DRUG:	BHV-3000 (rimegepant)
STUDY NUMBER(S):	BHV3000-305
PROTOCOL(S) TITLE:	BHV3000-305: A Phase 2/3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Rimegepant in Migraine Prevention
IND NUMBER:	109886
SPONSOR:	Biohaven Pharmaceuticals, Inc.
ORIGINAL PROTOCOL DATE:	27 July 2018
VERSION NUMBER:	V09
VERSION DATE:	25 August 2020

NCT Number: NCT03732638

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: A Phase 2/3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Rimegepant in Migraine Prevention

Study No: BHV3000-305

Original Protocol Date: 27 July 2018

Protocol Version No: V09 (Amendment 08)

Protocol Version Date: 25 August 2020

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.

SUMMARY OF CHANGES

Change	Section(s) Affected	Summary *(changes are noted in bold)*
Allow for Study Medication to be shipped to a subject due to COVID-19 Pandemic	Section 4.3 / Table 2 / Footnote 6	Original Wording: [6] Subjects should finish a bottle of study medication before starting a new bottle. Study drug will be dispensed at monthly (every 4 weeks) study visits, as needed. Unscheduled visits to dispense study medication may be scheduled as needed. Updated Wording: [6] Subjects should finish a bottle of study medication before starting a new bottle. Study drug will be dispensed at monthly (every 4 weeks) study visits, as needed. Unscheduled visits to dispense study medication may be scheduled as needed. **Due to the COVID-19 Pandemic, study medication may be shipped to a subject, with up to an 8-week supply. Proper documentation must be maintained in the subject's source records including shipping vendor, tracking number, confirmation of receipt by subject, and all other relevant information.** Rationale: This change was included to allow flexibility in cases where the COVID-19 Pandemic impacts study visits.
Allow for Remote Visits (ex: Telephone, Telemedicine) due to COVID-19 Pandemic	Section 4.3 / Table 2 / Footnote 10	Original Wording: [10] While on-study, all visit windows are used for scheduling purposes and all efforts should be made to return subjects to the 28-day schedule if scheduling changes are made at any previous visit(s). Updated Wording: [10] While on-study, all visit windows are used for scheduling purposes and all efforts should be made to return subjects to the 28-day schedule if scheduling changes are made at any previous visit(s). **Due to the COVID-19 Pandemic, visits may be conducted remotely (ex: telephone, telemedicine) and must be documented within the source records as being conducted remotely. All procedures not able to be completed due to a visit being conducted remotely must be**

		reported as a protocol deviation and can be performed at the next visit, where appropriate to do so based on subject presentation. In cases where a Week 64 / End of Treatment (EOT) visit occurs remotely in order to be completed during the protocol required window and due to the COVID-19 Pandemic, the subject should return to the site within the 8 Week Follow-up Safety Visit timeframe (8 weeks from last dose, -2 to +14 days), to complete all procedures that weren't able to be completed remotely. Procedures completed at the Week 64 / EOT Remote Visit do not need to be repeated. Rationale: This change was included to allow flexibility in cases where the COVID-19 Pandemic impacts study visits.
Allow for Remote Visits (ex: Telephone, Telemedicine) due to COVID-19 Pandemic	Section 4.3.3 / Open-label Extension Phase (52 weeks)	New wording: **Due to the COVID-19 Pandemic, visits may be conducted remotely (ex: telephone, telemedicine) and must be documented within the source records as being conducted remotely. All procedures not able to be completed due to a visit being conducted remotely must be reported as a protocol deviation and can be performed at the next visit, where appropriate to do so based on subject presentation.**
Allow for flexibility and to ensure completion of the Week 64 visit due to visits being impacted by the COVID-19 Pandemic	Section 4.3.4 / End of Treatment (Week 64)	Original Wording: Subjects will return to the study at the end of Week 64 (±3 days), or at end of treatment for early discontinuations, for review of the electronic diary, assessment of medication compliance, assessment of tolerability and safety (including vital signs, laboratory tests, and electrocardiography) (Table 2). Subjects will return the unused study medication and electronic subject diary to the study site. Subjects who do not complete the Double-blind, Treatment Phase and/or do not enter or complete the Open-label, Extension Phase should complete the End of Treatment Visit, 2-Week Follow up Safety Visit and 8-Week Follow up Safety Visit. Updated Wording:

		Subjects will return to the study at the end of Week 64 (±3 days), or at end of treatment for early discontinuations, for review of the electronic diary, assessment of medication compliance, assessment of tolerability and safety (including vital signs, laboratory tests, and electrocardiography) (Table 2). **In cases where a Week 64 / End of Treatment (EOT) visit occurs remotely in order to be completed during the protocol required window and due to the COVID-19 Pandemic, the subject should return to the site within the 8 Week Follow-up Safety Visit timeframe (8 weeks from last dose, -2 to +14 days), to complete all procedures that weren't able to be completed remotely. Procedures completed at the Week 64 / EOT Remote Visit do not need to be repeated.** Subjects **must** return the unused study medication and electronic subject diary to the study site. Subjects who do not complete the Double-blind, Treatment Phase and/or do not enter or complete the Open-label, Extension Phase should complete the End of Treatment Visit, 2-Week Follow up Safety Visit and 8-Week Follow up Safety Visit. Rationale: This change was included to allow flexibility in cases where the COVID-19 Pandemic impacts study visits and reinforces requirement for unused study medication to be returned.
Allow for flexibility and to ensure completion of the 8-Week Follow-up Safety Labs due to visits being impacted by the COVID-19 Pandemic	Synopsis / Study Schematic Section 4.2 / Figure 1 / Study Schematic Section 4.3 / Table 2 / Header titled: 8-Week Follow-up Safety Visit (8 weeks ±2 days after EOT visit) Section 4.3.6 / 8-Week Follow up Safety Visit	<u>Original Wording:</u> 8-Week Follow-up Safety Visit (8 weeks ±2 days after EOT visit) <u>Updated Wording:</u> 8-Week Follow-up Safety Visit (**8 weeks (-2 to +14 days)** after EOT visit) Rationale: This change was included to allow flexibility to the final safety follow-up visit in cases where the COVID-19 Pandemic impacts this visit, requiring it to be conducted remotely at the 8-week follow-up timepoint. Subjects should be contacted at the 8-week follow-up timepoint to collect safety information, per protocol, and then should return to the office

		within 2 weeks to have the laboratory tests completed. Tests may also be performed locally, if needed, in cases where a study site is not open to laboratory test collection.
Corrected Typographical Errors and Made Wording Clarifications	Protocol Version 8	Corrected typographical errors and clarified wording throughout the document

BHV3000-305
BHV3000-305: A Phase 2/3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Rimegepant in Migraine Prevention

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 Pharmaceuticals, Inc., 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 Pharmaceuticals, Inc.

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 Pharmaceuticals, Inc. 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 Phase 2/3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Rimegepant in Migraine Prevention

Rationale: Rimegepant is being developed for the treatment of migraine. Effectiveness for the acute treatment of migraine was initially 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] Efficacy was confirmed in two pivotal Phase 3 trials using the current registrational co-primary endpoints of Pain Freedom and Freedom from Most Bothersome Symptom at 2 hours after dosing.

This study is being conducted to evaluate the efficacy, safety, and tolerability of rimegepant for the prevention of migraine.

Target Population: The study will recruit male and female subjects, 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.[2] Per their own report, subjects must have migraine onset prior to age 50, migraine attacks that last 4-72 hours (if not treated) and have had, 4-18 ***migraine attacks*** of moderate to severe intensity per 4 weeks period within the 12 weeks prior to the screening visit. After a 28-day observation period of standard of care, up to approximately 800 eligible subjects will be randomized to receive rimegepant or placebo, with dosing on an every other day (EOD) dosing schedule. At the completion of the 12-week double-blind, treatment phase, subjects will be evaluated for entry into the 52-week open label, extension phase if laboratory test results meet protocol entry criteria (Table 2).

Number of Subjects: Approximately 1500 subjects will be screened to randomize up to approximately 800 subjects to rimegepant or placebo. It is estimated that approximately 675 subjects will be entered into the open-label extension phase.

Objectives:

Primary Objective:

- To compare the efficacy of rimegepant to placebo as a preventive treatment for migraine, as measured by the reduction from baseline in the mean number of migraine days per month in the last 4 weeks of the double-blind treatment phase. (A month is defined as 4 weeks for the purpose of this protocol.)

Secondary Objectives:

- To compare the efficacy of rimegepant to placebo on the proportion of subjects that have at least a 50% reduction from baseline in the mean number of moderate to severe migraine days per month in the last 4 weeks of the double-blind treatment phase.

- To compare the efficacy of rimegepant to placebo on the reduction from baseline in the mean number of migraine days per month over the entire course of the double-blind treatment phase.

- To compare the frequency of use of rescue medications between rimegepant and placebo in the last 4 weeks of the double-blind treatment phase.

- To compare the efficacy of rimegepant to placebo on the reduction from baseline in the mean number of migraine days per month in the first 4 weeks of the double-blind treatment phase.

