DRUG:	BHV-3000 (rimegepant)
STUDY NUMBER(S):	BHV3000-201
PROTOCOL(S) TITLE:	BHV3000-201: A Multicenter, Open Label Long-Term Safety Study of BHV-3000 in the Acute Treatment of Migraine
IND NUMBER:	109886
SPONSOR:	Biohaven Pharmaceutical Holding Company Limited
ORIGINAL PROTOCOL DATE:	19 May 2017
VERSION NUMBER:	V05
VERSION DATE:	22 June 2018

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: A Multicenter, Open Label, Long-Term Safety Study of BHV-3000 in the Acute Treatment of Migraine

Study No: BHV3000-201

Original Protocol Date: 19 May 2017

Protocol Version No: V05

Protocol Version Date: 22 June 2018

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.

Name and Title	Signature Approval	Date
PPD		

SUMMARY OF CHANGES

Change	Section(s) Affected	Summary
1. Add group of subjects with history of 4-14 moderate to severe migraines/month.	Synopsis, Target Population;, Synopsis, Study Design; Section 1.4.1 Study Design Rationale; Section 4.1 Study Design and Duration; Section 4.3.2 Long Term Treatment Phase; Section 4.3.3 End of Treatment; Section 7.2.2 Selection and Timing of Dose and Administration	Add new group of subjects with a history of 4-14 moderate to severe migraines/month who will dose every other day for 12 weeks. Subjects in this group can take a tablet of rimegepant on non-dosing days to treat a migraine of mild to severe intensity.
2. Clarify the number of subjects to be screened and assigned rimegepant.	Synopsis, Number of Subjects; Section 4.3.1 Screening visit / Observation Phase; Section 5, Population	Clarified the targeted number of subjects to be screened and assigned treatment.
3. Added study schema for 4-14 moderate to severe migraines/month group	Study Schematic	Added a separate schematic for 12 weeks of treatment for subjects in the 4-14 moderate to severe migraines/month group.
4. Clarify Table 1, Schedule of assessments for separate patient groups	Schedule of Assessments	Added a new schedule of assessments for subjects in the 4-14 moderate to severe migraines/month, every other day dosing group.
5. Clarify prophylactic migraine medication	Section 5.2 Inclusion Criteria, Inclusion criterion 2f; Section 5.5 Standard of Care and	Clarified that prophylactic migraine medication regimen should not change during the course of the study.

	Prophylactic Migraine Medication	
6. Added exclusion criteria	Section 5.3 Exclusion Criteria: Exclusions l and m	Added exclusion of BMI $\geq$ 30 kg/m^2 and exclusion of history of gallstones or cholecystectomy
7. Modified exclusion criterion	Section 5.3 Exclusion Criteria: Exclusion i	Modified HbA1c to exclude those with HbA1c $\geq$ 6.5%.
8. Modified prohibited medications	Section 5.4, Prohibited Concomitant Medications	Further clarified that Depakene and valproate are both prohibited medications. Added new prohibited medication of Lamictal (lamotrigine)
9. Clarified prophylactic and standard of care migraine medications	Section 5.5, Prophylactic and Standard of Care Medications	Clarified that if a patient takes a tablet of study drug and experiences a migraine later that day, after dosing with study drug for the day, the patient should take their standard of care migraine medication as described in this section of the protocol. Patients are not allowed to take more than one tablet of study medication per calendar day.
10. Clarified discontinuation rule for specific S-STS scores	Section 6.5 Early Discontinuation From the Study	Added criterion for early termination from study due to scores on the Sheehan-Suicidality Tracking Scale per Section 6.2.5
11. Added definitions for terms mild,	Section 8.1.1, Definitions for Serious Adverse Events	Added definition of terms for mild, moderate and severe adverse events.

moderate and severe		
12. Updated sample size calculations	Section 9.2, Sample Size	Updated sample size of the subpopulation and corresponding sample size calculations.
13. Included references to Table 2	Various	Added references to Table 2, when discussion study procedures, etc.

BHV3000-201
BHV3000-201: A Multicenter, Open Label, Long-Term Safety Study of BHV-3000 in in 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 Biohaven Pharmaceutical Holding Company 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 Biohaven Pharmaceutical Holding Company 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 the regulations stated in the Federal Code of Regulations for 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 Biohaven Pharmaceutical Holding Company Limited or specified designees. I will discuss the material with them to ensure that they are fully informed about BHV-3000 and the study.

Principal Investigator Name (printed) Signature

_____ _____

Date Site Number

STUDY SUMMARY (SYNOPSIS)

Title: A Multicenter, Open Label, Long-Term Safety Study of BHV-3000 in 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 was demonstrated in a 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 [1].

This study is being conducted to further characterize the safety and tolerability of rimegepant during longer term treatment of patients with migraine.

Target Population: The study will recruit male and female patients, 18 years of age or older with at least a one-year history of migraine (with or without aura) consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd edition, beta version [2]. Patients must have migraine onset prior to age 50, migraine attacks that last 4-72 hours (if not treated) and have had 2-14 migraine attacks of moderate to severe intensity per month within the 3 months prior to the screening visit. A separate group of patients with a history of 4-14 moderate to severe migraines/month during the 3 months prior to the screening visit, will be enrolled and will dose with one tablet of study drug every other day for 12 weeks. After a 30-day observation period of standard of care, up to approximately 2000 eligible patients will be assigned to receive rimegepant. Patients who have participated in BHV3000-301, BHV3000-302 or BHV3000-303 (or another clinical trial with rimegepant) may be considered for participation in this long term safety study if all eligibility criteria are met, however participation in this study is not guaranteed. Enrollment into this study will initially be open to patients with 2-8 moderate to severe migraine attacks per month (primarily the patients from BHV-3000-301 and BHV-3000-302) for approximately three months. After approximately three months, study enrollment will open for patients with a history of 9-14 migraine attacks of moderate to severe intensity per month within the 3 months prior to the screening visit. Lastly, study enrollment will open for subjects in the every other day dosing group who have a history of 4-14 moderate to severe migraines/month during the 3 months prior to the screening visit.

Number of Subjects: Approximately 2800 patients will be screened to assign up to approximately 2000 patients to rimegepant.

Of the 2000 patients assigned to rimegepant, up to approximately:

- 1200 will have a history of 2-8 moderate to severe migraine attacks per month,
- 600 will have a history of 9-14 moderate to severe migraine attacks per month, and
- 200 will have a history of 4-14 moderate to severe migraine attacks per month in the every other day dosing group.

Objectives: **Primary Objective:** To evaluate the safety and tolerability of rimegepant.

Secondary Objectives:

- To evaluate the frequency of ALT or AST > 3x ULN with concurrent elevations in bilirubin > 2x ULN in subjects treated with rimegepant.
- To evaluate the frequency and severity of hepatic-related adverse events and the frequency of hepatic-related treatment discontinuations.

Exploratory Objectives:

- To evaluate the frequency of subjects with elevated liver function tests (AST, ALT or total bilirubin).
- To evaluate the frequency of subjects with ALT or AST elevations > 3x ULN in temporal association with nausea, vomiting, anorexia, abdominal pain or fatigue.
- To explore the contributions of gender, age and exposure to rimegepant to abnormalities in AST, ALT, or bilirubin.
- To investigate the time on treatment and cumulative exposure associated with: (1) hepatic related SAEs and treatment discontinuations; (2) elevations in ALT or AST > 3x ULN with concurrent elevations in bilirubin > 2x ULN.

- To evaluate the number of headache days and severity of migraine attacks while subjects are treated with rimegepant relative to the observational period.
- To evaluate the effect of rimegepant treatment compared to baseline on the 20-Item Migraine-Specific Quality of Life Questionnaire v 2.1 (MSQoL).
- To evaluate the effect of rimegepant treatment compared to baseline on the Migraine Preference of Medication (PoM).
- To examine the scores on the Sheehan Suicidality Tracking Scale.
- To evaluate the effect of rimegepant treatment compared to baseline on the Satisfaction with Medication survey.
- To evaluate the effect of rimegepant treatment compared to baseline on the Migraine Disability Assessment (MIDAS)
- To evaluate the effect of rimegepant treatment compared to baseline on the Clinical Global Impression – change (CGI-c) scale.

Study Design:

This is a multicenter, open-label study to assess the safety and tolerability of long term use of rimegepant, taken up to one tablet per calendar day, in patients with migraine.

The Screening phase includes a screening visit and a 30 day Observation Period. For subjects to be eligible for the study, they must have 2-14 migraine attacks of moderate to severe intensity per month in the 3 months prior to the Screening Visit. Patients enrolled in the every other day dosing group must have had 4-14 migraine attacks of moderate to severe intensity per month during the 3 months prior to the screening visit. Enrollment into this study will initially be open to patients with 2-8 moderate to severe migraine attacks per month (primarily the patients from BHV-3000-301 and BHV-3000-302) for approximately three months. After approximately three months, study enrollment will open for patients with a history of 9-14 migraine attacks of moderate to severe intensity per month within the 3 months prior to the screening visit. Lastly, study enrollment will open for subjects in the every other day dosing group (4-14 moderate to severe migraines/month).

Upon the completion of the screening visit, patients will be provided an electronic diary (eDiary) to document each day of the 30 day Observation Period if a migraine occurred, the migraine intensity and if the migraine was treated. Patients will record the standard of care migraine treatment received on a paper diary. After completing the 30 day Observational Period, the patient will return to the clinic with both diaries for the Baseline Visit. At the Baseline Visit, eligibility for continued participation in the study will be assessed before study medication will be dispensed. After the investigator reviews the results of the baseline laboratory assessments and determines the patient's continued eligibility, the site staff will inform the patient whether or not they are eligible to start dosing in the Long Term Treatment phase. If eligible for the Long Term Treatment Phase, patients will be instructed that they can take study medication at the onset of a migraine (of mild to severe intensity). Patients in the 2-8 or 9-14 moderate to severe migraines/month groups will be instructed that they can take a maximum of one tablet of rimegepant per calendar day during the 52 week Long Term Treatment phase at the onset of a migraine (of mild to severe intensity).

Patients in the every other day dosing group (history of 4-14 moderate to severe migraines/month) will be instructed that they must take one tablet of rimegepant every other calendar day. If patients in this group have a migraine on a day that they are not scheduled to dose with rimegepant, they may take a rimegepant tablet to treat a migraine of mild, moderate or severe intensity. Therefore, patients in this group can take a maximum of one tablet of rimegepant per calendar day for 12 weeks.

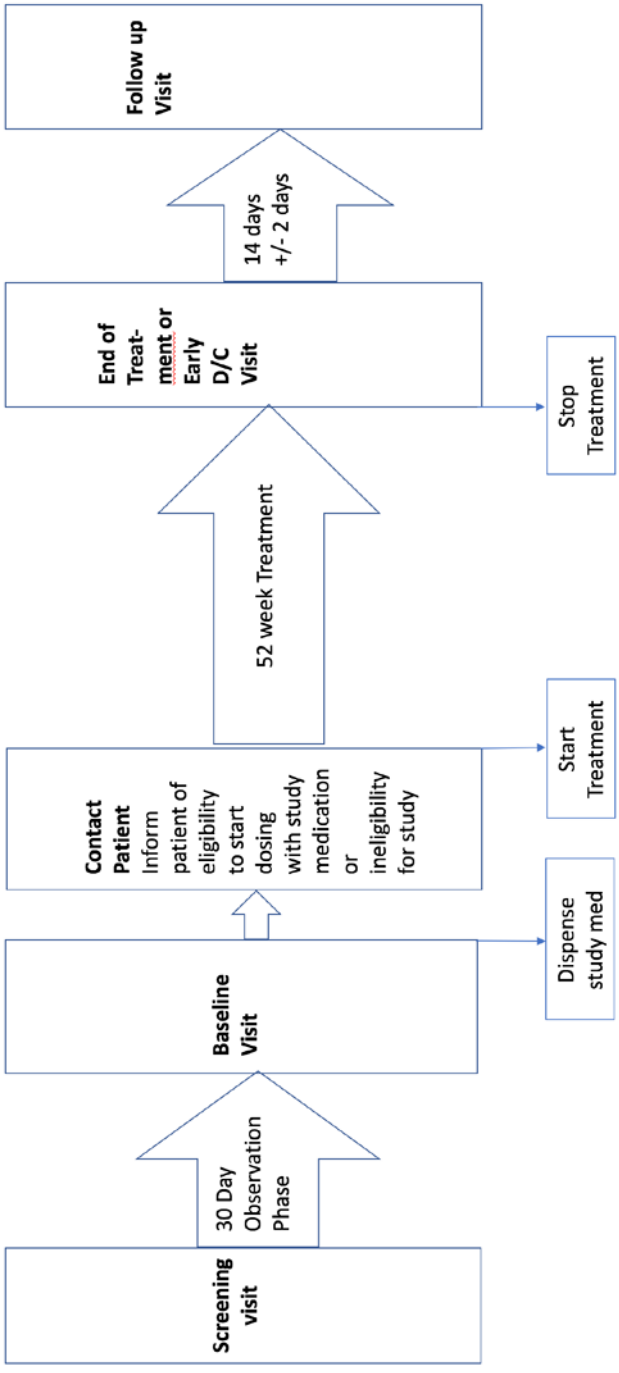
Patients are required to record their migraine occurrence and severity and all study medication doses in the eDiary. Patients are also required to continue to record the standard of care migraine treatment taken on a paper diary. Patients will also use the eDiary to complete the Preference of Medication (PoM) questionnaire and the Satisfaction with Medication (SM) questionnaire at specified study timepoints.

