethinyl Estradiol and Norgestimate in Healthy Female Subjects*. 2012, Bristol-Myers Squibb Company.
15. BHV3000-109-CSR, *A Partially Double-blind, Randomized, Crossover Study to Assess the Effects of Rimegepant on QTc Interval Using a Therapeutic Dose As Well As a Supratherapeutic Dose Compared to Placebo and Moxifloxacin in Healthy Subjects: A Thorough QTc Study. 2019, Biohaven Pharmaceuticals, Inc.*
16. CN170004, *Phase 1 open-label, randomized single sequence study with two dose groups to compare the pharmacokinetics of BMS-927711 in migraine subjects during an acute migraine attack and during nonmigraine period*. 2012, Bristol-Myers Squibb Company.
17. CN170003, *A Phase 2b, adaptive, double-blind, randomized, multi-center outpatient, dose-ranging trial to evaluate the efficacy and safety of BHV-92771 for the acute treatment of moderate or severe migraine.* Bristol-Myers Squibb Company.

18. Marcus, R., et al., *BMS-927711 for the acute treatment of migraine: a double-blind, randomized, placebo controlled, dose-ranging trial.* Cephalalgia, 2014. **34**(2): p. 114-25.
19. Hougaard, A. and P. Tfelt-Hansen, *Review of dose-response curves for acute antimigraine drugs: triptans, 5-HT1F agonists and CGRP antagonists.* Expert Opin Drug Metab Toxicol, 2015. **11**(9): p. 1409-18.
20. BHV3000-301-CSR, *A Phase 3, Double-blind, Randomized, Placebo-controlled, Safety and Efficacy Trial of BHV-3000 (rimegepant) for the Acute Treatment of Migraine. Biohaven Pharmaceuticals, Inc; 2019.*
21. BHV3000-302-CSR, *A Phase 3, Double-blind, Randomized, Placebo-controlled, Safety and Efficacy Trial of BHV-3000 (rimegepant) for the Acute Treatment of Migraine. Biohaven Pharmaceuticals, Inc; 2019.*
22. BHV3000-303-CSR, *A Phase 3, Double-blind, Randomized, Placebo-controlled, Safety and Efficacy Trial of BHV-3000 (rimegepant) Orally Disintegrating Tablet (ODT) for the Acute Treatment of Migraine. Biohaven Pharmaceuticals, Inc; 2019.*
23. Vos, T., et al., *Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010.* Lancet, 2012. **380**(9859): p. 2163-96.
24. Liu, R., et al., *Health-care utilization for primary headache disorders in China: a population-based door-to-door survey.* J Headache Pain, 2013. **14**: p. 47.
25. Buse, D.C., M.F. Rupnow, and R.B. Lipton, *Assessing and managing all aspects of migraine: migraine attacks, migraine-related functional impairment, common comorbidities, and quality of life.* Mayo Clin Proc, 2009. **84**(5): p. 422-35.
26. Luo, N., et al., *A satisfaction survey of current medicines used for migraine therapy in China: is Chinese patent medicine effective compared with Western medicine for the acute treatment of migraine?* Pain Med, 2014. **15**(2): p. 320-8.
27. APA, *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: DSM-5 5th Edition*. 5th ed, ed. A.P. Association. 2013: American Psychiatric Publishing.