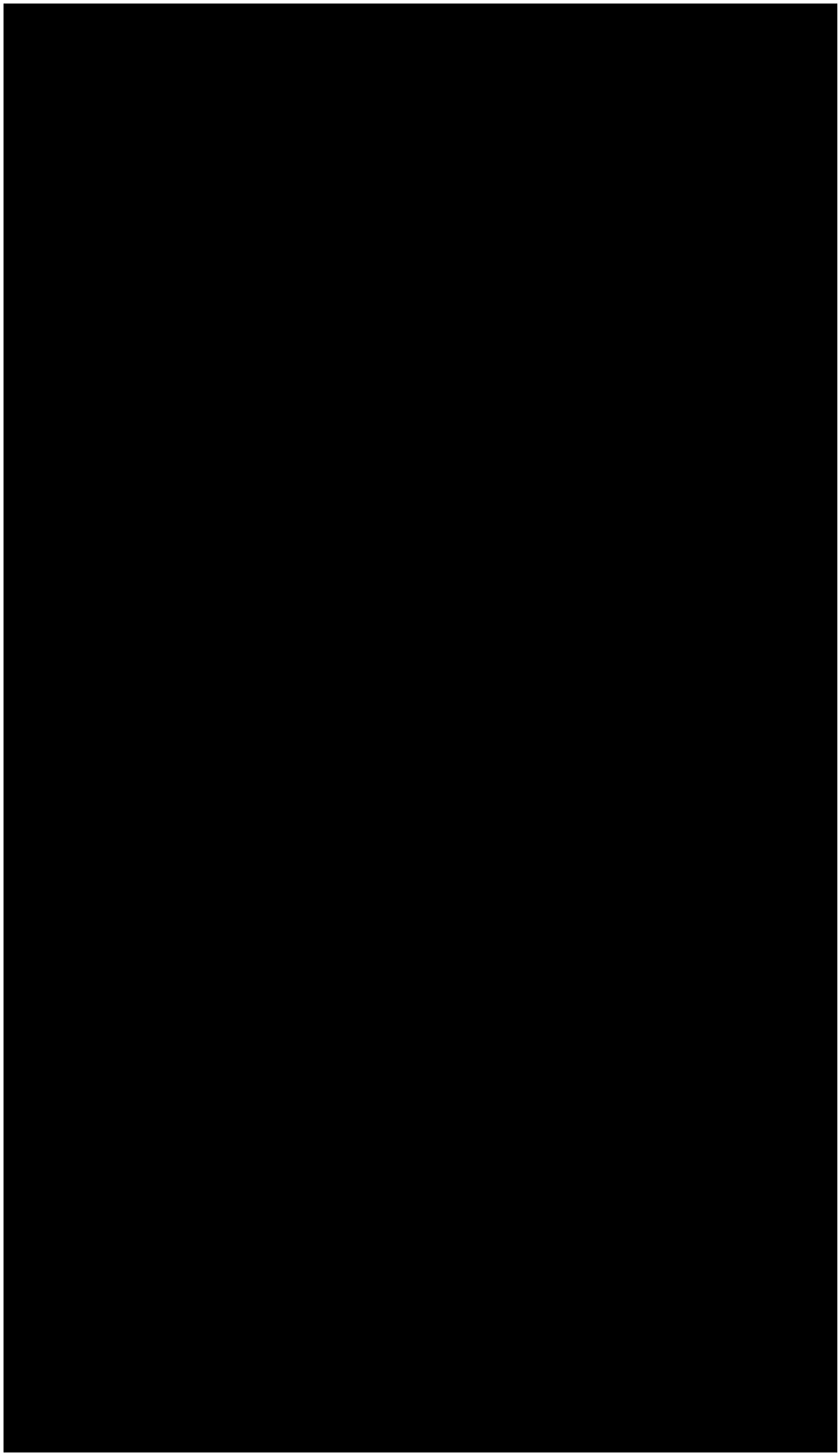
- To evaluate the safety and tolerability of rimegepant.

- 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 of hepatic-related adverse events (AEs) and the frequency of hepatic-related treatment discontinuations in subjects treated with rimegepant.

- To compare the change from baseline in the Migraine-Specific Quality-of-Life Questionnaire v 2.1 (MSQ) role function - restrictive domain score at Week 12 of the double-blind treatment phase between rimegepant and placebo.

- To compare the change from baseline in the Migraine Disability Assessment (MIDAS) total score at Week 12 of the double-blind treatment phase between rimegepant and placebo.



Study Design: This is a multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of rimegepant in migraine prevention with an open-label extension phase.

The Screening phase includes a screening visit and a 28-day Observation Period. For subjects to be eligible for the study, they must report having had 4-18 ***migraine attacks*** of moderate to severe intensity per month in the 3 months prior to the Screening Visit, and at least 6 ***migraine days*** and no more than 18 ***headache days*** during the 28-day Observation Period which will be documented in the eDiary.

Upon completion of the Screening visit, subjects will be provided an electronic diary (eDiary) to document each day of the 28-day Observation Period if a migraine occurred and the migraine intensity. Subjects will record the standard of care migraine treatment received on a paper diary and female subjects will record their menstrual period information on a paper log. After completing the 28-day Observation Period, the subject will return to the clinic with both diaries for the Baseline Visit.

Subjects will have blood drawn for baseline lab profiles at the Pre-Randomization Lab Visit; this visit must occur within 96 hours (4 days) of the Baseline Visit. Sites are encouraged to complete this visit within 96 hours (4 days) of the Baseline Visit, however, if scheduling

challenges arise, site staff may use an additional +2 day window for this visit to occur within 144 hours (or 4 days, +2 days). Subjects will then return for the Baseline (Randomization) Visit.

At the Baseline Visit, eligibility for continued participation in the study will be assessed before randomization occurs and before study medication is dispensed. Subjects will be instructed that they must take one tablet of blinded study drug every other calendar day. If subjects have a migraine during the double-blind phase of the study, if needed, they may treat the migraine with their standard of care medication and continue to take study medication on their regular schedule (scheduled dosing days only).

At the completion of the 12-week double-blind, treatment phase, subjects will be evaluated for entry into the 52-week open-label, extension phase following laboratory results within acceptable ranges per protocol (Table 2). During the open-label, extension phase, subjects will be instructed that they must take one tablet of study medication every other calendar day. If subjects have a migraine on a day that they are not scheduled to dose with study drug, they may take one tablet of rimegepant on that calendar day to treat a migraine. Therefore, during the open-label, extension phase, subjects can take a maximum of one tablet of study drug per calendar day for this 52-week period.

Subjects are required to record their migraine occurrence and severity and all study medication doses in the eDiary. Subjects are also required to record the rescue medication taken on a paper diary and female subjects will record their menstrual period information on a paper log. Subjects will also use the eDiary to complete the Preference of Medication (PoM) and the Satisfaction with Medication (SM) scales at specified study timepoints.

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

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 subject, assessment of study medication compliance, monitoring of tolerability and safety (including vital signs, laboratory tests, and electrocardiography).

Study visits will occur at Screening (Enrollment), Pre-Randomization Lab Visit which should occur within 96 hours (+48 hours) of the Baseline Visit, Baseline (Randomization), Week 2, Week 4, Week 8, and Week 12. At the completion of the 12-week double-blind, treatment phase, subjects will be evaluated for entry into the 52-week open-label, extension phase following laboratory results within acceptable ranges per protocol (Table 2). Visits occur at Week 14, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64 / End of Treatment (EOT). Subjects will return to the study site at the end of Week 64 for the End of Treatment (EOT) Visit. There is a Follow-up Visit 14 days after the EOT Visit and 8 weeks after the EOT visit for assessment of LFTs. Subjects who do not complete the Double-blind, Treatment Phase and/or do not enter or complete the Open-label, Extension Phase should complete the End of Treatment Visit, the 2-Week Follow-up Safety Visit, and the 8-Week Follow-up Safety 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 potential DILI events should be reported as a serious adverse event (SAE). See Section 8.1.5 Potential Drug Induced Liver Injury (DILI).

Primary Endpoint:

Change from baseline (observation period) in the mean number of migraine days per month in the last four weeks (Weeks 9 to 12) of the double-blind treatment phase.

Secondary Endpoints:

Achievement of at least a 50% reduction from baseline in the mean number of moderate to severe migraine days per month in the last 4 weeks of the double-blind treatment phase.

Change from baseline in the mean number of migraine days per month over the entire double-blind treatment phase (Weeks 1 to 12).

The mean number of rescue medication days per month in the last 4 weeks of the double-blind treatment phase. Rescue medications include the rescue medications defined in this protocol (please refer to Section 5.5)

Change from baseline in the mean number of migraine days per month in the first 4 weeks (Weeks 1 through 4) of the double-blind treatment phase.

The frequency of unique subjects with adverse events, serious adverse events, adverse events leading to discontinuation and clinically significant laboratory test abnormalities from case report forms and clinical laboratory evaluations.

The frequency of unique subjects with AST or ALT elevations > 3x ULN, concurrently with bilirubin elevations > 2x ULN.

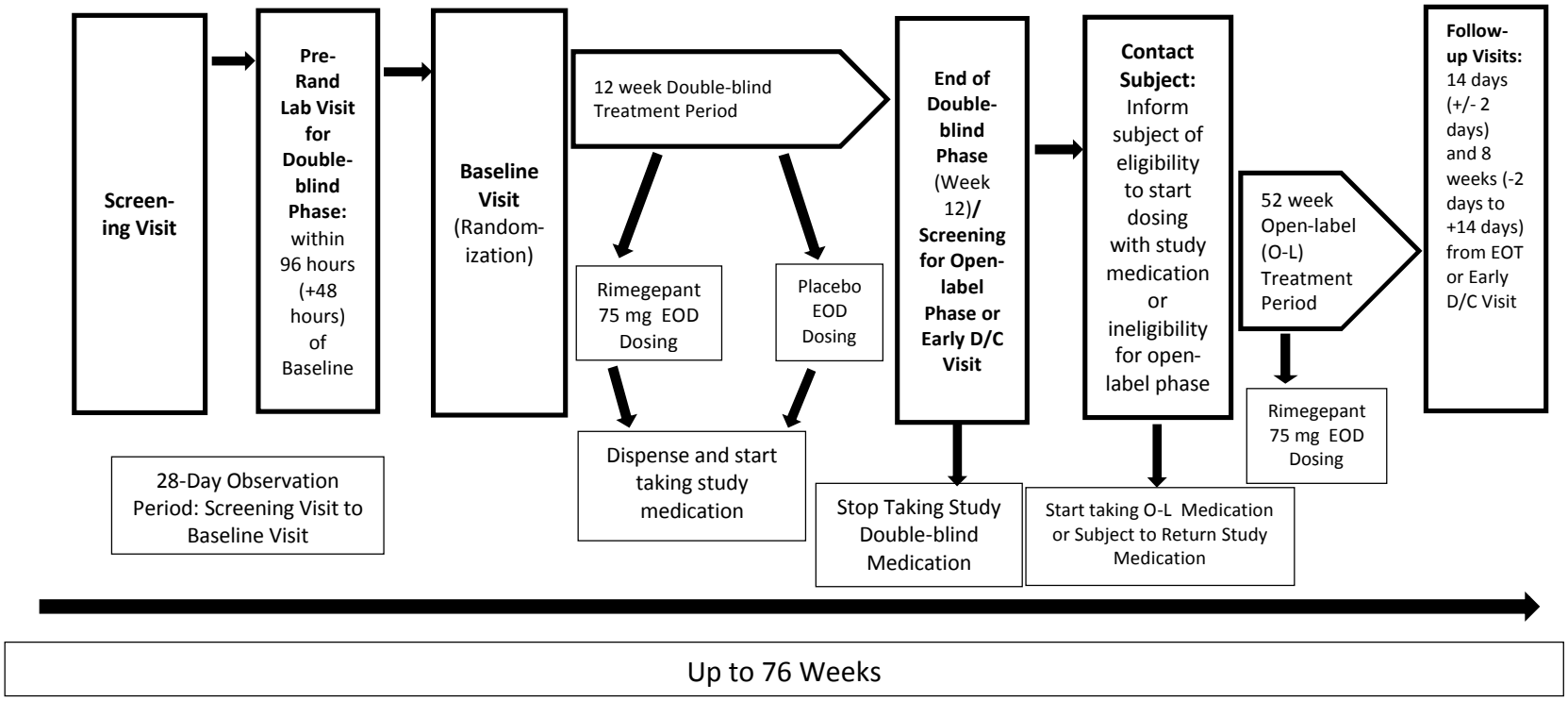
The frequency of unique subjects with hepatic-related adverse events and hepatic-related adverse events leading to treatment discontinuation from case report forms.