At select study visits, patients will complete or will be administered the Migraine-specified Quality-of-Life Questionnaire v 2.1 (MQoLQ), the Migraine Disability Assessment (MIDAS), Clinical Global Impression – change (CGI-c) scale, and the Sheehan Suicidality Tracking Scale (S-STS) on paper forms, at specified study visits.

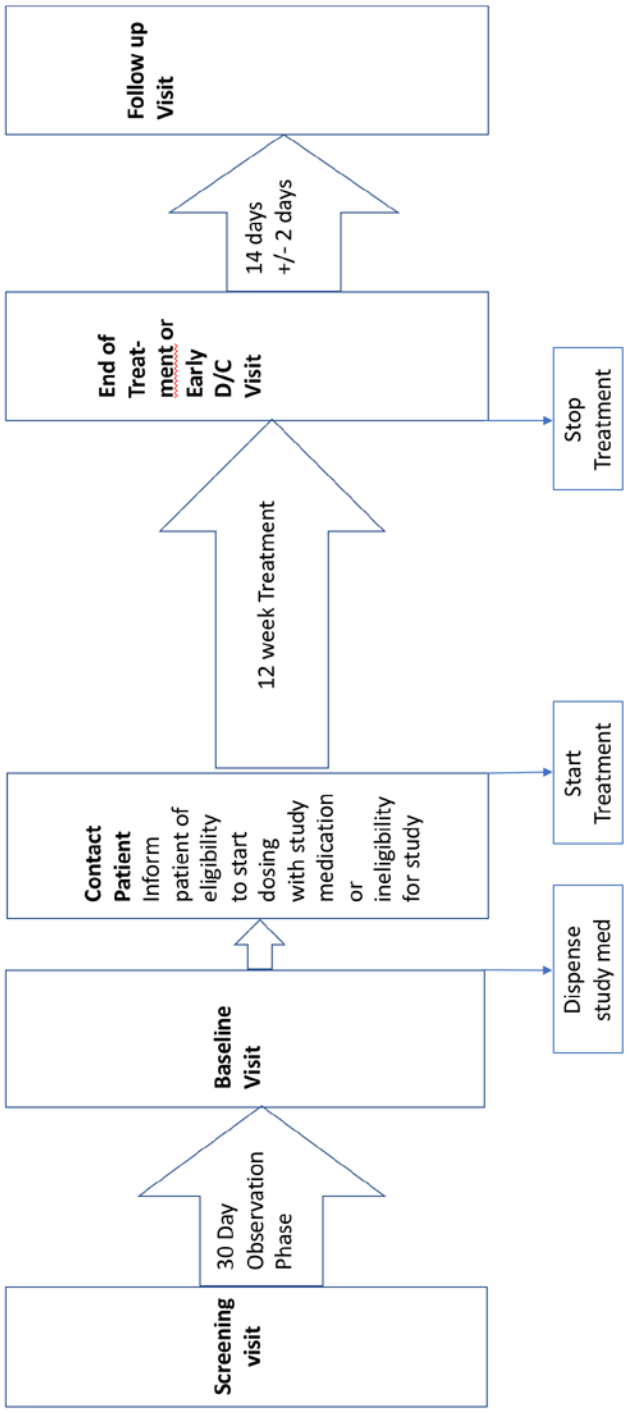
Additional assessments and visit schedule are outlined in the procedural table in Section 4.3. Procedures include study personnel review of the eDiary and paper diary with the patient, assessment of study medication compliance, monitoring of tolerability and safety (including vital signs, laboratory tests, and electrocardiography). Study visits will be

	approximately every two weeks during the first month and then every 4 weeks until Week 52 for subjects in the 2-8 moderate to severe migraine/month group or the 9-14 moderate to severe migraine/month group. Study visits will be approximately every two weeks during the first month and then every 4 weeks until Week 12 for subjects in the every other day dosing group (those with history of 4-14 moderate to severe migraines/month). Patients will return to the study site at the end of Week 52 (or Week 12 for subjects in the every other day dosing group (history of 4-14 moderate to severe migraines/month)) (+/- 7 days) for the End of Treatment Visit. There is a Follow-up Visit 14 days (+/- 2 days) after the Week 12/52/EOT Visit. To closely monitor for potential drug induced liver injury, guidance on reporting potential drug-induced liver injury (DILI) events is provided in the protocol. Lab results that meet predefined LFT abnormality criteria as DILI should be reported as a serious adverse event (SAE). See Section 8.1.5, Potential Drug Induced Liver Injury (DILI).
Primary Endpoint:	The frequency and severity of adverse events that occur in at least 5% of treated subjects, the frequency of serious adverse events, adverse events leading to discontinuation and clinically significant laboratory abnormalities during the treatment period will be assessed. The frequency of AEs, SAEs, AEs leading to discontinuation are determined from case report forms, and are tabulated based on the number of unique subjects. The frequency of clinically significant laboratory abnormalities are determined from laboratory data, and are also tabulated based on the number unique subjects.
Secondary Endpoints:	The frequency of AST or ALT elevations > 3x ULN, concurrently with bilirubin elevations > 2x ULN, will be assessed by tabulating the number of unique subjects with this pairing of events. The frequency of hepatic-related adverse events and hepatic-related treatment discontinuations will be tabulated from case report forms and will be based on unique subjects reporting such events. Severity will be assessed as the worst severity observed while the subject is on treatment.

STUDY SCHEMATIC (up to 52 weeks of treatment 2-8 and 9-14 moderate to severe migraines/month groups)



STUDY SCHEMATIC (up to 12 weeks of treatment for the 4-14 moderate to severe migraines/month, every other day dosing group)



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AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
bid	Twice Daily
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CGI-c	Clinical Global Impressions- change scale
C_{max}	Maximum Plasma Concentration
CONMED	Concomitant Medication
CRF	Case Report Form
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
ECG	Electrocardiogram
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HR	Heart Rate
ICF	Informed Consent Form
IB	Investigator's Brochure
ICH	International Conference on Harmonization

ICF	Informed Consent Form
IEC	Independent Ethics Committee
HIS	International Headache Society
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous
IWRS	Interactive Web Response System
kBq	Kilobecquerel
kg	Kilogram
L	Liters
LFTs	Liver Function Tests
MBq	Megabecquerel
mg	Milligram
MIDAS	Migraine Disability Assessment
MQoLQ	Migraine Quality of Life Questionnaire
min	Minute
mmHg	Millimeters Mercury
NOEL	No Observed Effect Level
NOAEL	No Observed Adverse Event Level
PK	Pharmacokinetic
Po	By Mouth, Orally
QD	Once Daily
QTc	Interval between Q-wave and T-wave in the cardiac cycle
SAE	Serious Adverse Event

S-SST	Sheehan Suicidality Tracking scale
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

1 INTRODUCTION AND RATIONALE

1.1 Background

BHV-3000 (rimegepant, /rih-MEJ-eh-pant/) is a calcitonin gene-related peptide (CGRP) receptor antagonist in development for the acute treatment of migraine. A comprehensive and durable efficacy profile for rimegepant was demonstrated in an 812 patient Phase 2b double-blind, randomized, placebo controlled, dose-ranging trial where migraine sufferers received either placebo, sumatriptan (100 mg) or rimegepant (10, 25, 75, 150, 300 or 600 mg) (Study CN170003)[1]. A dose of 75 mg was selected as the optimal dose for Phase 3 clinical trials, given that larger doses showed a similar efficacy profile and there was negligible benefit identified with higher doses. Rimegepant at 75 mg showed statistically significant comprehensive efficacy across all four traditional endpoints at 2 hr (pain, nausea, photophobia and phonophobia) which was durable as evidenced by the presence of pain freedom and pain relief which persisted through 24 hr and 48 hr showing significant difference from placebo on the corresponding 2-24 and 2-48 hr pain endpoints.

1.2 CGRP's Role in 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 following possible mechanisms:

- **Blocking Neurogenic Inflammation:** Binding of CGRP receptor antagonists to CGRP receptors located on mast cells would inhibit inflammation caused by trigeminal nerve release of CGRP onto mast cells within the tough outer covering of the brain, or the meninges.

- **Decreasing Artery Dilation:** By blocking the CGRP receptors located in smooth muscle cells within vessel walls, CGRP receptor antagonists would inhibit the pathologic dilation of intracranial arteries without the unwanted effect of active vasoconstriction.

- **Inhibiting Pain Transmission:** Binding of CGRP receptor antagonists to CGRP receptors would suppress the transmission of pain by inhibiting the central relay of pain signals from the trigeminal nerve to the caudal trigeminal nucleus.

1.3 Product Development Background

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

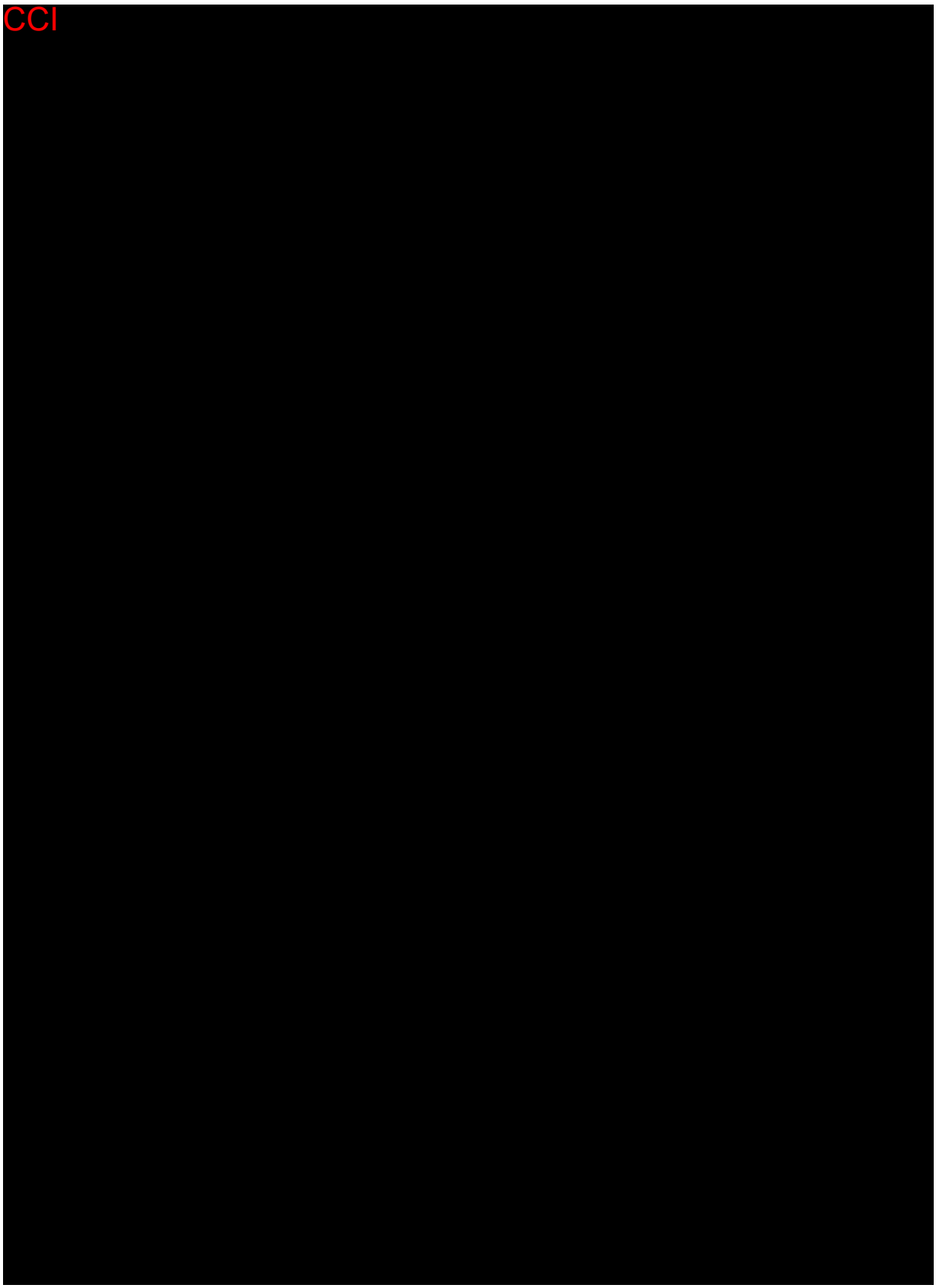
1.3.1 Non-clinical Studies

1.3.1.1 Non-clinical 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 potential to contract coronary vessels. While sumatriptan and zolmitriptan exhibited progressive contraction of human coronary vessels at increasing concentrations, the CGRP receptor antagonist compounds leading up to identification of 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 contraction 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.