The mean change from baseline in the MSQ role function - restrictive domain score at Week 12 of the double-blind treatment phase.

The mean change from baseline in MIDAS total score at Week 12 of the double-blind treatment phase.

STUDY SCHEMATIC

Up to 12 weeks of double-blind treatment with every other day dosing, followed by up to 52 weeks of open-label treatment with at least every other day dosing



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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
bid	Twice Daily
BP	Blood Pressure
BUN	Blood Urea Nitrogen
[redacted]	[redacted]
C_{max}	Maximum Plasma Concentration
CONMED	Concomitant Medication
CRF	Case Report Form
CRPS	Complex Regional Pain Syndrome
CTCAE	Common Terminology Criteria for Adverse Events
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
EDC	Electronic Data Capture
EOD	Every Other Day
FAS	Full analysis set
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
[redacted]	[redacted]
MBq	Megabecquerel
MDZ	Midazolam
mg	Milligram
MIDAS	Migraine Disability Assessment
MSQ	Migraine-Specific Quality-of-Life Questionnaire

min	Minute
mmHg	Millimeters Mercury
NOEL	No Observed Effect Level
NOAEL	No Observed Adverse Event Level
O-L	Open-label
PK	Pharmacokinetic
PO	By Mouth, Orally
[redacted]	
QD	Once Daily
QTc	Interval between Q-wave and T-wave in the cardiac cycle
SAE	Serious Adverse Event
[redacted]	
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

Migraine is a common and debilitating neurological disorder that affects approximately 15% of the adult population. It is characterized by moderate-to-severe episodic unilateral pulsating headaches that last for 4 to 72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea and/or photophobia and phonophobia.[1] BHV-3000 (rimegepant) is a calcitonin gene-related peptide (CGRP) receptor antagonist in development for the acute treatment of migraine. The CGRP receptor is located within pain-signaling pathways, intracranial arteries and mast cells and its activation is thought to play a causal role in migraine pathophysiology. For example, research and clinical studies have shown: serum levels of CGRP are elevated during migraine attacks, infusion of intravenous CGRP produces persistent pain in migraine sufferers and non-migraine sufferers, and treatment with anti-migraine drugs normalize CGRP levels. Additionally, multiple clinical studies show that small molecule CGRP receptor antagonists, which inhibit the binding of endogenous CGRP to CGRP receptors, are effective in aborting migraine attacks. Treatment with a CGRP receptor antagonist is believed to relieve migraine through the possible mechanisms of 1) blocking neurogenic inflammation, 2) decreasing artery dilation, and 3) inhibiting pain transmission. There is widespread agreement that this new approach avoids the cardiovascular effects produced by active vasoconstriction associated with the current standard triptan therapy (non-selective 5-HT1B/1D agonists (e.g., sumatriptan [Imitrex™])).

1.2 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 Clinical Adverse Event Profile

Rimegepant appears to be generally safe and well tolerated in humans when given as single oral doses up to the maximum dose of 1500 mg and multiple oral doses up to the maximum daily dose of 600 mg for 14 days. The ongoing BHV3000-201 study is a Phase 2/3, 52-week, open-label, safety study with rimegepant 75 mg that is designed to enroll approximately 2000 subjects to receive rimegepant up to once daily. Please refer to the 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

The demonstrated efficacy of rimegepant in the three pivotal Phase 3 registrational trials in the acute treatment of migraine and the safety profile observed to date in the Phase 2/3 BHV3000-201 long-term open-label safety study with up to daily dosing for as long as 1 year suggest that rimegepant may have an important role in the treatment of migraine.

This study is being conducted to evaluate the efficacy, safety, and tolerability of rimegepant for the prevention of migraine. It will also further define the safety profile of rimegepant administration for as long as 64 weeks. Approximately 800 subjects will dose with blinded study drug at least every other day for a period of approximately 12 weeks, followed by an additional 52 weeks with open-label rimegepant with scheduled dosing every other day as well. During the open-label portion of the study, on days without scheduled rimegepant dosing, subjects may take up to 1 tablet of rimegepant per calendar day as needed for acute treatment of migraine.

1.4.1 Study Design Rationale

This is a 12-week multicenter, randomized, double-blind, placebo controlled evaluation of the safety and efficacy of rimegepant 75 mg tablet taken every other day for the prevention of migraine with a 52-week open-label extension phase. Up to approximately 800 subjects will be randomized and assigned treatment in the double-blind phase of the study; it is estimated that approximately 675 subjects will enter the open-label phase of the study. During the double-blind phase, subjects will be instructed that they must take one tablet of blinded study drug every other calendar day. If subjects have a migraine during the double-blind phase of the study, if needed, they may treat the migraine with their standard of care medication and continue to take study medication on their regular schedule (scheduled dosing days only).

During the open-label phase of the study, subjects will be required to take one tablet of rimegepant every other calendar day. However, if subjects have a migraine on a day that they are not scheduled to dose with rimegepant, they may take 1 tablet of rimegepant on that calendar day to treat the migraine. Dosing with more than 1 tablet of study medication per calendar day is not permitted. Therefore, subjects can take a maximum of one tablet of study drug per calendar day for the 52 weeks of the open-label phase.

The study will randomize approximately 800 subjects and it is expected that approximately 675 subjects will enter the open-label phase of the study. During the double-blind phase, the subjects will be randomized in a 1:1 ratio to the rimegepant or placebo treatment groups, stratified by current use of prophylactic migraine medications (yes or no).

1.4.2 Dose Selection

The Phase 2b dose-ranging study CN170003 established that rimegepant 75 mg is the minimum effective dose for the acute treatment of migraine. The three Phase 3 studies BHV3000-301, BHV3000-302, and BHV3000-303 confirmed this efficacy using the current registrational endpoints for acute treatment of migraine. In addition, several CGRP antagonists have been shown to be effective for the prevention of migraine. This observation and the flat dose-response with rimegepant and other CGRP receptor antagonists suggest that rimegepant 75 mg every other day (EOD) may be an effective dose for the prevention of migraine. The pharmacokinetic profile of rimegepant supports the dosing schedule of this protocol with up to daily dosing.

1.5 Research Hypothesis

Rimegepant is safe and effective treatment for the prevention of migraine.

2 STUDY OBJECTIVES

2.1 Primary

- To compare the efficacy of rimegepant to placebo as a preventive treatment for migraine, as measured by the reduction from baseline in the mean number of migraine days per month in the last four weeks of the double-blind treatment phase. (A month is defined as 4 weeks for the purpose of this protocol).

2.2 Secondary

- To compare the efficacy of rimegepant to placebo on the proportion of subjects that have at least a 50% reduction from baseline in the mean number of moderate to severe migraine days per month in the last 4 weeks of the double-blind treatment phase.

- To compare the efficacy of rimegepant to placebo on the reduction from baseline in the mean number of migraine days per month over the entire course of the double-blind treatment phase.

- To compare the frequency of use of rescue medications between the rimegepant and placebo in the last 4 weeks of the double-blind treatment phase.

- To compare the efficacy of rimegepant to placebo on the reduction from baseline in the mean number of migraine days per month in the first 4 weeks of the double-blind treatment phase.

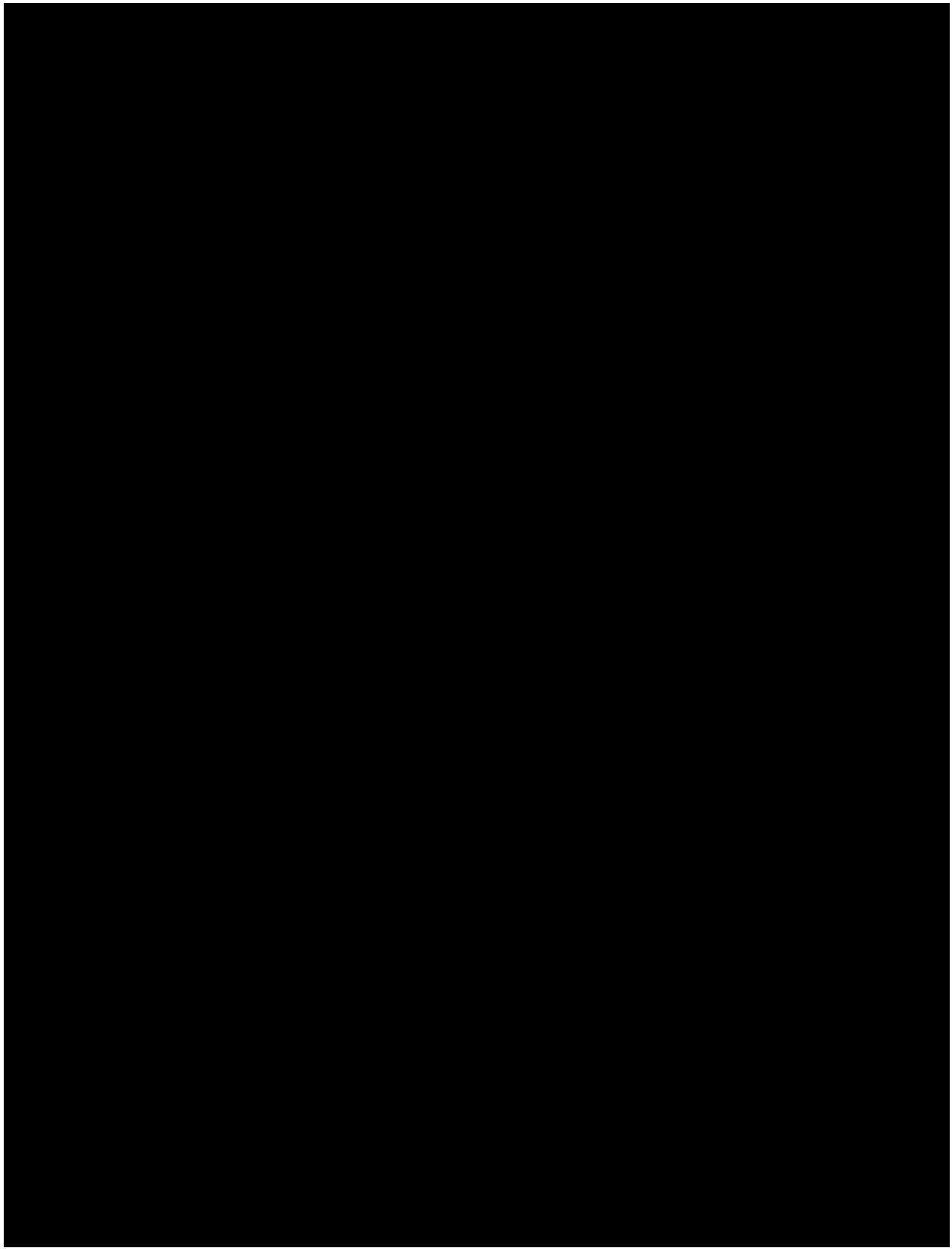
- To evaluate the safety and tolerability of rimegepant.