1.3.1.2 Non-clinical Toxicology

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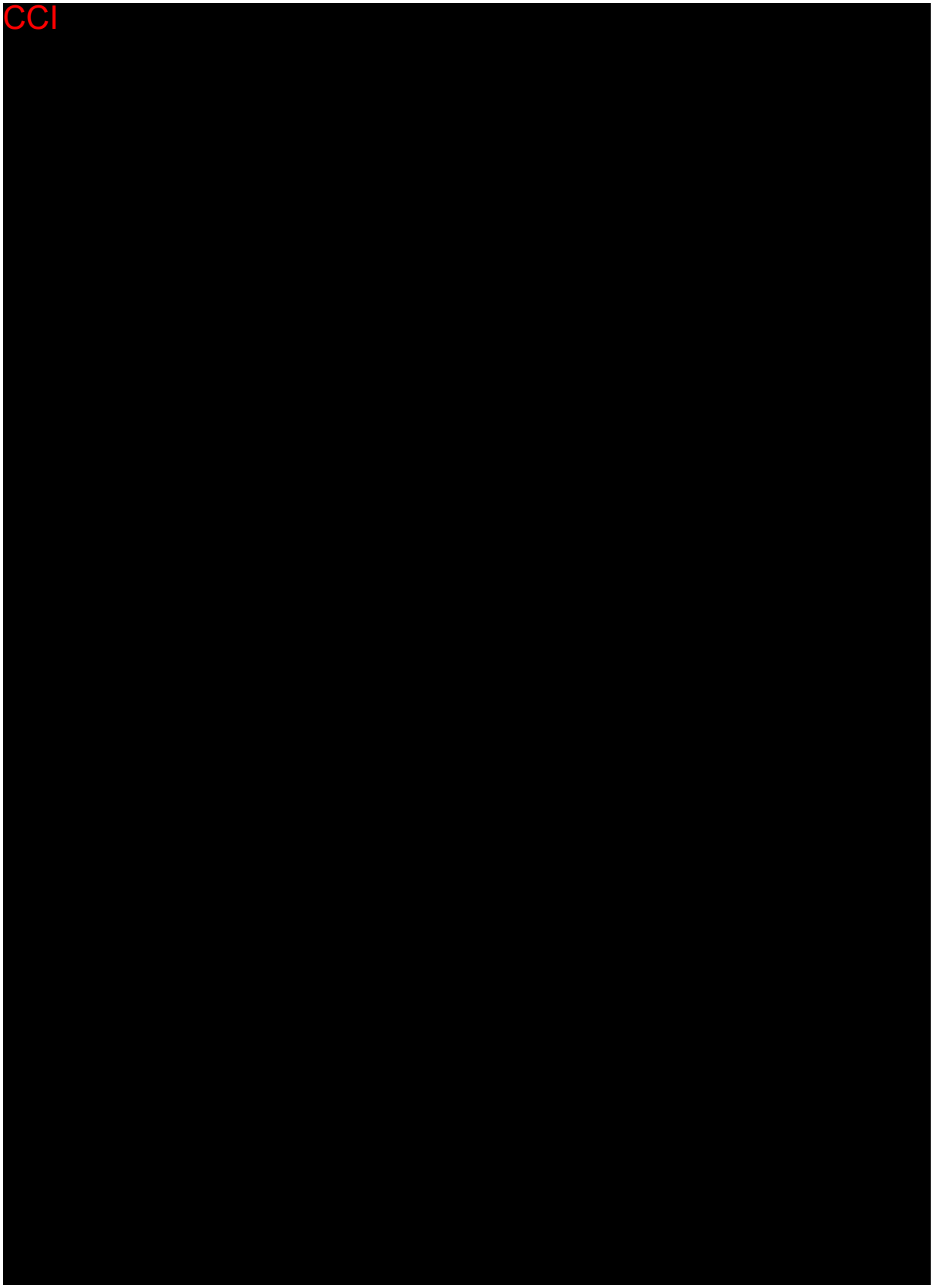
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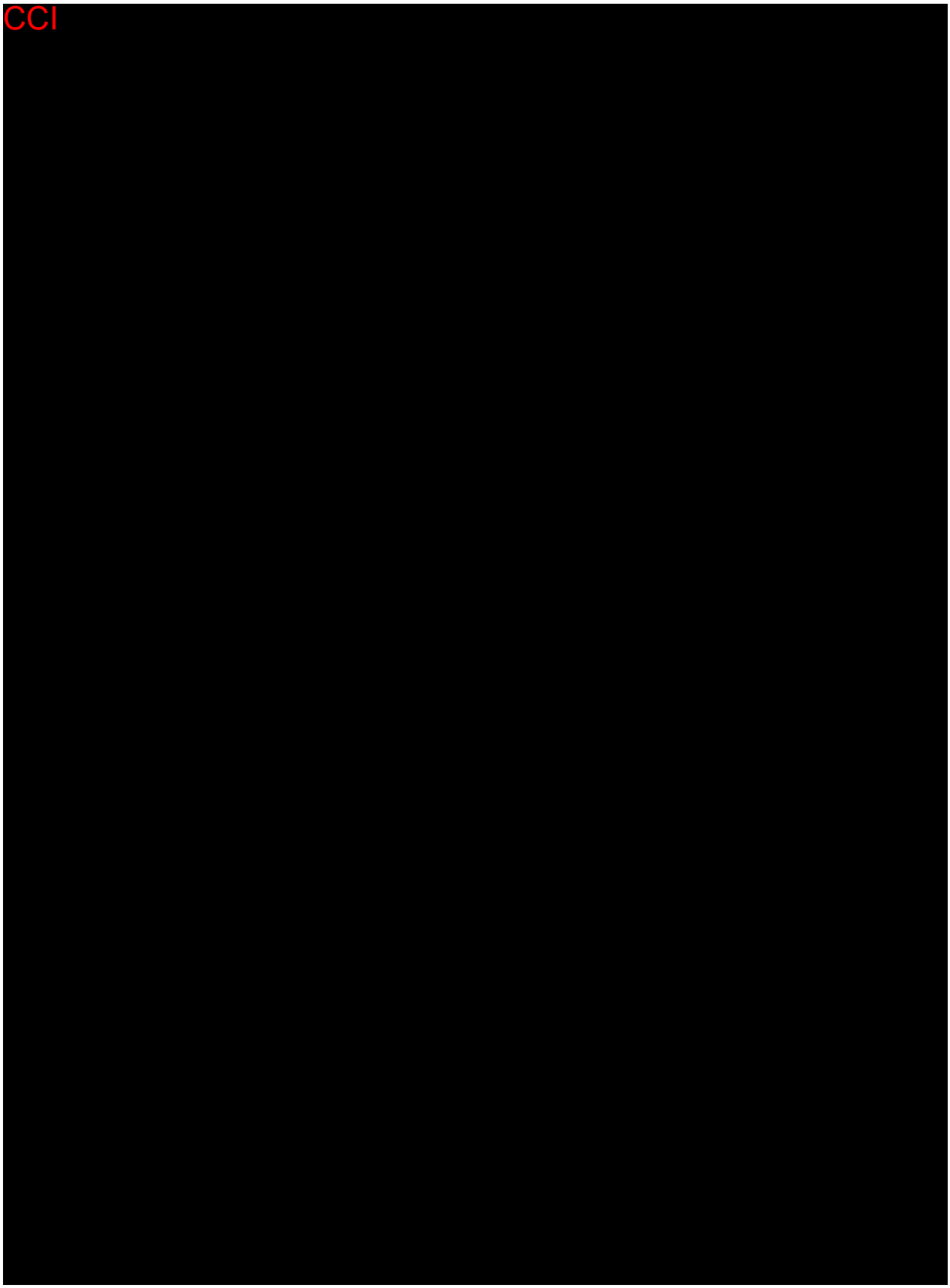
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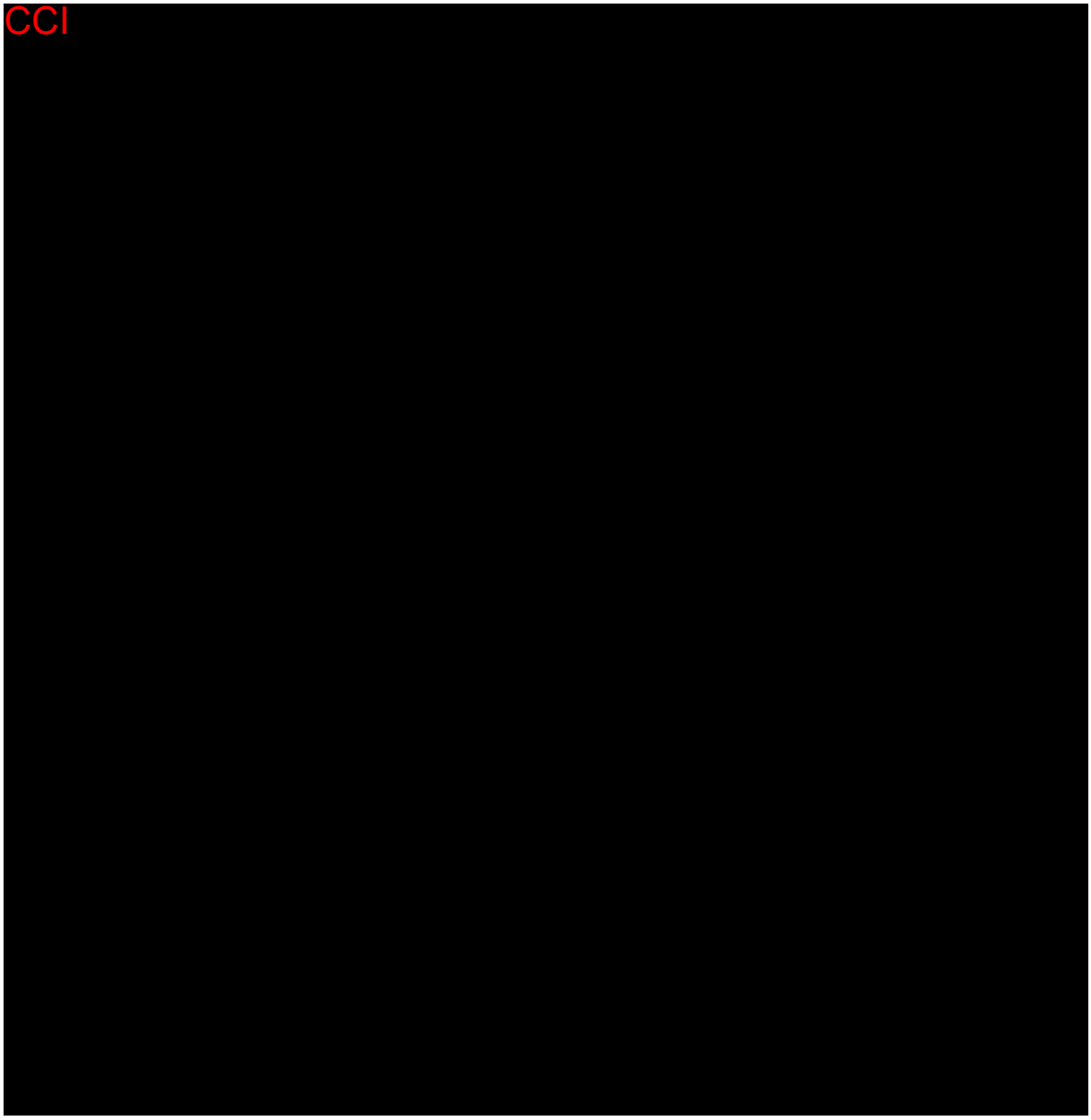