- 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 of hepatic-related adverse events and the frequency of hepatic-related treatment discontinuations in subjects treated with rimegepant.

- To compare the change from baseline in the Migraine-Specific Quality-of-Life Questionnaire v 2.1 (MSQ) role function - restrictive domain score at Week 12 of the double-blind treatment phase between rimegepant and placebo.

- To compare the change from baseline in the Migraine Disability Assessment (MIDAS) total score at Week 12 of the double-blind treatment phase between rimegepant and placebo.



3 STUDY ENDPOINTS

3.1 Primary

- Change from baseline (observation period) in the mean number of migraine days per month in the last 4 weeks (Weeks 9 through 12) of the double-blind treatment phase.

3.2 Secondary

- Achievement of at least a 50% reduction from baseline in the mean number of moderate to severe migraine days per month in the last 4 weeks of the double-blind treatment phase.
- Change from baseline in the mean number of migraine days per month over the entire double-blind treatment phase (Weeks 1 to 12).
- The mean number of rescue medication days per month in the last 4 weeks of the double-blind treatment phase. Rescue medications allowed in the 2 phases of this study are specified in Protocol Section 5.5.
- Change from baseline in the mean number of migraine days per month in the first 4 weeks (Weeks 1 through 4) of the double-blind treatment phase.
- The frequency of unique subjects with adverse events, serious adverse events, adverse events leading to discontinuation and clinically significant laboratory test abnormalities, from case report forms and clinical laboratory evaluations.
- The frequency of unique subjects with of AST or ALT elevations > 3x ULN, concurrently with bilirubin elevations > 2x ULN.
- The frequency of unique subjects with hepatic-related adverse events and hepatic-related adverse events leading to treatment discontinuation from case report forms.
- The mean change from baseline in the MSQ role function - restrictive domain score at Week 12 of the double-blind treatment phase.
- The mean change from baseline in the MIDAS total score at Week 12 of the double-blind treatment phase.

3.3 Measures of Interest

Not Applicable

3.4 Definition of Migraine Days

A Migraine Day is defined as any calendar day which the subject experiences a qualified migraine headache (onset, continuation or recurrence of the migraine headache). A qualified migraine headache is defined as a migraine with or without aura, lasting for ≥30 minutes, and meeting at least one of the following criteria (A and/or B):

A) ≥ 2 of the following pain features:

- Unilateral location,
- Pulsating quality (throbbing),
- Moderate or Severe pain intensity,
- Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)

B) ≥ 1 of the following associated symptoms:

- Nausea and/or Vomiting,
- Photophobia and phonophobia

During the double-blind, treatment phase, if the subject takes a migraine-specific medication (i.e. triptan or ergotamine) during aura or to treat a headache on a calendar day, then it will be counted as a migraine day regardless of the duration and pain features/associated symptoms. The use of study medication on non-scheduled dosing days is only permitted during the open-label, extension phase. ***Dosing with study medication on non-scheduled dosing days is not permitted during the double-blind, treatment phase***.

A moderate to severe migraine day is a migraine day with a migraine reported with moderate or severe pain intensity.

For the full definition of Migraine Days, please refer to Section 15.3 Appendix 3.

3.5 Definition of Headache Days

A Headache Day is any calendar day in which the subject experiences a qualified headache (initial onset, continuation, or recurrence of the headache). A qualified headache is defined as:

- A qualified migraine headache (including an aura-only event that is treated with acute migraine-specific medication), or
- A qualified non-migraine headache, which is a headache that lasts ≥ 30 minutes and is not a qualified migraine headache, or
- A headache of any duration for which acute headache treatment is administered.

4 STUDY PLAN

4.1 Study Design and Duration

This is a multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of rimegepant in migraine prevention with an open-label extension phase.

The Screening phase includes a screening visit and a 28-day Observation Period. For subjects to be eligible for the study, they must have reported having had 4-18 ***migraine attacks*** of moderate to severe intensity per month in the 3 months prior to the Screening Visit, and at least 6 ***migraine days*** and no more than 18 ***headache days*** during the 28-day Observation Period which will be documented in the eDiary.

Upon the completion of the screening visit, subjects will be provided an electronic diary (eDiary) to document each day of the 28-day Observation Period if a migraine occurred, the migraine intensity and if the migraine was treated. Subjects will record the standard of care migraine treatment received on a paper diary and female subjects will record their menstrual period information on a paper log. After completing the 28-day Observation Period, the subject will return to the clinic with both diaries for the Baseline Visit.

Subjects will have blood drawn for baseline lab profiles at the Pre-Randomization Lab Visit; this visit must occur within 96 hours (4 days) of the Baseline Visit. Sites are encouraged to complete this visit within 96 hours (4 days) of the Baseline Visit, however, if scheduling challenges arise, site staff may use an additional +2 day window for this visit to occur within 144 hours (or 4 days, +2 days). Subjects will then return for the Baseline (Randomization) Visit.

At the Baseline Visit, eligibility for continued participation in the study will be assessed before randomization occurs and study medication will be dispensed. Subjects will be instructed that they must take one tablet of blinded study drug every other calendar day. If subjects have a migraine during the double-blind phase of the study, if needed, they may treat the migraine with their standard of care medication and continue to take study medication on their regular schedule (scheduled dosing days only).

At the completion of the 12-week double-blind phase, subjects may be entered into the 52-week open-label phase following laboratory test results within acceptable ranges per protocol (Table 2). During the open-label, extension phase, subjects will be instructed that they must take one tablet of study medication every other calendar day. If subjects have a migraine on a day that they are not scheduled to dose with study drug, they may take 1 tablet of rimegepant on that calendar day to treat a migraine. During the open-label, extension phase, subjects can take a maximum of one tablet of study drug per calendar day for this 52-week period.

Subjects are required to record their migraine occurrence and severity and all study medication doses in the eDiary. Subjects are also required to record the rescue medication taken on a paper diary and female subjects will record their menstrual period information on a paper log. [redacted]

[redacted]

At select study visits, subjects will complete or will be administered the Migraine-Specific Quality-of-Life Questionnaire v 2.1 (MSQ v 2.1), the Migraine Disability Assessment (MIDAS), [redacted], and the Sheehan Suicidality Tracking Scale (S-STS) on paper forms.

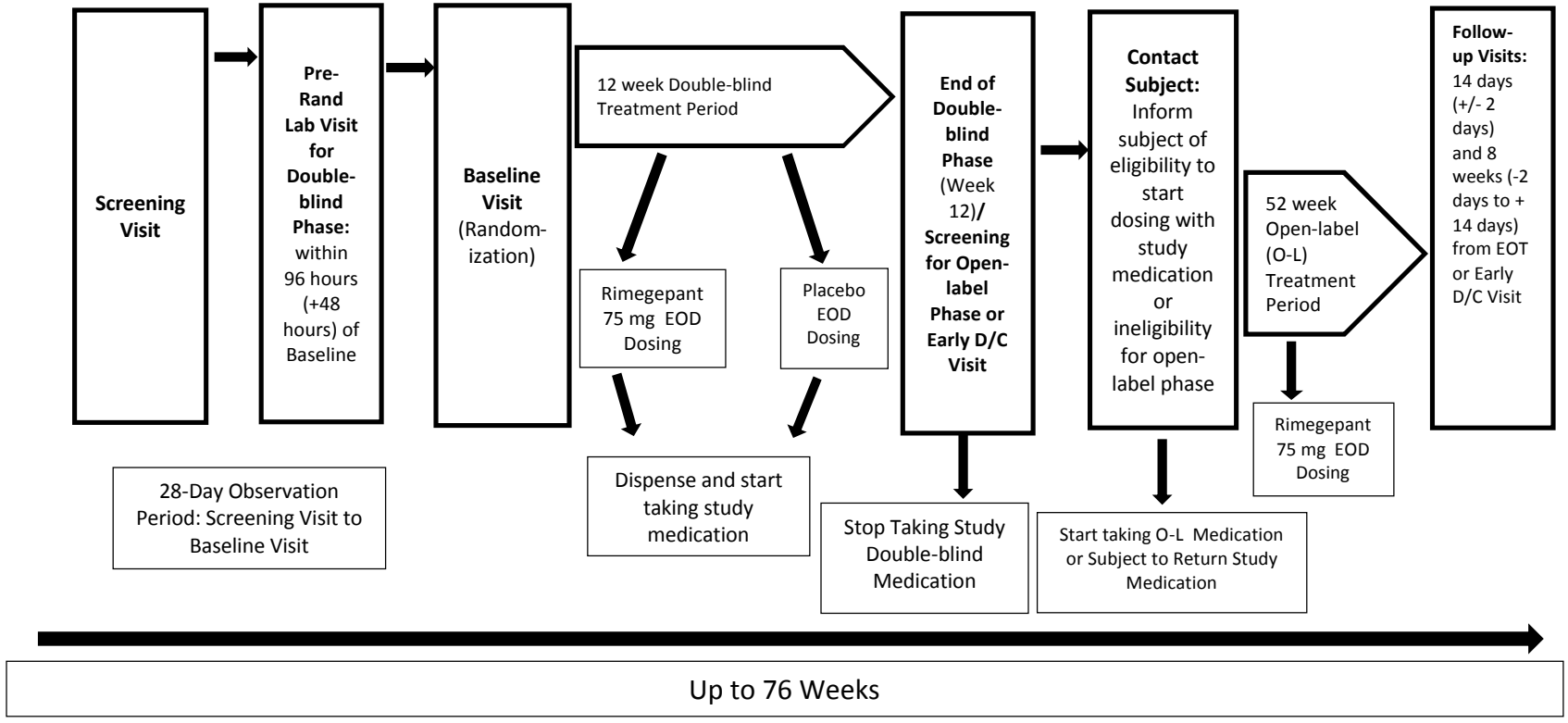
Additional assessments and visit schedule are outlined in the procedural table in Section 4.3. Procedures include study personnel review of the eDiary and paper diary with the subject, assessment of study medication compliance, monitoring of tolerability and safety (including vital signs, laboratory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

Study visits will occur at Screening (Enrollment), Pre-Randomization Lab Visit which must occur within 96 hours (+48 hours) of the Baseline Visit, Baseline (Randomization), Week 2, Week 4, Week 8, and Week 12. At the completion of the 12-week double-blind phase, Subjects may enter into the 52-week open-label phase if they continue to meet study entry criteria and laboratory test results are acceptable per protocol (See Exclusion Criterion 8 in Section 5.3) (Table 2). Visits occur at Week 14, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64 / End of Treatment (EOT). Subjects will return to the study site at the end of Week 64 for the End of Treatment (EOT) Visit. There is a Follow-up Visit 14 days after the EOT Visit and 8 weeks after the EOT visit for assessment of LFTs. Subjects who do not complete the Double-blind, Treatment Phase and/or do not enter or complete the Open-label, Extension Phase should complete the End of Treatment Visit, the 2-Week Follow-up Safety Visit, and the 8-Week Follow-up Safety 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 1. Up to 12 Weeks of Double-blind Treatment with Every Other Day Dosing, Followed by Up To 52 Weeks of Open-label Treatment with at Least Every Other Day (EOD) Dosing



4.3 Schedule of Assessments

Table 1. Schedule of Assessments – Double-Blind Treatment Phase[9, 10]

Procedure	**Screening Visit**	**Observation Period**[10] (28 days, + 3 days)	**Pre-Randomization Laboratory Visit:** must occur within 96 hours of Baseline (Randomization) Visit[11]	**Baseline (**Randomization) **Visit** (Day 1)	**Week 2** (Day 14 +/- 2 days)	**Week 4** (Day 28 +3 days)	**Weeks 8 (**Day 56) **and 12** (Day 84) (all visits + 3 days)
Eligibility Assessments							
Informed Consent	X						
[redacted]	X						
Inclusion/Exclusion Criteria	X			X			
Medical History	X						
Migraine History (signs/symptoms/prior treatment/frequency/intensity)	X						
Rescue Medication paper diary, Concomitant Medication paper diary and Menstrual Period paper log (female subjects)[1]	X	X	X	X	X	X	X
Randomize subject / IWRS[2]				X			
Safety Assessments							
Physical Examination	X			X		X	X
Vital Signs / Physical Measurements[3]	X			X		X	X

Procedure	**Screening Visit**	**Observation Period**[10] (28 days, + 3 days)	**Pre-Randomization Laboratory Visit:** must occur within 96 hours of Baseline (Randomization) Visit[11]	**Baseline (**Randomization) **Visit** (Day 1)	**Week 2** (Day 14 +/- 2 days)	**Week 4** (Day 28 +3 days)	**Weeks 8 (**Day 56) **and 12** (Day 84) (all visits + 3 days)
Clinical Safety Laboratory Testing	X			X		X	X
Liver Function Test (LFTs)	X		X	X	X	X	X
Lipid Panel				X			
ECG	X			X		X	
Urinalysis				X			
Urine Drug Screen for drugs of abuse	X						
FSH, if applicable, to determine WOCBP status	X						
Pregnancy Test	X (urine)		X (serum)	X (urine)		X (urine)	X (urine)
AE, SAE, and Concomitant Procedure assessment[4]	X		X	X	X	X	X
Sheehan Suicidality Tracking Scale	X			X	X	X	X
Clinical Drug Supplies / Study Supplies							
Dispense Study Medication[5]				X		X	X
Administer study medication[6]					X	X	X
Electronic Diary (eDiary) dispensed	X						

Procedure	**Screening Visit**	**Observation Period**[10] (28 days, + 3 days)	**Pre-Randomization Laboratory Visit:** must occur within 96 hours of Baseline (Randomization) Visit[11]	**Baseline (**Randomization) **Visit** (Day 1)	**Week 2** (Day 14 +/- 2 days)	**Week 4** (Day 28 +3 days)	**Weeks 8 (**Day 56) **and 12** (Day 84) (all visits + 3 days)
Enter use of study medication in eDiary				X	X	X	X
Return unused study medication to site for compliance check					X	X	X
eDiary returned / reviewed for completness[7]		X	X	X	X	X	X
Other Assessments							
Daily report of migraine occurrence and severity reported by subject in eDiary[8]		X	X	X	X	X	X
Migraine-Specific Quality-of-Life Questionnaire (MSQ) v 2.1				X			X (week 12 only)
[redacted]							[redacted]
[redacted]							[redacted]
[redacted]							[redacted]
Migraine Disability Assessment (MIDAS)				X			X (week 12 only)

[1] Concomitant medications, including prophylactic and standard of care migraine medications, taken during Observation Period and rescue medication taken during the Treatment Phase should be recorded in the subject's paper diary and reviewed by study personnel at each visit. Female subjects will also record menstrual period information on the paper diary which should be reviewed by study personnel at each visit.
[2] The actual baseline visit date should be used for IWRS enrollment date and eligibility date.

[3] Height measured at Screening Visit only. Weight, body temperature, respiratory rate, blood pressure, and heart rate will be collected at all timepoints where indicated. Sitting arterial systolic and diastolic blood pressure and radial artery pulse rate will be measured.
[4] SAEs, AEs, and Concomitant Procedures must be reported after subject signs informed consent. SAEs should be reported from signing of consent through the 8-week Follow up Safety Visit. Non-serious AEs should be reported from signing of consent through 2-Week Follow up Safety Visit.
[5] Subjects should finish a bottle of study medication before starting a new bottle. Study drug will be dispensed at monthly (every 4 weeks) study visits, as needed. Unscheduled visits to dispense study medication may be scheduled as needed. At the Week 12 Visit, the open-label study medication will be dispensed and subjects will be instructed not to begin taking rimegepant until confirmation from site staff pending lab results.
[6] Subjects must take their study medication every other day, regardless of whether or not they have a migraine. Subjects must report each tablet they take in the eDiary. Doses are not required to be taken in the office on days of a study visit, however dosing requirements and compliance should be discussed with subjects at all visits.
[7] The Observation Period to determine eligibility is 28 days +3 days**.** The "+3" days window is included for scheduling purposes only. Subjects with less than 24 completed eDiary reports during the Observation Period will not be considered for participation due to non-compliance with the eDiary. Subjects in the Double-blind, Treatment phase who demonstrate poor compliance will be discussed with the Sponsor and corrective training will be completed by the site with the subject.
[8] The electronic subject diary (eDiary) will be dispensed at the Screening Visit, after all Screening Procedures are completed. The subject will be trained on the use of the eDiary. The subject will use the eDiary every day during the Observation Period and Treatment Phase to report migraine occurrence, migraine severity and if the subject treated the migraine.
[9] Subjects who do not complete the Double-blind, Treatment Phase or do not enter the Open-label, Extension Phase should complete the End of Treatment Visit and 2-Week and 8-Week Follow-up Safety Visits.
[10] While on-study, all visit windows are used for scheduling purposes and all efforts should be made to return subjects to the 28-day schedule if scheduling changes are made at any previous visit(s).
[11] The duration between the Pre-Randomization Lab Visit and the Randomization Visit is 4 days. The "+2" days window is included ***for scheduling purposes only***. Every effort should be made to collect the Pre-Randomization Lab Visit samples as close to, and within, the 4 days prior to the Randomization Visit as possible. However, for scheduling convenience, this window may be up to 6 days (between the Pre-Randomization Lab Visit and the Randomization Visit).

Table 2. Schedule of Assessments – Open-label Extension Phase Including End of Treatment (EOT)[10] & Follow-up Visits

Procedure	**Phone visit** to confirm eligibility based on laboratory criteria[1]	**Week 14** (Day 98 ± 3 days)	**Week 16 (Day 112) and 20 (Day 140)** (±3 days)	**Visits every 4 weeks Week 24 (Day 168) to Week 64 (Day 448)** / EOT (±3 days)	**2-Week Follow-up Safety Visit** (14 days after EOT visit ± 2 days)	**8-Week Follow-up Safety Visit (8 weeks (-2 days to +14 days) after EOT visit)**
Confirm Week 12 Laboratory Results	X					
Rescue Medication paper diary, Concomitant Medication paper diary and Menstrual Period paper log (female subjects)[2]		X	X	X	X[3]	X (Concomitant Medication paper diary only) [3]
Safety Assessments						
Physical Examinations			X (Week 16 only)	X (Week 24 and 64 / EOT only)		
Vital Signs / Physical Measurements[4]			X	X	X	
Clinical Safety Laboratory Testing			X (Week 16 only)	X (Week 24, 48, and 64 / EOT only)		
Liver function tests (LFTs)		X	X	X	X	X
Lipid Panel				X (Week 24 and 64 / EOT only)		
ECG			X (Week 16 only)	X (Week 24, 48, and 64 / EOT only)	X	
Urinalysis				X (Week 64 / EOT only)		
Pregnancy Test			X (urine)	X (urine)	X (urine)	X (serum)

Procedure	**Phone visit** to confirm eligibility based on laboratory criteria[1]	**Week 14** (Day 98 ± 3 days)	**Week 16 (Day 112) and 20 (Day 140)** (±3 days)	**Visits every 4 weeks Week 24 (Day 168) to Week 64 (Day 448)** / EOT (±3 days)	**2-Week Follow-up Safety Visit** (14 days after EOT visit ± 2 days)	**8-Week Follow-up Safety Visit (8 weeks (-2 days to +14 days) after EOT visit)**
AE, SAE, and Concomitant Procedure Assessment[5]		X	X	X	X	X[5]
Sheehan Suicidality Tracking Scale		X	X	X	X	
Clinical Drug Supplies / Study Supplies						
Dispense Study Medication [1, 6]			X	X-all visits except Week 64 / EOT		
Administer Study Medication[7]		X	X	X		
Enter Use of Study Medication in eDiary		X	X	X		
Return unused study medication to site for compliance check		X	X	X		
eDiary returned/reviewed for completeness[8]		X	X	X		
Other Assessments						
Daily report of migraine occurrence and severity reported by subject in eDiary[9]		X	X	X		
Migraine-Specific Quality-of-Life Questionnaire (MSQ) v 2.1				X (Weeks 24 and 64 only)		
[redacted]						