1.3.2.7.1 CN170003

Study CN170003 [3] 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

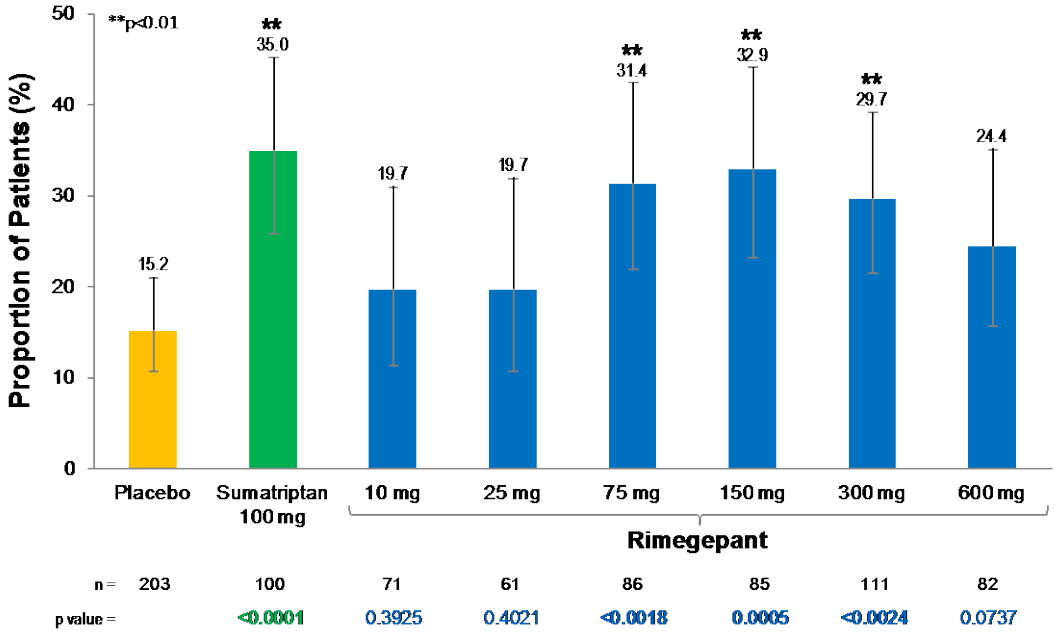
assigned sumatriptan; the remainder were assigned to one of six rimegepant groups based on a Bayesian analysis of the observed response rates. Subjects were instructed to treat one migraine of moderate or severe pain intensity and then return to the clinic within 7 days.

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 [1]. 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 [8].

Rimegepant at 75 mg showed statistically significant efficacy across all four traditional endpoints at 2 hr (pain, nausea, photophobia and phonophobia) which was durable and persisted through 24 hr. At 2 hr following a single oral dose of 75 mg, patients 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) (Figure 1).

Figure 1: Phase 2b Primary Endpoint: Rimegepant Pain Freedom at 2 hours Post Dose (+/- 95% Confidence)



In conclusion, Study CN170003 [3] demonstrated that rimegepant is superior to placebo in the acute treatment of migraines. The selection of 75 mg rimegepant as the dose for the Phase 3 pivotal efficacy studies 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), durability of effect as well as benefit on secondary outcome measures as presented above (see also Section 1.4.2).

1.3.4 Clinical Adverse Event Profile

To date, 7 clinical studies have been completed in healthy volunteers and migraineurs that inform PK, metabolic interactions, safety, tolerability and efficacy. In total, the current data suggests a favorable benefit-risk profile for rimegepant in the acute treatment of migraine attacks. Efficacy was established in Study CN170003, and the overall database suggests a favorable safety profile. Clinical experience with rimegepant has also allowed the characterization of safety and tolerability at substantial multiples of the intended therapeutic exposure and intended frequency of use. Rimegepant has been assessed in single doses up to 1500 mg and in multiple doses from 75 mg to 600 mg with 14-days of dosing (including 300 mg twice daily), where the higher doses yielded exposures more than 60 times greater in AUC and 30 times higher in Cmax as compared to the mean therapeutic exposure of a single 75 mg dose. These high exposure multiples were generally well tolerated and safe.

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. Please refer to the 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.

1.4 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 [9] and the Global Burden of Disease Survey 2010 rates migraine as the seventh highest specific cause of disability worldwide. Annually, migraines affect approximately 15% of the adult population in the United States [10], comprising approximately 33 million adults. Approximately 62% of migraineurs have one or more attack per month, and approximately 25% have one or more per week [11]. Approximately 80% of individuals are unable to work or function normally during a migraine attack, with 53% reporting severe impairment and/or requiring bedrest [12, 13]. Comorbid conditions associated with migraine include depression, anxiety and cardiovascular disease [14].

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 [9]. In part, this burden is attributed to limitations of current standard-of-care pharmacotherapies, which are contraindicated for use in over 2.6 million American migraine sufferers with known cardiovascular disease as well as many others with multiple cardiovascular (CV) risk factors. The US Prescribing Information (USPI) for triptans includes warnings and precautions for migraine patients with risk factors for cardiovascular disease and states that high risk patients, 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 patients with a history of ischemic heart disease, coronary artery vasospasm, history of stroke, peripheral vascular disease or uncontrolled hypertension. Even in patients 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. According to a recent study published in the journal Headache, an estimated 2.6 million migraine sufferers in the United States have a cardiovascular event, condition or procedure that limits the potential of triptans as a treatment option. 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 is expected to address these cardiovascular limitations. As discussed in Section 1.3.1.1, 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 [3] demonstrated the efficacy of rimegepant in the acute treatment of migraine, with and without aura, at doses of 75 mg and above. Doses above 75 mg were not associated with clinically significant differences in efficacy and therefore 75 mg is the selected dose for Phase 3.

The open label, long-term safety study proposed herein will further assess the safety of rimegepant (75 mg) for the acute treatment of migraine. This study is being conducted to further characterize the safety and tolerability of rimegepant during longer term treatment of patients with migraine. Importantly, it will help define the safety profile of rimegepant dosing on an as needed (up to daily basis for a period up to 1 year. Approximately 200 subjects will dose at least every other day, but not more than once per calendar day, for a period of approximately 12 weeks.

1.4.1 Study Design Rationale

This is a multicenter, open label evaluation of the safety and tolerability of long term use of rimegepant 75 mg tablet taken as needed (up to one tablet per day upon onset of a migraine of mild, moderate or severe intensity) for the acute treatment of migraine for up to 52 weeks. This study will also evaluate at least every other day dosing in approximately 200 patients for up to 12 weeks. Up to approximately 2000 patients will be assigned treatment, in this study.

1.4.2 Dose Selection Rationale

Study CN170003 was a double-blind, randomized, placebo-controlled, dose-ranging trial of rimegepant for the acute treatment of migraine [1]. 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 [8]. rimegepant at 75 mg showed statistically significant broad efficacy across all four traditional endpoints at 2 hr (pain, nausea, photophobia and phonophobia) which was durable and persisted through 24 hr. At 2 hr following a single oral dose of 75 mg, patients 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 hr, patients 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 hr measures, where rimegepant at 75 mg produced significant 2-24 hr sustained pain freedom (27.9%, $p < 0.0001$) and 2-24 hr sustained pain relief (69.8%, $p < 0.0001$) vs. placebo (7.4% and 42.4%, respectively).

1.4.3 Other Rationale related to the compound/study

Prior to initiation of Phase 3, a Phase 1 crossover study to assess the safety, tolerability and pharmacokinetics of a single dose of the rimegepant tablet in healthy volunteers will be conducted to ensure PK comparability with the previously studied capsule (rimegepant free-base). The Investigator Brochure will be updated to include these study results when available.

1.5 Research Hypothesis

Long term treatment dosing with rimegepant, up to one tablet per day, is safe and well tolerated in the acute treatment of migraine.

2 STUDY OBJECTIVE

2.1 Primary

To evaluate the safety and tolerability of rimegepant.

2.2 Secondary

Secondary Objectives:

- To evaluate the frequency of elevations in ALT or AST > 3x ULN with concurrent elevations in bilirubin > 2x ULN in subjects treated with rimegepant.
- To evaluate the frequency and severity of hepatic-related adverse events and the frequency of hepatic-related treatment discontinuations.

Exploratory Objectives:

- To evaluate the frequency of subjects with elevated liver function tests (AST, ALT or total bilirubin).
- To evaluate the frequency of subjects with ALT or AST elevations > 3x ULN in temporal association with nausea, vomiting, anorexia, abdominal pain or fatigue.
- To explore the contributions of gender, age and exposure to rimegepant to abnormalities in AST, ALT, or bilirubin.
- To investigate the time on treatment and cumulative exposure associated with: (1) hepatic related SAEs and treatment discontinuations; (2) elevations in ALT or AST > 3x ULN with concurrent elevations in bilirubin > 2x ULN.
- To evaluate the number of headache days and severity of migraine attacks while subjects are treated with rimegepant relative to the observational period.
- To evaluate the effect of rimegepant treatment compared to baseline on the 20-Item Migraine-Specific Quality of Life Questionnaire v 2.1 (MSQoL).
- To evaluate the effect of rimegepant treatment compared to baseline on the Migraine Preference of Medication (PoM).

- To examine the scores on the Sheehan Suicidality Tracking Scale.
- To evaluate the effect of rimegepant treatment compared to baseline on the Satisfaction with Medication survey.
- To evaluate the effect of rimegepant treatment compared to baseline on the Migraine Disability Assessment (MIDAS)
- To evaluate the effect of rimegepant treatment compared to baseline on the Clinical Global Impression – change (CGI-c) scale.

3 STUDY ENDPOINTS

3.1 Primary

The frequency and severity of adverse events that occur in at least 5% of treated subjects, the frequency of serious adverse events, adverse events leading to discontinuation and clinically significant laboratory abnormalities during the treatment period will be assessed. The frequency of AEs and SAEs are determined from case report forms, and are tabulated based on the number of unique subjects. The frequency of clinically significant laboratory abnormalities are determined from laboratory data, and are also tabulated based on the number unique subjects.

3.2 Secondary

The frequency of AST or ALT elevations above 3x ULN, concurrently with bilirubin elevations above 2x ULN, will be assessed by tabulating the number of unique subjects with this pairing of events.

The frequency of hepatic related adverse events and hepatic related treatment discontinuations will be tabulated from case report forms and will be based on unique subjects reporting such events.

3.3 Measures of Interest

Not Applicable

4 STUDY PLAN

4.1 Study Design and Duration

This is a multicenter, open-label study to assess the safety and tolerability of long term use of rimegepant, taken up to one tablet per calendar day, in patients with migraine.

The Screening phase includes a screening visit and a 30 day Observation Period. For subjects to be eligible for the study, they must have 2-14 migraine attacks of moderate to severe intensity per month in the 3 months prior to the Screening Visit. Patients enrolled in the every other day dosing group must have had 4-14 migraine attacks of moderate to severe intensity per month within the 3 months prior to the screening visit. Enrollment into this study will initially be open to patients with 2-8 moderate to severe migraine attacks per month (primarily the patients from BHV-3000-301 and BHV-3000-302) for approximately three months. After approximately three months, study enrollment will open for patients with a history of 9-14 migraine attacks of moderate to severe intensity per month within the 3 months prior to the screening visit. Lastly, study enrollment will open for subjects in the every other day dosing group (4-14 moderate to severe migraines/month).

Upon completion of the screening visit, patients will be provided an eDiary to document on each day of the 30 day Observation Period if a migraine occurred, the migraine intensity and if the migraine was treated. Patients will record the standard of care migraine treatment received on a paper diary. After completing the 30 day Observational Period, the patient will return to the clinic with both diaries for the Baseline Visit. At the Baseline Visit, eligibility for continued participation in the study will be assessed before study medication will be dispensed. After the investigator reviews the results of the baseline laboratory assessments and determines continued eligibility, the site staff will inform the patient whether or not they are eligible to start dosing in the Long Term Treatment phase. If eligible for the Long Term Treatment Phase, in the 2-8 or 9-14 moderate to severe migraines/month groups, patients will be instructed that they can take study medication at the onset of a migraine (of mild to severe intensity). Patients can take a maximum of one tablet of rimegepant per day during the 52 week Long Term Treatment phase at the onset of a migraine (mild, moderate or severe intensity).

Patients in the every other day dosing group (history of 4-14 moderate to severe migraines/month) will be instructed that they must take one tablet of rimegepant every other calendar day, regardless of whether or not the patient has a migraine. If patients in this group have a migraine on a day that they are not scheduled to dose with rimegepant, they may take a rimegepant tablet to treat a migraine of mild, moderate or severe intensity. Therefore, patients in this group can take a maximum of one tablet of rimegepant per calendar day for up to 12 weeks.

Patients are required to record their migraine occurrence and severity and all study medication doses in the eDiary and are required to continue to record the standard of care migraine treatment taken on a paper diary. Patients will also use the eDiary to complete

the Preference of Medication (PoM) questionnaire and the Satisfaction with Medication (SM) questionnaire at specified study timepoints.

At select study visits, patients will complete or will be administered the Migraine-specified Quality-of-Life Questionnaire v 2.1 (MQoLQ), the Migraine Disability Assessment (MIDAS), Clinical Global Impressions-change (CGI-c) scale, and the Sheehan Suicidality Tracking Scale (S-STS) on paper forms, at specified study visits.

Additional assessments and visit schedule are outlined in the procedural table in Section 4.3. Procedures include study personnel review of the eDiary and paper diary with the patient, assessment of study medication compliance, monitoring of tolerability and safety (including vital signs, laboratory tests, and electrocardiography). Study visits will be approximately every two weeks during the first month and then every 4 weeks until Week 52 for subjects in the 2-8 moderate to severe migraine/month group or the 9-14 moderate to severe migraine/month group.

Study visits will be approximately every two weeks during the first month and then every 4 weeks until Week 12 for subjects in the every other day dosing group (those with history of 4-14 moderate to severe migraines/month).

Patients will return to the study site at the end of Week 52 (or Week 12 for subjects in the every other day dosing group (history of 4-14 moderate to severe migraines/month)) (+/- 7 days) for the End of Treatment Visit. There is a Follow-up Visit 14 days (+/- 2 days) after the Week 12/52/EOT Visit.

To closely monitor for potential drug induced liver injury, guidance on reporting potential drug-induced liver injury (DILI) events is provided in the protocol. Lab results that meet predefined LFT abnormality criteria as DILI should be reported as a serious adverse event (SAE). See Section 8.1.5, Potential Drug Induced Liver Injury (DILI).

4.2 Study Schematic

Figure 2: Study Schematic (Up to 52 Weeks Treatment for 2-8 and 9-14 moderate to severe migraines/month groups)

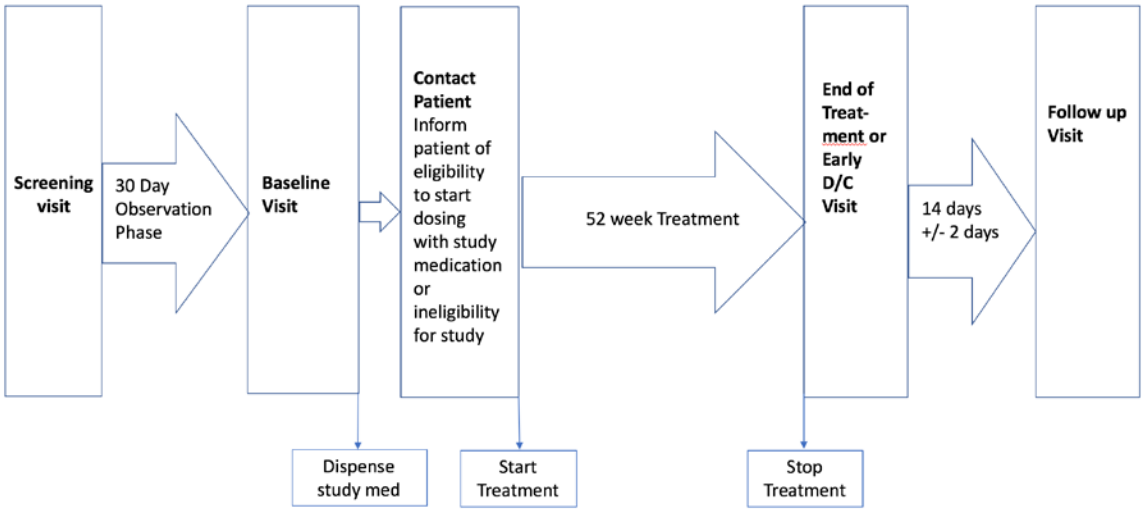
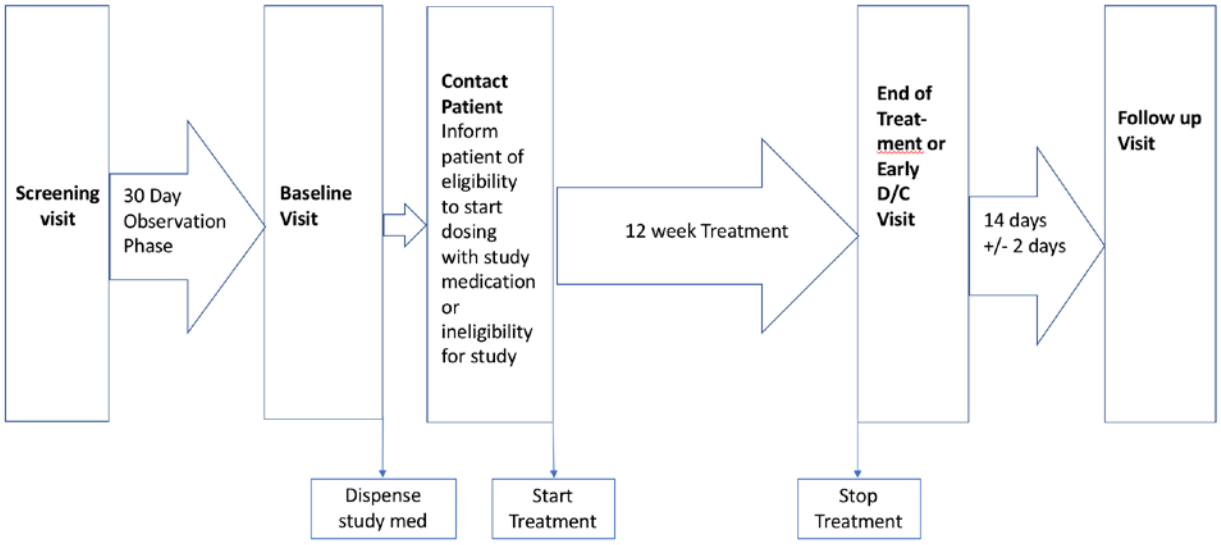


Figure 3: Study Schematic (Up to 12 Weeks Treatment for the 4-14 moderate to severe migraines/month, every other day dosing group)



4.3 Schedule of Assessments

Table 1: Schedule of Assessments (for 2-8 moderate to severe and 9-14 moderate to severe migraines /month group)

Procedure	Screening Visit	Observational Period (30 days, +/- 2 days)	Baseline Visit (Day 1)	Phone visit to confirm eligibility based on laboratory criteria[1]	Week 2 (Day 15 +/- 2 days)	Week 4 (Day 29 +/- 2 days)	Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 (or Early Termination) (all visits +/- 7 days)	Week 2 Follow-up Safety Visit (14 days after EOT visit +/- 2 days)
Eligibility Assessments								
Informed Consent	X							
Inclusion/Exclusion Criteria	X		X	X				
Medical History	X							
Migraine History (signs/symptoms/prior treatment/frequency/intensity)	X							
Prophylactic and standard of care migraine medication	X	X	X		X	X	X	X[3]

[1] Study eligibility must be confirmed by baseline laboratory results prior to first dose of study medication. Sites must contact patients by phone to confirm study eligibility with subject prior to subject taking first dose.
[3] Collect if treatment with conmed is required for an AE or if conmed is considered related to AE

Procedure	**Screening Visit**	**Observational Period (30 days, +/- 2 days)**	**Baseline Visit (Day 1)**	**Phone visit to confirm eligibility based on laboratory criteria[1]**	**Week 2 (Day 15 +/- 2 days)**	**Week 4 (Day 29 +/- 2 days)**	**Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 (or Early Termination) (all visits +/- 7 days)**	**Week 2 Follow-up Safety Visit (14 days after EOT visit +/- 2 days)**
recorded on paper diary/ Concomitant Medication[2]								
Safety Assessments								
Physical Examination	X[4]		X			X	X (Weeks 24 and 52/early termination only)	
Vital Signs[5]/Physical Measurements[6]	X		X			X	X	X
Clinical Safety Laboratory Testing	X[6]		X			X	X (Weeks 24 and 52/early termination	

[2] Concomitant medication, including prophylactic and standard of care migraine medication, taken during the Observational Period and Long term treatment phase should be recorded the patient's paper diary and reviewed by the study personnel at each study visit
[4] If the end of treatment physical exam from BHV-3000-301/-302 was done within 4 weeks of the screening visit for BHV-3000-201, it does not need to be completed at screening.
[5] If the end of treatment vital signs from BHV3000-301/-302 were done on the same day of the screening visit for BHV3000-201, the vitals do not need to be completed at screening.
[6] Height measured at the Screening Visit only. 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 radial artery pulse rate will be measured.

Procedure	**Screening Visit**	**Observational Period (30 days, +/- 2 days)**	**Baseline Visit (Day 1)**	**Phone visit to confirm eligibility based on laboratory criteria[1]**	**Week 2 (Day 15 +/- 2 days)**	**Week 4 (Day 29 +/- 2 days)**	**Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 (or Early Termination) (all visits +/- 7 days)**	**Week 2 Follow-up Safety Visit (14 days after EOT visit +/- 2 days)**
							only)	
Liver function tests (LFTs)	X[7]		X		X	X	X	X
Lipid panel			X				X (Weeks 24 and 52/early termination only)	
ECG	X		X			X	X (Weeks 24 and 52/early termination only)	X
Urinalysis			X				X (Week 52/early termination only)	

[7] If the end of treatment laboratory tests from BHV-3000-301/-302 were done within 2 weeks of the screening visit for BHV-3000-201, the labs do not need to be completed at screening.

Procedure	**Screening Visit**	**Observational Period (30 days, +/- 2 days)**	**Baseline Visit (Day 1)**	**Phone visit to confirm eligibility based on laboratory criteria[1]**	**Week 2 (Day 15 +/- 2 days)**	**Week 4 (Day 29 +/- 2 days)**	**Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 (or Early Termination) (all visits +/- 7 days)**	**Week 2 Follow-up Safety Visit (14 days after EOT visit +/- 2 days)**
Urine Drug Screen for drugs of abuse[8]	X							
FSH, if applicable, to determine WOCBP status[9]	X							
Pregnancy Test	X (urine)		X (urine and serum)			X (urine)	X (urine)	X (urine)
AE and SAE assessment[10]	X		X		X	X	X	X
Sheehan Suicidality Tracking Scale[11]	X		X		X	X	X	X
Clinical Drug Supplies/Study Supplies								

[8] If the end of treatment urine drug screen from BHV3000-301/-302 was done on the same day of the screening visit for BHV3000-201, the urine drug screen does not need to be completed at screening
[9] If WOCBP status was determined in BHV-3000-301 or -302, the patient is considered to have the same status in BHV-3000-201.
[10] SAEs and AEs must be reported after patient signs informed consent.
[11] If the end of treatment Sheehan Suicidality Tracking Scale from BHV3000-301/-302 was done on the same day of the screening visit for BHV3000-201, the Sheehan Suicidality Tracking Scale does not need to be completed at screening

Procedure	**Screening Visit**	**Observational Period (30 days, +/- 2 days)**	**Baseline Visit (Day 1)**	**Phone visit to confirm eligibility based on laboratory criteria[1]**	**Week 2 (Day 15 +/- 2 days)**	**Week 4 (Day 29 +/- 2 days)**	**Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 (or Early Termination) (all visits +/- 7 days)**	**Week 2 Follow-up Safety Visit (14 days after EOT visit +/- 2 days)**
Dispense Study Medication[12]			X			X	X	
Administer study medication[13]				X	X	X	X	
Enter use of study medication in eDiary				X	X	X	X	
Return unused study medication to site for compliance check					X	X	X	
Electronic Diary Dispensed	X							
Electronic Diary returned/reviewed for completeness[14]			X		X	X	X	
Other Assessments								

[12] Patients should finish a bottle of study medication before starting a new bottle. Study drug will be dispensed at monthly study visits as needed. Unscheduled visits to dispense study medication may be scheduled as needed.
[13] Patients will be instructed that they can take their study medication at the onset of a migraine (mild, moderate or severe intensity), up to one tablet per calendar day. Patients must report each tablet they take in the eDiary.
[14] Subjects with 6 or more missed evening diary reports per month, for 2 months (sequential or non-sequential months), should be discontinued for lack of study compliance.

Procedure	**Screening Visit**	**Observational Period (30 days, +/- 2 days)**	**Baseline Visit (Day 1)**	**Phone visit to confirm eligibility based on laboratory criteria[1]**	**Week 2 (Day 15 +/- 2 days)**	**Week 4 (Day 29 +/- 2 days)**	**Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 (or Early Termination) (all visits +/- 7 days)**	**Week 2 Follow-up Safety Visit (14 days after EOT visit +/- 2 days)**
Daily report of migraine occurrence and severity reported by patient in eDiary[15]		X	X		X	X	X	
Migraine Specified Quality of Life Questionnaire (MQoLQ) v 2.1			X				X (Weeks 12, 24, 36 and 52/early termination only)	
Preference of Medication (PoM)							X (Weeks 24 and 52/early termination only)	
Satisfaction with Medication (SM) Survey							X (Weeks 24 and 52/early termination only)	

[15] The electronic patient diary will be dispensed at the Screening Visit, after all Screening Procedures are completed. The patient will be trained on the use of the eDiary. The patient will use the eDiary every day during the Observation Phase and Long Term Treatment Phase to report migraine occurrence, migraine severity and if the patient treated the migraine.