Procedure	**Phone visit** to confirm eligibility based on laboratory criteria[1]	**Week 14** (Day 98 ± 3 days)	**Week 16 (Day 112) and 20 (Day 140)** (±3 days)	**Visits every 4 weeks Week 24 (Day 168) to Week 64 (Day 448)** / EOT (±3 days)	**2-Week Follow-up Safety Visit** (14 days after EOT visit ± 2 days)	**8-Week Follow-up Safety Visit (8 weeks (-2 days to +14 days) after EOT visit)**
[redacted]						
Migraine Disability Assessment (MIDAS)				X (Weeks 24 and 64 only)		

[1] Study eligibility must be confirmed by Week 12 laboratory results prior to first dose of study medication, which is dispensed at the Week 12 visit. Sites must contact subject by phone to confirm study eligibility prior to subject taking first dose.
[2] Concomitant medications, including prophylactic and rescue medications, taken during the Open-label, Extension Phase should be recorded in the subject's paper diary and reviewed by study personnel at each visit. Female subjects will also record menstrual period information on the paper log which should be reviewed by study personnel at each visit.
[3] Collect if treatment with concomitant medication is required for an AE or if concomitant medication is considered related to AE.
[4] Weight, body temperature, respiratory rate, blood pressure, and heart rate will be collected at all timepoints where indicated. Sitting arterial systolic and diastolic blood pressure and radial artery pulse rate will be measured.
[5] SAEs, AEs, and Concomitant Procedures must be reported after subject signs informed consent. SAEs should be reported from signing of consent through the 8-week Follow up Safety Visit. Non-serious AEs should be reported from signing of consent through 2-Week Follow up Safety Visit.
[6] Subjects should finish a bottle of study medication before starting a new bottle. Study drug will be dispensed at monthly (every 4 weeks) study visits, as needed. Unscheduled visits to dispense study medication may be scheduled as needed. Due to the COVID-19 Pandemic, study medication may be shipped to a subject, with up to an 8-week supply. Proper documentation must be maintained in the subject's source records including shipping vendor, tracking number, confirmation of receipt by subject, and all other relevant information.
[7] Subjects must take their study medication every other day, regardless of whether or not they have a migraine. During the open-label, extension phase only, if subjects have a migraine on a day that they are not scheduled to take a tablet of study medication, if needed, they may take a study medication tablet to treat a migraine on that calendar day. Therefore, subjects can take a maximum of one (1) tablet of study medication per calendar day. Subjects must report each tablet they take in the eDiary. Doses are not required to be taken in the office on days of a study visit, however dosing requirements and compliance should be discussed with subjects at all visits.
[8] During the Open-Label, Extension Phase, subjects with 6 or more missed evening reports and 3 or more missed dosing entries per month for 2 months (sequential or non-sequential months) should be considered for discontinuation from the study for poor compliance, after discussion with Sponsor. Month is defined as 4 weeks for the purpose of this protocol.

[9] The subject will be trained on the use of the eDiary. The subject will use the eDiary every day during the Extension Phase to report migraine occurrence, migraine severity and if the subject treated the migraine.

[10] While on-study, all visit windows are used for scheduling purposes and all efforts should be made to return subjects to the 28-day schedule if scheduling changes are made at any previous visit(s). Due to the COVID-19 Pandemic, visits may be conducted remotely (ex: telephone, telemedicine) and must be documented within the source records as being conducted remotely. All procedures not able to be completed due to a visit being conducted remotely must be reported as a protocol deviation and can be performed at the next visit, where appropriate to do so based on subject presentation. In cases where a Week 64 / End of Treatment (EOT) visit occurs remotely in order to be completed during the protocol required window and due to the COVID-19 Pandemic, the subject should return to the site within the 8 Week Follow-up Safety Visit timeframe (8 weeks from last dose, -2 to +14 days), to complete all procedures that weren't able to be completed remotely. Procedures completed at the Week 64 / EOT Remote Visit do not need to be repeated.

4.3.1 Screening Visit / Observation Period (28 days)

Approximately 1500 subjects will be screened to randomize up to approximately 800 subjects to study medication (rimegepant or matching placebo).

Before any study procedures are performed, subjects must sign informed consent. After informed consent, subjects will be enrolled in the IWRS system. The subject's migraine history and medical history will be collected at the Screening Visit. All subjects will continue to use their migraine prophylactic and/or standard of care medications during the 28-day Observation Period. Subjects will undergo all screening procedures as detailed in Table 1, after which they will be provided an eDiary to document each day during the 28-day Observation Period the occurrence and severity of migraines. Subjects will also record all migraine standard of care treatments taken during the Observation Period on a paper diary and female subjects will record their menstrual period information on a paper log. After completing the 28-day Observation Period, Subjects will return to the clinic, and both their eDiary and paper diary will be reviewed for completeness.

During this period, and within 96 hours +48 hours (4 days +2 days) of the Randomization Visit, subjects must return to the study site for the Pre-Randomization Laboratory Visit. See Table 1 for laboratory tests performed. Subjects then return to the site for the Randomization Visit; if the subject is not eligible, the subject will be considered a Screen Failure.

If the subject meets inclusion/exclusion criteria, the subject may enter the double-blind treatment phase.

4.3.1.1 Pre-Randomization (Laboratory) Visit

Within 96 hours +48 hours (4 days +2 days) of the Randomization Visit, subjects must return to the study site for the Pre-Randomization (Laboratory) Visit. This visit occurs within the Observation Period. Safety labs and a serum pregnancy test for WOCBP will be obtained and compliance with the eDiary will be assessed. If the subject continues to meet study entry criteria and laboratory test results are acceptable per protocol, the subject will be randomized at the Baseline Visit into the double-blind treatment phase. If the laboratory results are not acceptable per protocol, the subject is determined to be a Screen Failure and must return to the study site to return the eDiary. Repeat testing because of liver function test (LFT) abnormalities will not be permitted.

4.3.2 Randomized, Double-blind Treatment Phase (12 weeks)

Once completing the Screening/Observational Period, subjects will return to the study site for the Baseline Visit. Subjects who continue to meet all inclusion/exclusion criteria and have been compliant with the eDiary may enter the Treatment Phase, pending review of additional laboratory test results; see Section 4.3.1.1. Because laboratory results from the Randomization (Baseline) Visit will be available after the subject may have been determined to be otherwise eligible for the study, had been randomized, and started treatment, there is the possibility that exclusionary laboratory results from the Randomization Visit may result in early discontinuation from the study.

Subjects 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 subjects have a migraine during the double-blind phase of the study, if needed, they may treat the migraine with their standard of care medication and continue to take study medication on their regular schedule (scheduled dosing days only).

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

Subjects will also use the eDiary to complete the Preference of Medication (PoM) and Satisfaction with Medication (SM) scales. The Migraine-Specific Quality-of-Life Questionnaire v 2.1 (MSQ), 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)

Study visits will be approximately every two weeks during the first month and then every 4 weeks, until Week 12 (Table 1). At each visit, the eDiary will be reviewed by site staff for completeness and compliance. Study medication compliance and concomitant medication use and menstrual period information (female subjects) will be reviewed (and compared to the eDiary and paper diary entries, where applicable) and subjects will be dispensed additional study medication as needed. Additional safety (including laboratory tests and ECGs) will be performed per the schedule outlined in Table 1.

4.3.3 Open-label Extension Phase (52 weeks)

It is estimated that approximately 675 subjects will be entered into the open-label extension phase.

As indicated in Table 1, laboratory tests will be performed at the Week 12 visit (final visit of the double-blind treatment phase of the study). Subjects who continue to meet all inclusion/exclusion criteria and have been compliant with the eDiary may enter the open-label extension phase, pending review of laboratory test results. Subjects will be dispensed study medication and will be instructed that they cannot take study medication until laboratory results

confirm study eligibility. Subjects may be contacted by telephone; an office study visit is not required.

Subjects 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 subjects in this group have a migraine on a day that they are not scheduled to dose with study medication, they may take 1 study medication tablet on that calendar day to treat a migraine. Therefore, if needed, subjects can take a maximum of one tablet of study medication per calendar day for 52 weeks during the Open-label, Extension Phase.

The electronic subject diary will be completed by subjects to capture dosing of study medication and the frequency and severity of migraines during the Open-label, Extension Phase.

Subjects will also use the eDiary to complete [redacted] and [redacted]. The Migraine-Specific Quality-of-Life Questionnaire v 2.1 (MSQ), the Sheehan Suicidality Tracking Scale (S-STS), Migraine Assessment Disability (MIDAS) and [redacted] will be completed, or administered by the investigator, on paper at specified study visits (Table 2).

Study visits will be approximately every two weeks during the first month and then every 4 weeks, until Week 64 (Table 2). At each visit, the eDiary will be reviewed by site staff for completeness and compliance. Study medication compliance and concomitant medication use and menstrual period information (female subjects) will be reviewed (and compared to the eDiary and paper diary entries, where applicable) and subjects will be dispensed additional study medication as needed. Additional safety (including laboratory tests and ECGs) will be performed per the schedule outlined in Table 2.

Due to the COVID-19 Pandemic, visits may be conducted remotely (ex: telephone, telemedicine) and must be documented within the source records as being conducted remotely. All procedures not able to be completed due to a visit being conducted remotely must be reported as a protocol deviation and can be performed at the next visit, where appropriate to do so based on subject presentation.

4.3.4 End of Treatment (Week 64)

Subjects will return to the study at the end of Week 64 (±3 days), or at end of treatment for early discontinuations, for review of the electronic diary, assessment of medication compliance, assessment of tolerability and safety (including vital signs, laboratory tests, and electrocardiography) (Table 2). In cases where a Week 64 / End of Treatment (EOT) visit occurs remotely in order to be completed during the protocol required window and due to the COVID-19 Pandemic, the subject should return to the site within the 8 Week Follow-up Safety Visit timeframe (8 weeks from last dose, -2 to +14 days), to complete all procedures that weren't able to be completed remotely. Procedures completed at the Week 64 / EOT Remote Visit do not need to be repeated. Subjects must return the unused study medication and electronic subject diary to the study site. Subjects who do not complete the Double-blind, Treatment Phase and/or

do not enter or complete the Open-label, Extension Phase should complete the End of Treatment Visit, 2-Week Follow up Safety Visit and 8-Week Follow up Safety Visit.

4.3.5 2-Week Follow up Safety Visit

Subjects will return to the study site 14 days after the Week 64/EOT Visit or early discontinuation visit, if applicable, (+/- 2 days) to collect laboratory tests, vital signs, electrocardiography, and assessment of AEs/ SAEs. Subjects will return the prophylactic and rescue medication paper diary and menstrual period (female subjects) paper logs which should be reviewed one final time by study staff. Subjects must continue to track any concomitant medications and therefore must maintain the Concomitant Medication Use Log paper diary through this visit. Investigators should assess subjects for AEs consistent with drug dependency or withdrawal effects and report as appropriate (see Section 7.4).

4.3.6 8-Week Follow up Safety Visit

Subjects will return to the study site 8 weeks after the Week 64/EOT Visit or early discontinuation visit, if applicable (8 weeks (-2 days to +14 days)) to collect liver function tests (LFTs), assessment of SAEs and to have a serum pregnancy test performed (WOCBP). Subjects will return the Concomitant Medication Use Log paper diary for documenting concomitant medications.

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 subjects or investigators. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

5 POPULATION

5.1 Number of Subjects

It is anticipated that up to approximately 1500 subjects may be screened in order to randomize up to approximately 800 subjects to study medication (rimegepant or placebo). It is estimated that approximately 675 subjects will enter the open-label phase.

5.2 Inclusion Criteria

1. Signed Written Informed Consent

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

    b) Subjects must be able to read.

2. Target Population

    Subject 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[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) Per subject report, 4-18 migraine attacks of moderate or severe intensity per month within the last 3 months prior to the Screening Visit (month is defined as 4 weeks for the purpose of this protocol)

    d) 6 or more migraine days during Observation Period

    e) Not more than 18 ***headache days*** during the Observation Period

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

    g) Subjects on prophylactic migraine medication are permitted to remain on therapy if the dose has been stable for at least 3 months (12 weeks) prior to the Observation Period, and the dose is not expected to change during the course of the study.

        i. Subjects may remain on one (1) medication with possible migraine-prophylactic effects, excluding CGRP antagonists [biologic or small-molecule], during the double-blind treatment phase.

ii. Concomitant use of a CGRP antagonist, such as erenumab or fremanezumab, is prohibited.

iii. Subjects who previously discontinued prophylactic migraine medication must have done so at least 90 days prior to the Screening Visit.

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

3. Age and Reproductive Status

a) Male and female subjects ≥ 18 years

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 (24 weeks) 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) Subject has a history of basilar migraine or hemiplegic migraine

b) Subjects with headaches occurring 19 or more days per month (migraine or non-migraine) in any of the 3 months prior to the Screening Visit.

2. Medical History and Concurrent Diseases

a) Subject history of HIV disease

b) Subject history with current evidence of uncontrolled, unstable or recently diagnosed cardiovascular disease, such as ischemic heart disease, coronary artery vasospasm, and cerebral ischemia. Subjects with myocardial infarction (MI), acute coronary syndrome (ACS), percutaneous coronary intervention (PCI), cardiac surgery, stroke or transient ischemic attack (TIA) during 6 months (24 weeks) prior to screening.

c) Uncontrolled hypertension or uncontrolled diabetes (however, subjects can be included who have stable hypertension and/or diabetes for 3 months (12 weeks) prior to screening). Blood pressure greater than 150 mm Hg systolic or 100 mm Hg diastolic after 10 minutes of rest is exclusionary.

d) Subjects with major depressive episode within the last 12 months, major depressive disorder or any anxiety disorder requiring more than 1 medication for each disorder. Medications to treat major depressive disorder or an anxiety disorder must have been at a stable dose for at least 3 months prior to the Screening visit.

e) Active chronic pain syndromes (such as fibromyalgia, chronic pelvic pain, complex regional pain syndrome [CRPS]).

f) Subjects with other pain syndromes (including trigeminal neuralgia), psychiatric conditions, dementia, or significant neurological disorders (other than migraine) that, in the Investigator's opinion, might interfere with study assessments

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

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

i) The subject 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

j) History of, treatment for, or evidence of, alcohol or drug abuse within the past 12 months (48 weeks) or subjects who have met DSM-V criteria 9 for any significant substance use disorder within the past 12 months (48 weeks) from the date of the screening visit

k) History of use of opioid- or barbiturate- (e.g. butalbital) containing medication for 4 or more days per month during the 3 months (12 weeks) prior to Screening Visit.

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

i. Detectable levels of cocaine, amphetamine and phencyclidine (PCP) in the drug screen are exclusionary. Subjects who have positive drug screen for amphetamines and who are on a prescribed amphetamine medication for an approved indication (e.g., ADHD) will be allowed into the study at the Investigator's discretion. The determination by the Investigator must be well documented in the subject's source medical records. The stimulant dose must be stable from 3 months (12 weeks) prior to baseline until the end of treatment visit occurs.

ii. Detectable levels of marijuana in the drug screen are not exclusionary, if in the investigator's documented opinion the subject does not meet DSM-V criteria [9] for substance use disorder, and the positive test does not signal a clinical condition that would impact the safety of the subject or interpretation of the study results.

m) 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.

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

o) Body mass index $\geq$ 33.0 kg/m^2

p) 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 ≤ 40 ml/min/1.73m^2

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

    c) Left Bundle Branch block

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

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

    f) Serum bilirubin (Total, Direct or Indirect) > 1 x ULN (Only abnormal values of between 1-1.5x ULN may be repeated once for assessment of eligibility during the screening period at the Screening Visit only. Abnormal bilirubin results obtained at the Pre-Randomization Laboratory Visit may not be repeated.)

    g) 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 at the Screening Visit only. Abnormal AST or ALT results obtained at the Pre-Randomization Laboratory Visit may not be repeated.)

    h) Neutrophil count ≤ 1000/µL (or equivalent)

    i) HbA1c ≥ 6.5%

6. Prohibited Medications

    a) History of use of analgesics (e.g. nonsteroidal anti-inflammatory drugs [NSAIDs] or acetaminophen) on ≥ 15 days per month during the 3 months (12 weeks) prior to the Screening Visit.

    b) Subjects taking a prohibited medication (Refer to Section 5.4).

7. 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. Subjects with less than 24 completed eDiary reports during the Observation Period will not be considered for participation due to non-compliance with the eDiary.

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 any multiple dose BHV3000 (rimegepant) study, such as BHV3000-201, regardless of the number of doses taken. Subjects may be considered for BHV3000-305 if the subject participated in any of the following single dose studies: BHV3000-301, BHV3000-302, or BHV3000-303, but did not participate in any multiple dose rimegepant study**.** Note that subjects who were considered screen failures in a past BHV3000 study may be considered after discussion with the Sponsor and written approval is received. Subjects who were considered screen failures from BHV3000-305 may be considered for re-screening provided the ineligibility was due to one of the eligibility items adjusted in Amendment 03 (Protocol Version 04): exceeded number of headache days (previously greater than 13) or didn't meet number eDiary entries during Observation Period (previously at least 26). Subjects may also be considered for re-screening provided the ineligibility was due to the eligibility item adjusted in Amendment 04 (Protocol Version 05): BMI less than 33.0 kg/m^2 (previously BMI less than or equal to $30kg/m^2$). Subjects who were considered screen failures from BHV3000-305 for other reasons should be discussed with the Sponsor and approval must be granted prior to considering for re-screening. Adequate documentation in source records must support the previously failed criteria.

h) Subjects are excluded if they have had no therapeutic response with > 2 of the 8 medication categories for prophylactic treatment of migraine listed in Appendix 4 after an adequate therapeutic trial. Additional details can be found in Section 15.4 Appendix 4.

i) Participation in any other investigational clinical trial while participating in this clinical trial. Subjects with an exclusionary match found in the CTS Database will be excluded.

j) Past participation in a clinical trial within 30 days prior to the Screening Visit. Note: Subjects who were considered screen failures within the last 30 days should not be considered as excluded.

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 (> 12 weeks)

4. Use of narcotic medication, such as opioids (e.g. morphine, codeine, oxycodone and hydrocodone) or barbiturates is prohibited starting from 2 days prior to the Baseline Visit and throughout the study, including the 8-Week Follow-up Safety 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 Period must be stopped at least 2 days prior to baseline visit. Acetaminophen as a rescue medication as described in Section 5.5 is allowed during the Double-blind, Treatment phase.

6. Use of triptans is prohibited during the Open-label Extension phase.

7. The use of CGRP antagonists (biologic [e.g. Aimovig™ and Ajovy™] or small molecule) other than rimegepant is prohibited during the study.

8. Use of marijuana is prohibited during the study.

9. Concomitant use of strong CYP3A4 inhibitors with rimegepant is prohibited during the double-blind, treatment phase of the study. If use of a strong CYP3A4 inhibitor is required during the open-label, extension phase, 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 Section 15.2 Appendix2.

10. Concomitant use of strong CYP3A4 inducers with rimegepant is prohibited during the double-blind, treatment phase of the study. If use of a strong CYP3A4 inducer is required during the open-label, extension phase, 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 Section 15.2 Appendix 2.

11. Concomitant use of CYP2C9 inhibitors with rimegepant is prohibited during the double-blind, treatment phase of the study. If use of a CYP2C9 inhibitor is required during the open-label, extension phase, such as fluconazole, amiodarone, or fluvoxamine, dosing with rimegepant should be stopped and should not start again until 14 days after the last dose of the CYP2C9 inhibitor.

12. Concomitant use of CYP2C9 inducers with rimegepant is prohibited during the double-blind, treatment phase of the study. If use of a CYP2C9 inducer is required during the open-label, extension phase, such as carbamazepine, aprepitant, or rifampin, dosing with rimegepant should be stopped and should not start again until 14 days after the last dose of the CYP2C9 inducer.

13. Concomitant use of atypical antipsychotics such as Abilify (aripiprazole), Zyprexa (olanzapine), Seroquel (quetiapine), Geodon (ziprasidone), or Risperdal (risperidone) or Depakote/Depakene (valproic acid/valproate) is prohibited during the study.