Procedure	**Screening Visit**	**Observational Period (30 days, +/- 2 days)**	**Baseline Visit (Day 1)**	**Phone visit to confirm eligibility based on laboratory criteria[1]**	**Week 2 (Day 15 +/- 2 days)**	**Week 4 (Day 29 +/- 2 days)**	**Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 (or Early Termination) (all visits +/- 7 days)**	**Week 2 Follow-up Safety Visit (14 days after EOT visit +/- 2 days)**
Clinical Global Impression – change (CGI-c)							X (Weeks 12, 24, 36 and 52/early termination only)	
Migraine Disability Assessment (MIDAS)			X				X (Weeks 12, 24, 36 and 52/early termination only)	

Table 2: Schedule of Assessments (for 4-14 moderate to severe migraines/month (every other day dosing) group)

Procedure	**Screening Visit**	**Observational Period (30 days, +/- 2 days)**	**Baseline Visit (Day 1)**	**Phone visit to confirm eligibility based on laboratory criteria**	**Week 2 (Day 15 +/- 2 days)**	**Week 4 (Day 29 +/- 2 days)**	**Weeks 8 and 12 (or Early Termination) (all visits +/- 7 days)**	**Week 2 Follow up Safety Visit (14 days after EOT visit +/- 2 days)**
Eligibility Assessments								
Informed Consent	X							
Inclusion/Exclusion Criteria	X		X	X				
Medical History	X							
Migraine History (signs/symptoms/prior treatment/frequency/intensity)	X							
Prophylactic and standard of care migraine medication recorded on paper diary/ Concomitant Medication[16]	X	X	X		X	X	X	X[17]
Safety Assessments								
Physical Examination	X[18]		X			X	X (Week 12 /early	

[16] Concomitant medication, including prophylactic and standard of care migraine medication, taken during the Observational Period and Long term treatment phase should be recorded the patient's paper diary and reviewed by the study personnel at each study visit
[17] Collect if treatment with conmed is required for an AE or if conmed is considered related to AE
[18] If the end of treatment physical exam from BHV-3000-303 was done within 4 weeks of the screening visit for BHV-3000-201, it does not need to be completed at screening.

Procedure	**Screening Visit**	**Observational Period (30 days, +/- 2 days)**	**Baseline Visit (Day 1)**	**Phone visit to confirm eligibility based on laboratory criteria**	**Week 2 (Day 15 +/- 2 days)**	**Week 4 (Day 29 +/- 2 days)**	**Weeks 8 and 12 (or Early Termination) (all visits +/- 7 days)**	**Week 2 Follow up Safety Visit (14 days after EOT visit +/- 2 days)**
							termination only)	
Vital Signs[19]/Physical Measurements[20]	X		X			X	X	X
Clinical Safety Laboratory Testing	X		X			X	X (Week 12/early termination only)	
Liver function tests (LFTs)	X		X		X	X	X	X
Lipid panel			X				X (Week 12/early termination only)	
ECG	X		X			X	X (Week 12/early termination only)	X

[19] If the end of treatment vital signs from BHV3000-303 were done on the same day of the screening visit for BHV3000-201, the vitals do not need to be completed at screening.
[20] Height measured at the Screening Visit only. 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 radial artery pulse rate will be measured.

Procedure	**Screening Visit**	**Observational Period (30 days, +/- 2 days)**	**Baseline Visit (Day 1)**	**Phone visit to confirm eligibility based on laboratory criteria**	**Week 2 (Day 15 +/- 2 days)**	**Week 4 (Day 29 +/- 2 days)**	**Weeks 8 and 12 (or Early Termination) (all visits +/- 7 days)**	**Week 2 Follow up Safety Visit (14 days after EOT visit +/- 2 days)**
Urinalysis			X				X (Week 12/early termination only)	
Urine Drug Screen for drugs of abuse[21]	X							
FSH, if applicable, to determine WOCBP status[22]	X							
Pregnancy Test	X (urine)		X (urine and serum)			X (urine)	X (urine)	X (urine)
AE and SAE assessment[23]	X		X		X	X	X	X
Sheehan Suicidality Tracking Scale[24]	X		X		X	X	X	X
Clinical Drug								

[21] If the end of treatment urine drug screen from BHV3000-303 was done on the same day of the screening visit for BHV3000-201, the urine drug screen does not need to be completed at screening
[22] If WOCBP status was determined in BHV-3000-303, the patient is considered to have the same status in BHV-3000-201.
[23] SAEs and AEs must be reported after patient signs informed consent.
[24] If the end of treatment Sheehan Suicidality Tracking Scale from BHV3000-303 was done on the same day of the screening visit for BHV3000-201, the Sheehan Suicidality Tracking Scale does not need to be completed at screening

Procedure	**Screening Visit**	**Observational Period (30 days, +/- 2 days)**	**Baseline Visit (Day 1)**	**Phone visit to confirm eligibility based on laboratory criteria**	**Week 2 (Day 15 +/- 2 days)**	**Week 4 (Day 29 +/- 2 days)**	**Weeks 8 and 12 (or Early Termination) (all visits +/- 7 days)**	**Week 2 Follow up Safety Visit (14 days after EOT visit +/- 2 days)**
Supplies/Study Supplies								
Dispense Study Medication[25]			X			X	X	
Administer study medication[26]				X	X	X	X	
Enter use of study medication in eDiary				X	X	X	X	
Return unused study medication to site for compliance check					X	X	X	
Electronic Diary Dispensed	X							
Electronic Diary returned/reviewed for completeness[27]			X		X	X	X	

[25] Patients should finish a bottle of study medication before starting a new bottle. Study drug will be dispensed at monthly study visits. Unscheduled visits to dispense study medication may be scheduled as needed.
[26] Patients in the 4-14 moderate to severe migraines/month group will be instructed that they must take their study medication every other day, regardless of whether or not they have a migraine. If patients in this group have a migraine on a day that they are not scheduled to take a tablet of rimegepant, they may take a rimegepant tablet to treat a migraine of mild to severe intensity. Therefore, patients can take a maximum of one tablet of rimegepant per calendar day. Patients must report each tablet they take in the eDiary.
[27] Subjects with 6 or more missed evening diary reports per month, for 2 months (sequential or non-sequential months), should be discontinued for lack of study compliance.

Procedure	**Screening Visit**	**Observational Period (30 days, +/- 2 days)**	**Baseline Visit (Day 1)**	**Phone visit to confirm eligibility based on laboratory criteria**	**Week 2 (Day 15 +/- 2 days)**	**Week 4 (Day 29 +/- 2 days)**	**Weeks 8 and 12 (or Early Termination) (all visits +/- 7 days)**	**Week 2 Follow up Safety Visit (14 days after EOT visit +/- 2 days)**
Other Assessments								
Daily report of migraine occurrence and severity reported by patient in eDiary[28]		X	X		X	X	X	
Migraine Specified Quality of Life Questionnaire (MQoLQ) v 2.1			X				X (Week 12/early termination only)	
Preference of Medication (PoM)							X (Week 12/early termination only)	
Satisfaction with Medication (SM) Survey							X (Week 12/early termination only)	

[28] The electronic patient diary will be dispensed at the Screening Visit, after all Screening Procedures are completed. The patient will be trained on the use of the eDiary. The patient will use the eDiary every day during the Observation Phase and Long Term Treatment Phase to report migraine occurrence, migraine severity and if the patient treated the migraine.

Procedure	**Screening Visit**	**Observational Period (30 days, +/- 2 days)**	**Baseline Visit (Day 1)**	**Phone visit to confirm eligibility based on laboratory criteria**	**Week 2 (Day 15 +/- 2 days)**	**Week 4 (Day 29 +/- 2 days)**	**Weeks 8 and 12 (or Early Termination) (all visits +/- 7 days)**	**Week 2 Follow up Safety Visit (14 days after EOT visit +/- 2 days)**
Clinical Global Impression – change (CGI-c)							X (Week 12/early termination only)	
Migraine Disability Assessment (MIDAS)			X				X (Week 12/early termination only)	

4.3.1 Screening Visit / Observation Period (30 days)

Approximately 2800 patients will be screened to assign up to approximately 2000 patients to rimegepant.

Before any study procedures are performed, patients must sign informed consent. After informed consent, patients will be enrolled in the IWRS system. The patient's migraine history and medical history will be collected at the Screening Visit. All patients will continue to use their migraine prophylactic or standard of care medications during the 30 day observation period. Patients will undergo all screening procedures as detailed in Table 1 and Table 2, after which they will be provided an eDiary to document each day during the 30 day Observation Phase the occurrence and severity of migraines and if the migraine was treated. Patients will also record all migraine standard of care treatments taken during the Observation Phase on a paper diary. After completing the 30 day Observation Phase, patients will return to the clinic, and both their eDiary and paper diary will be reviewed for completeness.

If the patient meets inclusion/exclusion criteria, they may enter the Long Term Treatment Phase.

4.3.2 Long Term Treatment Phase (12 weeks or 52 Weeks)

Once completing the Screening/Observational Period, patients will return to the study site for the Baseline Visit. Patients who continue to meet all inclusion/exclusion criteria and have been compliant with the eDiary may enter the Long Term Treatment Phase. At the Baseline Visit, patients will be dispensed study medication and will be instructed they cannot take study medication until baseline laboratory results confirm study eligibility. After the investigator reviews the results of the baseline laboratory assessments and determines the patient's continued eligibility, the site staff will inform the patient whether or not they are eligible to start dosing in the Long Term Treatment phase. This contact with the patient must be documented in the patient's medical record.

There are two different dosing schedules in this study. If eligible, patients in the 2-8 moderate to severe migrains/month and 9-14 moderate to severe migraines month groups will be instructed that they can take study medication at the onset of a migraine (of mild to severe intensity). Patients will also be instructed that they can take a maximum of one tablet of

rimegepant per calendar day during the Long Term Treatment Phase at the onset of a migraine (mild, moderate or severe intensity).

Patients in the 4-14 moderate to severe migraines/month group will be instructed that they must take one tablet of study drug every other calendar day, regardless of whether they have a migraine on that day or not. If patients in this group have a migraine on a day that they are not scheduled to dose with rimegepant, they may take a rimegepant tablet to treat a migraine of mild, moderate or severe intensity. Therefore, patients can take a maximum of one tablet of rimegepant per calendar day for 12 weeks.

The electronic patient diary will be completed by patients to capture dosing of study medication and the frequency and severity of migraines during the Treatment Phase.

Patients will also use the eDiary to complete the Preference of Medication (PoM) and Satisfaction with Medication (SM) questionnaire. The Migraine-Specified Quality of Life questionnaire v 2.1 (MSQoL), The Sheehan Suicidality Tracking Scale (S-STS), Migraine Assessment Disability (MIDAS) and Clinical Global Impression (CGI-c) will be completed, or administered by the investigator, on paper at specified study visits (Table 1 and Table 2).

Study visits will be approximately every two weeks during the first month and then every 4 weeks, until Week 52 (Table 1). At each visit the eDiary will be reviewed by site staff for completeness and compliance. Study drug compliance and concomitant medication use will be reviewed (and compared to the eDiary and paper diary entries) and patient will be dispensed additional study drug as needed. Additional safety (including laboratory tests and ECGs) will be performed per the schedule outlined in Table 1 and Table 2.

4.3.3 End of Treatment (Weeks 12 or 52)

Patients will return to the study at the end of Week 12 or 52 (+/- 7 days) for review of the electronic diary, assessment of medication compliance, assessment of tolerability and safety (including vital signs, laboratory tests, and electrocardiography) (Table 1 and Table 2). Patients will return the unused study medication and electronic patient diary to the study site.

4.3.4 Follow up Safety Visit

Patients will return to the study site 14 days after the Week 12/52/EOT Visit (+/- 2 days) to collect laboratory tests, vital signs, electrocardiography, and AEs. Investigators should assess patients for AEs consistent with drug dependency or withdrawal effects and report as appropriate (see Section 7.4).

4.4 Post Study Access to Therapy (if applicable)

At the end of the study the sponsor will not continue to supply study drug to patients or investigators. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

5 POPULATION

Of the approximately 2000 patients assigned to treatment in this study, approximately:

- 1200 will have a history of 2-8 moderate to severe migraine attacks per month,
- 600 will have a history of 9-14 moderate to severe migraine attacks per month, and
- 200 will have a history of 4-14 moderate to severe migraine attacks per month (every other day dosing group).

5.1 Number of Subjects

It is anticipated that up to approximately 2800 patients may be screened in order to assign up to approximately 2000 patients to rimegepant.

5.2 Inclusion Criteria

1. **Signed Written Informed Consent**

    a) Written informed consent must be obtained from the patient 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**

Patient has at least 1 year history of migraine (with or without aura) consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd Edition, beta version [2], including the following:

a) Age of onset of migraines prior to 50 years of age

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

c) 2-14 migraine attacks of moderate or severe intensity per month within the last 3 months prior to the Screening Visit

(participants in the every other dosing group must have a history of 4-14 moderate to severe migraines/month within the last 3 months prior to the Screening Visit in the every other day dosing group)

d) 2 or more migraine days requiring treatment during Observation Phase

e) Ability to distinguish migraine attacks from tension/cluster headaches

f) Patients on prophylactic migraine medication are permitted to remain on therapy if the dose has been stable dose for at least 2 months prior to the Baseline Visit, and the regimen should not change during the course of the study.

g) Patients 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 patients ≥ 18 years

b) Women of childbearing potential (WOCBP) and non-sterile men 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 5.6 for the definition of WOCBP. Males with vasectomy are considered surgically sterile provided the procedure occurred greater than 6 months prior to study participation.

c) At the Baseline Visit, WOCBP must have a negative pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) before dosing with study drug

4. **Other Inclusion Criteria**

a) 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 the finding not clinically significant, that it will not introduce additional risk factors, nor

interfere with the study procedures (not including exclusion criteria listed in Section 5 below)

5.3 Exclusion Criteria

1. **Target Disease Exclusion**
   a) Patient has a history of basilar migraine or hemiplegic migraine

2. **Medical History and Concurrent Diseases**
   a) Patient history of HIV disease

   b) Patient history with current evidence of uncontrolled, unstable or recently diagnosed cardiovascular disease, such as ischemic heart disease, coronary artery vasospasm, and cerebral ischemia. Patients with myocardial infarction (MI), acute coronary syndrome (ACS), percutaneous coronary intervention (PCI), cardiac surgery, stroke or transient ischemic attack (TIA) during 6 months prior to screening.

   c) Uncontrolled hypertension or uncontrolled diabetes (however, patients can be included who have stable hypertension and /or diabetes for 3 months prior to screening). Blood pressure greater than 150 mm Hg systolic or 100 mm Hg diastolic after 10 minutes of rest is exclusionary.

   d) Patient has a current diagnosis of major depressive disorder or has had a major depressive episode within the last 12 months, other pain syndromes, psychiatric conditions, dementia, or significant neurological disorders (other than migraine) that, in the Investigator's opinion, might interfere with study assessments

   e) Patient has a history of gastric, or small intestinal surgery, or has a disease that causes malabsorption

   f) Patients has a history or diagnosis of Gilbert's Syndrome or any other active hepatic or biliary disorder

g) The patient has a history or current evidence of any unstable medical conditions (e.g., history of congenital heart disease or arrhythmia, known or 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

h) History of, treatment for, or evidence of, alcohol or drug abuse within the past 12 months or patients who have met DSM-V criteria [15] for any significant substance use disorder within the past 12 months from the date of the screening visit

i) Patients 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 patient or the interpretation of the study results. In addition:

   i. Detectable levels of cocaine, amphetamine and phencyclidine (PCP) in the drug screen are exclusionary. Patients who are positive for amphetamines on the urine drug screen may have their urine samples evaluated for further analysis at the investigator's discretion to rule out a false positive result

   ii. Detectable levels of marijuana in the drug screen are not exclusionary, if in the investigator's documented opinion the patient does not meet DSM-V criteria [15] for substance abuse or dependence; in the investigator's documented opinion, the positive test does not signal a clinical condition that would impact the safety of the patient or interpretation of the study results.

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.

k) Patient has current diagnosis of schizophrenia, major depressive disorder requiring treatment with atypical antipsychotics, bipolar disorder, or borderline personality disorder

l) Body mass index $\geq$ 30 kg/m^2

m) History of gallstones or cholecystectomy

3. **Allergies and Adverse Drug Reactions**
   a) History of drug or other allergy which, in the opinion of the investigator, makes the subject unsuitable for participation in the study

4. **Sex and Reproductive Status**
   a) WOCBP who are unwilling or unable to use an acceptable contraceptive method or abstinence to avoid pregnancy for the entire study period and for up to 8 weeks after last dose of study medication

   b) Women who are pregnant or breastfeeding.

   c) Women with a positive pregnancy test at screening 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 $\leq$ 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 $\geq$ 150 msec.

   e) Intraventricular Conduction Defect with a QRS duration $\geq$ 150 msec.

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

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

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

i) HbA1c ≥ 6.5%

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) Non-compliance with or inability to complete eDiary during Observation Period. Non-compliance is more than 4 missed evening reports during the Observation Period.
   d) Exposure to non-biological investigational agents (other than rimegepant) within the 30 days prior to Screening visit.

   e) Exposure to biological investigational agents within the 90 days prior to Screening visit.

   f) Score of > 0 on the Sheehan Suicidality Tracking Scale (See Section 6.2.5) for the period of 30 days prior to screening.

   g) Previous enrollment in study BHV3000-201.

   h) Participation in any other investigational clinical trial while participating in this clinical trial.

Please see Section 5.4 for Prohibited medications and Section 5.5 for allowable migraine Medications

5.4 Prohibited Concomitant Medication

The medications listed below are prohibited starting at the Baseline visit and during the course of this study or as specified.

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

2. Butterbur root or extracts should not be taken 14 days prior to the Baseline visit and throughout the study.

3. History of use of ergotamine medications on $\geq$ 10 days per month on a regular basis for $\geq$ 3 months

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

5. Use of acetaminophen or acetaminophen containing products for non-migraine indications after the Baseline visit is prohibited. Any use of acetaminophen or acetaminophen containing products for non-migraine indications during the Observation Phase must be stopped at least 2 days prior to baseline visit. Acetaminophen as a standard of care migraine medication as described in Section 5.5 is allowed during the Long-Term Treatment phase.

6. Use of triptans is prohibited during the Long Term Treatment phase.

7. Use of marijuana is prohibited during the study.

8. 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.

9. 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.

10. Concomitant use of atypical antipsychotics such as Abilify (aripiprazole), Zyprexa (olanzapine), Seroquel (quetiapine), Geodon (ziprasidone), or Risperdal (risperidone) or Depakote/Depakene (valproic acid/valproate) during the long-term treatment phase.

11. Concomitant use of LAMICTAL (lamotrigine) is prohibited during the study.

5.5 Prophylactic and Standard of Care Migraine Medications

Patients on prophylactic migraine medication are permitted to remain on therapy if the dose has been stable for at least 2 months prior to the Baseline Visit, and the regimen should not change during the course of the study.

Patients may take their previously prescribed standard of care medications: aspirin, ibuprofen, acetaminophen up to 1000 mg/day for a maximum of 2 consecutive days at a time (this includes Excedrin Migraine), naprosyn (or any other type of non-steroidal anti-inflammatory (NSAID)), antiemetics (e.g. metoclopramide or promethazine) or muscle relaxants for standard of care during the course of the study (Observation Period and Long Term Treatment Phase).

Use of triptans by patients without a contraindication to their use is allowed during the Observation Phase but must be discontinued at the baseline visit. As described above, use of triptans is prohibited during the Long Term Treatment phase. With the exception of triptans and acetaminophen as described in this section, patients are allowed to take standard of care migraine treatment, if needed, during the course of the study.

If a patient takes a tablet of study drug and experiences a migraine later that day, after dosing with study drug for the day, the patient should take their standard of care migraine medication as described in this section of the protocol. Patients are not allowed to take more than one tablet of study medication per calendar day.

Use of standard of care medication during Observation Period and Long Term Treatment Phase, will be recorded by the patient on a paper diary and reported to the site.

5.6 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 at screening) or

2. Woman with irregular menstrual periods and a documented serum follicle stimulating hormone (FSH) level > 35mIU/mL (at screening) 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) and men 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 at first treatment to 56 days **after** the last dose of study drug). The two methods should include one barrier method (ex. condom with spermicidal gel, intrauterine devices, cervical cap etc.) and one other method. The other method could include hormonal contraceptives or another barrier method.

WOCBP will complete a pregnancy test at Screening, Baseline, Week 4, Week 8 and at study visits every 4 weeks through the Week 52/end of treatment visit and at the follow up visit. If a WOCBP suspects that she might be pregnant she should immediately contact the study doctor.

5.7 Other Restrictions and Precautions (if applicable)

Not Applicable

5.8 Deviation from Inclusion/Exclusion Criteria and Study Procedures

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. 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
- Sample source documents, where applicable
- Investigator Brochure
- Interactive Web-based Response System (IWRS)
- Electronic Case Report Form (eCRF) instructions
- Electronic Diary: hand held electronic device (1 will be given to each patient)
- Instructions for the eDiary device and access to the portal
- Paper diary to record standard of care migraine medications
- Laboratory Kits and Laboratory Manual
- ECG Machine and Instructions
- Serious Adverse Event (SAE) forms
- Pregnancy Surveillance Forms
- Sheehan Suicidality Tracking Scale (S-STS) forms

- MIDAS forms
- CGI-c forms

All sites will use an Electronic Data Capture (EDC) tool to submit study data to the CRO. Electronic Case Report Forms (eCRFs) will be prepared for all data collection fields including Serious Adverse Events (SAE) Reporting. SAE data (including queries) will be submitted to the CRO using eCRFs.

The eDiary will be used to record all study medication dosing, to complete select patient-rated scales, and record migraine occurrence and severity. Any assessment completed by the patient in the eDiary will be transferred from the site/patient to the vendor and from the vendor to the CRO and Sponsor. No additional source documents are required for scales and assessments completed by the patient on the eDiary.

Safety laboratory, plasma, serum, instructions for all specimens collected will be provided by a designated central laboratory. ECG equipment, supplies, instructions and training materials will be supplied by a centralized ECG vendor.

6.2 Safety Assessments

6.2.1 Vital Signs and Physical Measurements (Height and Weight)

Vital signs, body weight and height will be recorded at the scheduled visits as outlined in Table 1 and Table 2

6.2.2 Electrocardiogram (ECG)

A standard 12-lead ECG will be recorded during the Screening Phase and at all scheduled visits as outlined in Table 1 and Table 2. A central ECG service will be utilized for reading all ECGs. The over read from the central ECG vendor should be used to determine eligibility for the study. The investigator will determine if any ECG abnormalities are clinically significant or not.

6.2.3 Physical Exam

Patients will undergo a routine physical examination during the Screening Phase and at all scheduled visits as outlined in Table 1 and Table 2. PE to include examination of heart, abdomen and lungs, with review of any other system to be guided by symptoms.

6.2.4 Laboratory Assessments

6.2.4.1 Safety Laboratory Testing

Blood and urine samples will be obtained as outlined in Table 1 or Table 2 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, patients should be fasting for a minimum of 8 hours before labs at Baseline, Weeks 4, 24 and 52/EoT (or Week 12/EoT in the 4-14 moderate to severe migraines/month, every other day dosing group).** However, if a patient is not fasting at a given visit, the blood draw should still be performed, and the non-fasting status should be documented.

1. **Clinical safety labs:**

   Hematology: Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelets;

   Chemistry: Sodium, potassium, chloride, bicarbonate, calcium; glucose, HbA1c, BUN (urea), serum creatinine, uric acid, LDH, total protein, albumin, CPK (with local lab fractionation, if central lab CK result is > 1.5 x ULN);

   eGFR using the estimated MDRD formula (calculated at central lab);

2. **LFTs**: AST, ALT, Alkaline Phosphatase and Bilirubin (Total, Direct, Indirect)

3. **Lipid panel:** Cholesterol, LDL, HDL, triglycerides

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

microscopic examination.

5. **Urine Drug Screen:** For drugs of abuse

6. **FSH:** For WOCBP at screening, to determine WOCBP status

6.2.4.2 Pregnancy Testing

WOCBP will complete pregnancy tests (serum or urine) at specified study visits, prior to taking study medication, and as outlined in Table 1 or Table 2.

6.2.5 Sheehan Suicidality Tracking Scale

The Sheehan STS (S-STS) is a prospective, patient self-reported or clinician administered rating scale that contains 16 questions to track both treatment-emergent suicidal ideation and behaviors[16, 17]. The S-STS will be completed on a paper form at the site. At the screening visit, the recall period for completing the S-STS is 30 days prior; at all other visits, the recall period for completing the S-STS is since the last visit. Any responses other than 0 must be immediately evaluated by the investigator. If the investigator determines that a subject is at risk of suicide or self-harm, appropriate measures to ensure the subject's safety and obtain mental health evaluation must be implemented. In such circumstances, the subject must immediately be discontinued from the study. The event should be recorded as either an AE or SAE as determined by the investigator and reported within 24 hours to the Sponsor. Any subject with a response greater than 0 to any question, excluding Question 2, must be immediately be discontinued from the study. Subjects with a response of 1 ("a little") to Question 2 will be discontinued per the investigator's assessment or if the response persists. Subjects with a response greater than 1 on Question 2 will be discontinued from the study immediately.

6.3 Efficacy Assessments

Not applicable.

6.4 Other Assessments

6.4.1 Daily Migraine Assessment of Severity/Frequency

The number of headache days and severity of migraine attacks during the period that subjects are treated with rimegepant relative to the observational period will be analyzed.

6.4.2 Migraine Quality of Life Questionnaire

Impact of treatment on patient-reported quality of life will be assessed using The Migraine Quality of Life Questionnaire (MQoLQ) version 2.1. The MQoLQ is a 15-item instrument that has been validated in migraine patients to measure the impact of treatment (within past 4 weeks) on migraine-specific domains: work, social function, energy, vitality, feelings, concerns, and migraine symptoms.[26]

6.4.3 Migraine Preference of Medicine

The Preference of Medication Scale (PoM) is a brief scale that captures the patients' perception of whether the medication they are taking has had a greater benefit compared with previous medications to treat their pain. The eDiary will be used to evaluate the Preference of Medication Scale.

6.4.4 Satisfaction with Medication Questionnaire

The Satisfaction with Medication (SM) Questionnaire is a brief questionnaire that captures the patients' perception of whether they are satisfied with their headache medication. The eDiary will be used to evaluate the Satisfaction with Medication Questionnaire.

6.4.5 Migraine Disability Assessment Test (MIDAS)

The Migraine Disability Assessment questionnaire is a retrospective patient self-reported scale of 5 questions that measures headache-related disability as lost time due to headache from paid work or school, household work and nonwork activities. The MIDAS will be completed on a paper form at the site [18].

6.4.6 Clinical Global Impression – Change (CGI-c)

The Clinical Global Impression-change scale is a brief observer-rated scale that rates patient total improvement relative to the investigator's past experience with other patients with the same diagnosis, with or without collateral information [19]. The CGI-c will be administered by the investigator or designee who has been trained on administration and will be completed on a paper form, at the site.

6.5 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, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study by Biohaven Pharmaceuticals
- 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
- No migraine treated with study medication prior to Week 8 visit of Long-Term Treatment Phase.
- Poor compliance with study procedures and visits, including poor completion compliance with evening reports in eDiary. Subjects with 6 or more missed evening reports per month, in 2 (sequential or non-sequential) months, should be discontinued from the study for poor compliance, after discussion with Sponsor.
- Please see section 6.2.5 for guidance on study discontinuation based on results from the S-STS.

All subjects who discontinue should comply with protocol specified End of Treatment procedures as outlined in Table 1 or Table 2. 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.

In this protocol, investigational product is rimegepant 75 mg tablet.

7.1.2 Non-investigational Product

Other medications used as support or rescue 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: standard of care for migraine treatment.

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. Please see the Pharmacy Manual for specific conditions. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor/CRO immediately.

7.2 Dose and Administration

7.2.1 Method of Assigning Patient Identification

Immediately after written informed consent is obtained and before performing any study-related procedures, the site staff must contact the IWRS to enter each subject into the IWRS. Each subject will be assigned an unique sequential 4-digit subject number through the IWRS (0001, 0002, 0003, etc.). This subject number must not be reused for any other participant in the study. Patients will maintain their subject number assigned at screening throughout the trial.

After confirming patient eligibility, registering a subject for Baseline will trigger a container number for the study medication. The study drug will be dispensed at baseline and as needed at the monthly study visits.

7.2.2 Selection and Timing of Dose and Administration

Study medication (rimegepant) will be assigned via the IWRS. There are no dose adjustments in this study and patients will receive 30 tablets of rimegepant in a bottle. Patients will be dispensed study medication at the Baseline Visit, and the patients in the 2-8 and 9-14 moderate to severe migraines per month groups will be instructed that they can take the one tablet of study medication per calendar day at the onset of a migraine of mild to severe intensity. Patients in the in the 2-8 and 9-14 moderate to severe migraines per month groups will dose for up to 52 weeks.

Patients in the 4-14 moderate to severe migraine group will also be dispensed study medication at the Baseline Visit and will be instructed to dose with one rimegepant tablet every other calendar day, regardless of whether they have a migraine on that day or not. If the patients in this group have a migraine (mild to severe intensity) on a non-dosing day, they may take a rimegepant tablet, for a maximum of one tablet per calendar day. Patients in the 4-14 moderate to severe migraines per month group will dose for up to 12 weeks.

Dosing of study medication is not to occur until after eligibility is confirmed based on the subject's baseline laboratory tests.

7.2.3 Dose Modifications

There will be no dose adjustments in this study.

7.2.4 Dose Interruptions

If a patient experiences an AE that requires interruption in study medication, the investigator should consult with the Sponsor medical monitor to evaluate the need for any additional tests prior to re-starting study medication.

7.3 Blinding and Unblinding

Not applicable.

7.4 Treatment Compliance

Responsible study personnel will dispense the study drug. Patients should finish a bottle of study medication before starting a new bottle. Accountability and compliance verification should be documented in the patient's study records.

Patients must be counseled on the importance of taking the study drug as directed (see Section 7.2.2). Treatment compliance, review of study medication doses reported in the eDiary and through review of returned study medication, should be assessed by site staff at each study visit. Discrepancies between doses reported in the eDiary, review of study medication and information provided by patient must be documented in the source record. Incorrect or missing dosing data and migraine data that are reported in the eDiary will be corrected through either a Data Clarification Record or a Medication Reconciliation Form. Investigators, should inform study participants that involuntary termination from the study will occur in cases where non-compliance is identified. Study staff should contact a patient in between the monthly study visits if the patient demonstrates non-compliance with the eDiary and document the contact in the source, to identify potential lost to follow up patients as early as possible.

Investigators must monitor patients for possible cases of abuse of study medication (patients taking study drug for non-therapeutic purposes, e.g. for psychoactive effects such as high or euphoria). Investigators should also assess study drug accountability discrepancies (e.g. missing study medication, loss of drug, or non-compliance cases in which more study medication was used, as compared to expected). Investigators should obtain more information and explanation from patients when there are study drug accountability discrepancies. See Section 8.1.1.

Cases of potential study medication abuse or overdose (including cases of non-compliance with study medication dosing instructions or patients who discontinue treatment without returning study medication) should be documented in the source record and reported as an AE or SAE as appropriate. Dosing errors (e.g. accidentally taking 2 tablets in one calendar day) should be reported as deviations.

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 BHV 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 patient or clinical investigation patient 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 relate to the investigational product.

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

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)

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

- Death
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received 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 (see Section 8.1.5)
- Abuse or Overdose of medication
  - Potential study medication abuse (including cases of excessive non-compliance with study medication dosing instructions or patients who discontinue treatment without returning study medication) should be documented in the source record and reported as an AE or SAE as appropriate. Investigators must monitor patients for possible cases of abuse of study medication (patients taking study drug for non-therapeutic purposes, e.g. for psychoactive effects such as high or euphoria). Investigators should obtain more information and explanation from patients when there are study drug accountability discrepancies
  - Potential study medication overdose is defined in Section 8.1.3

Definition of Terms

Mild: Is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: Is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.

Severe: Interrupts usual activities of daily living, significantly affects clinical status, or may required intensive therapeutic intervention.

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 serious 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 patient’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 up to and including the EOT 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.

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, must be reported to BHV (or designee) within 24 hours of the site's knowledge of the event. SAEs must be recorded in the EDC system on the AE and SAE electronic Case Report Form (eCRF). If the site cannot access the EDC to report the SAE within the required timeframe, the SAE should be reported using paper forms, which should be CCI [redacted]

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)

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 to BHV (or designee) using the same procedure used for the transmission of the initial SAE.

All SAEs should be followed to resolution or stabilization.

8.1.3 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both **excessive** and **medically important**.

All occurrences of overdose (suspected or confirmed) 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 treatments

administered.

Asymptomatic dosing errors (e.g. accidentally taking 2 tablets in one calendar day) should be reported as deviations.

8.1.4 Pregnancy

If, following the baseline visit, it is subsequently discovered that a study patient is pregnant or may have been pregnant at the time of the investigational produce 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 patient safety). Protocol-required procedures for the study discontinued and the follow-up must be performed on the patient unless contraindicated by the pregnancy (i.e., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the Biohaven (or designee) Medical Monitor of the event and complete the Pregnancy Form within 24 hours and in accordance with SAE reporting procedures as described in Section 8.1.2. The pregnancy should be reported using paper forms, which should be faxed to CCI [redacted]

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

AND

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

AND

3. No other immediately apparent possible causes of ALT or AST 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 instruction and whether the patient must discontinue from the trial and 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 initiation of study drug. Non-serious AE information should also be collected from the start of a placebo lead-in phase or other observational period intended to establish a baseline status for a patient.

Non-serious adverse events should be followed until conclusion or stabilization, ore 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 patient to have the study drug discontinued or interrupted;

3. Any laboratory abnormality that required the patient 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 a baseline value to be evaluable for endpoints based on values and changes from baseline 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.

9.2 Sample Size

With a sample size of roughly 2000 subjects, and with no events observed, the upper bound of a one-sided, 95% confidence interval for zero observations is roughly 0.0015. Hence, this sample size is large enough to rule out adverse events that occur at rates greater than 15 cases per 10,000 patients.

This study has a subpopulation of approximately 800 subjects with more frequent migraines that is expected to have a greater exposure to the study drug. With this sample size, and no events observed, the upper bound of a one-sided, 95% confidence interval for zero observations is roughly 0.00375. Hence, this sample size is large enough to rule out adverse events that occur at rates greater than 37.5 cases per 10,000 patients.

9.3 Statistical Methods

9.3.1 Primary Endpoint(s)

The investigators will determine the intensity of adverse events (AEs) and the relationship of AEs to study therapy. The investigators' terms will be coded and grouped by system organ class using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) available to the analyst. AEs will be presented by system organ class and preferred term. If a subject had an adverse event with different intensities over time, then only the greatest intensity will be reported. Tabulations will be made for adverse events that occur in at least 5% of

treated subjects, serious adverse events and adverse events leading to discontinuation. Other safety analyses will be described in the statistical analysis plan.

Laboratory abnormalities will be identified from on-treatment laboratory data using a pre-defined list of clinically significant abnormalities. The number of unique subjects with each abnormality will be tabulated.

9.3.2 Secondary Endpoint(s)

The frequency of subjects that have confirmed values of ALT or AST that exceed 3x the ULN concurrently with confirmed total bilirubin that exceeds 2x the ULN will be tabulated and presented with descriptive statistics and exact confidence intervals.

Both hepatic related AEs and hepatic related AEs leading to discontinuation will be summarized in a manner similar to that described for the primary endpoint.

9.3.3 Demographic and Baseline Characteristics

Tabulations of demographic and baseline characteristics are made for treated subjects. A separate set of tabulations will be made for subjects enrolled but not treated.

9.4 Interim Analysis

This is an open label study, single-arm, study designed to evaluate the safety and tolerability of rimegepant. As such, safety monitoring the primary concern. There is little concern, or opportunity, for inflation of type I (false-positive) error. During the course of the study laboratory, safety and exposure data will be monitored on an on-going basis. Summaries of these data will be produced roughly every 2 months for review by the sponsor and CRO. In addition, data may be locked, analyses conducted, and reports produced as required to support safety monitoring, administrative concerns, and regulatory requirements. A clinical study report will be produced after last patient last visit.

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 patient 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 Biohaven (or designee) immediately. A Serious breach is a breach of the conditions and principles of GCP in connection with the stud or protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the patients 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., lose of medical licensure, debarment).

10.2 Data and Safety Monitoring Committee

This study will not make use of a Data Safety Monitoring Committee (DMC). The study medication rimegepant has been tested and found to be well tolerated. Safety will be closely monitored via oversight by the investigators, Sponsor and CRO/designee. Summaries of LFTs and AEs will be reviewed roughly every 2 months by Sponsor/CRO.

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 patients, or, in those situations where consent cannot be given by patients, 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 patient's legal guardian or legally acceptable representative, and the patient subsequently becomes capable of making and communicating their informed consent during the study, then the consent must additionally be obtained from the patient.

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

The rights, safety, and well-being of study patients 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 patient. 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 patients 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 patient
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 patient 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

PPD

15.2 APPENDIX 2 - 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 3 - 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 potent CYP3A inhibitors is prohibited. Individual drug labels should be reviewed for specific information on propensity to inhibit CYP3A4 for a specific compound.

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 potent CYP3A inducers is prohibited. Individual product labels should be reviewed for specific information on propensity to induce CYP3A4 for a specific compound.

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/

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