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

15. Use of analgesics (e.g. nonsteroidal anti-inflammatory drugs [NSAIDs] or acetaminophen) on ≥ 15 days per month is prohibited during the study

16. Use of any investigational agent other than rimegepant from the Screening Visit through the 8-Week Follow-up Safety Visit.

5.5 Prophylactic and Rescue Medications

Subjects may not use more than 1 of the following medications with possible migraine-prophylactic effects if not otherwise prohibited by the protocol. Doses must be stable **within 3 months (12 weeks) prior to the start of the Observation Period** and throughout the study. Use of more than 1 of the following medications is prohibited within 3 months (12 weeks) prior to the start of the Observation Period and throughout the study.

Prophylactic migraine medications that are permitted during the study include:

- Topiramate, gabapentin
- Beta blockers (such as: atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol)
- Tricyclic antidepressants (such as: amitriptyline, nortriptyline, protriptyline)
- Venlafaxine, desvenlafaxine, duloxetine, milnacipran
- Flunarizine, verapamil, lomerizine

- Lisinopril, candesartan
- Clonidine, guanfacine
- Cyprohepatdine
- Methysergide
- Pizotifen
- Feverfew, magnesium (≥ 600 mg/day), riboflavin (≥ 100 mg/day)
- Botox®

The use of CGRP antagonists (biologic [e.g. Aimovig™, Ajovy™] or small molecule) other than rimegepant is prohibited during the study.

The use of triptan medications is prohibited during the Open-Label, Extension Phase of the study, but is allowed as rescue medication during the Double-blind, Treatment Phase.

During the Double-blind, Treatment Phase, subjects may use their permitted standard of care medication if needed for acute treatment of a migraine and record any medications taken on the appropriate paper diary. Permitted medications include the following rescue medications: triptans, aspirin, ibuprofen, baclofen, 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 rescue during the study, with the exception that ***triptans are prohibited during the Open-Label Extension Phase***. These are the only medications allowed for rescue. Subjects should continue taking study medication on scheduled dosing days.

If a subject takes a tablet of study drug and experiences a migraine later that day, after dosing with study drug for the day, the subject may take their ***rescue medication*** as described in this section of the protocol. ***During the double-blind, treatment phase, subjects are not allowed to take more than one tablet of study medication EVERY OTHER calendar day. During the open-label, extension phase, subjects are required to dose every other day, but may take 1 tablet of rimegepant on non-scheduled dosing days to treat a migraine. Subjects are not allowed to take more than one tablet of study medication per calendar day during the open-label, extension phase.***

Use of standard of care medication during Observation Period and use of rescue medication during the Treatment Phase, Extension Phase, and standard of care medication through to the 8-Week Follow-up Safety Visit will be recorded by the subject 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 (48 consecutive weeks) 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

3. Woman on hormone replacement therapy (HRT) who no longer menstruate

   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

   NOTE: Women on HRT who still menstruate and women with irregular menses should be considered as WOCBP

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 as outlined in Table 1 and Table 2. 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 subject)
- Instructions for the eDiary device and access to the portal
- Paper diary to record standard of care migraine medications and rescue medications
- Paper diary to record menstrual period information (female subjects)
- 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
- MSQ v 2.1 forms

[redacted]

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 daily to record all study medication dosing, rescue medication dosing occurrences (i.e., with triptans, ergotamine, or other), select subject-rated scales, and migraine occurrence, characteristics, and severity. Any assessment completed by the subject in the eDiary will be transferred from the site/subject 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 subject on the eDiary.

Safety laboratory, plasma, and 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

Subjects will undergo a routine physical examination during the Screening Phase and at all scheduled visits as outlined in Table 1 and Table 2. Physical examinations 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 and 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, subjects should be fasting for a minimum of 8 hours before laboratory tests.** However, if a subject is not fasting at a given visit, the blood draw should still be performed, and the non-fasting status should be documented.

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 CK result is > 5.0 x ULN).

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

2. **LFTs**: AST, ALT, Alkaline Phosphatase and Bilirubin (Total, Direct, Indirect). Additional tests may be obtained to evaluate laboratory abnormalities and/or adverse events; please refer to the Laboratory manual.

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

Additional tests may be obtained to evaluate laboratory abnormalities and/or adverse events; please refer to the Laboratory Manual.

6.2.4.2 Pregnancy Testing

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

6.2.5 Sheehan Suicidality Tracking Scale

The Sheehan STS (S-STS) is a prospective, subject-reported or clinician-administered rating scale that contains 16 questions to track both treatment-emergent suicidal ideation and behaviors.[10,11] 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 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

The eDiary will be used daily to record rescue medication dosing occurrences (i.e., with triptans, ergotamine, or other), and migraine occurrence, characteristics, and severity during the observation period, double-blind treatment phase, and open-label extension phase.

Efficacy assessments will be derived from eDiary data, and will include the number of migraine days by severity (total; moderate or severe) per month, number of rescue medication days per month, and MRM days per month, in each month by study period.

6.4 Other Assessments

6.4.1 Migraine-Specific Quality-of-Life Questionnaire v 2.1

Impact of treatment on subject-reported quality of life will be assessed using the Migraine-Specific Qualify-of-Life Questionnaire version 2.1 (MSQ v 2.1). The MSQ v 2.1 is a 14-item instrument that has been validated in 3 domains: role function - restrictive, role function - preventive, and emotional function.[12]

[redacted]

[redacted]

6.4.4 Migraine Disability Assessment (MIDAS) Questionnaire

The Migraine Disability Assessment (MIDAS) is a retrospective, subject-reported, 5-item questionnaire that measures headache-related disability as lost days due to headache from paid work or school, household work and non-work activities over a 3-month period. The MIDAS will be completed on a paper form at the site.[13]

[redacted]

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
- Exclusionary laboratory abnormality identified on the Randomization / Baseline Laboratory Report.
- 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
- Poor compliance with study procedures and visits, including poor completion compliance with evening reports in eDiary.

i. Subjects with less than 24 completed eDiary reports during the Observation Period will not be considered for participation due to non-compliance with the eDiary.

ii. Subjects in the Double-blind, Treatment Phase will be monitored closely for compliance with the eDiary and may not be considered for the Open-label, Extension Phase based on PI and / or Sponsor discretion if compliance is low. Subjects who demonstrate poor compliance will be discussed with the Sponsor and corrective training will be completed by the site with the subject.

iii. During the Open-Label, Extension Phase, subjects with 6 or more missed evening reports in the eDiary and 3 or more missed dosing entries per month for 2 months (sequential or non-sequential months) should be considered for discontinuation from the study for poor compliance, after discussion with Sponsor. Month is defined as 4 weeks for the purpose of this protocol.

- Please see Section 6.2.5 for guidance on study discontinuation based on results from the S-STS.

All subjects who discontinue or who do not enter the Open-label, Extension Phase should comply with protocol specified End of Treatment procedures as outlined in 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).

[redacted]

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 or matching placebo.

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 acute and preventive treatment and rescue medication 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 Subject Identification

Immediately after written informed consent is obtained and before performing any study-related procedures, the site staff must obtain a subject identification by adding a new subject in Rave. In this study, the Rave system will be utilized for obtaining subject identification and as the electronic data capture (EDC) system. Each subject will be assigned a unique sequential 4-digit subject number through Rave (0001, 0002, 0003, etc.). This subject number must not be reused for any other participant in the study. Subjects will maintain their subject number assigned at screening throughout the trial.

At the Baseline Visit, eligible subjects will be randomized in a 1:1 ratio to the rimegepant or placebo treatment groups. The randomization will be stratified by the use of prophylactic migraine medications (yes or no).

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

7.2.2 Selection and Timing of Dose and Administration

Study medication (rimegepant or matching placebo) will be assigned via the Rave system. There are no dose adjustments in this study and subjects will receive 30 tablets of rimegepant or placebo in a bottle. Subjects will be dispensed study medication at the Baseline Visit, and the subjects will be instructed that they must take ***one tablet every other calendar day, regardless of whether they have a migraine on that day or not.*** This is the scheduled dosing regimen for the double-blind treatment phase and the open-label, extension phase.

During the open-label, extension phase, subjects will receive open-label rimegepant. Subjects will be instructed that they must take one tablet every other calendar day, regardless of whether they have a migraine on that day or not. During the open-label, extension phase only, if a subject has a migraine on a non-scheduled dosing day, they may take 1 tablet of rimegepant as acute treatment for their migraine, if needed, with a maximum of one tablet per calendar day. This regimen of scheduled dosing on every other calendar day and as needed rimegepant dosing should be followed for up to 52 weeks in the open-label, extension phase. Subjects can take a maximum of one tablet of study medication per calendar day for 52 weeks during the open-label, extension phase.

Dosing should occur around the same time every other day (EOD) for migraine prevention. It is preferred that subjects dose every other day in the morning, however, it is more important that the subject consistently dose at approximately the same time every other day. The time of dosing should be consistent throughout the study for the EOD dosing days. If the subject has a migraine on a day when they ***already took study medication***, the subject can take their rescue medication in accordance with protocol restrictions. Subjects **must** be instructed that they

CANNOT take more than one tablet of study medication every other day during the double-blind, treatment phase. Subjects **must** be instructed to continue taking study medication every other calendar day during the open-label, extension phase. As noted above, subjects may treat a migraine with study medication on a non-scheduled dosing day, but subjects **must** be instructed that during the open-label, extension phase, they **CANNOT** take more than 1 tablet of rimegepant per calendar day.

7.2.3 Dose Modification

There will be no dose adjustments in this study.

7.2.4 Dose Interruptions

If a subject 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

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

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

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

7.4 Treatment Compliance

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

Subjects 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 subject 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 Subjects that involuntary termination from the study will occur in cases where non-compliance is identified. Study staff should contact a subject in between the monthly study visits if the subject demonstrates non-compliance with the eDiary and document the contact in the source, to identify potential lost to follow up subjects as early as possible.

Investigators must monitor subjects for possible cases of abuse of study medication (subjects 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 subjects 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 subjects 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 Biohaven (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 subject or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding for example) symptom, or disease temporally associated with the use of the investigational product, whether or not considered relate to the investigational product.

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

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 subjects 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 subjects for possible cases of abuse of study medication (subjects 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 subjects 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 require 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 Biohaven clinical studies (but may be considered non-serious AEs):

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

2. Elective surgery planned prior to signing consent;

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

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

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

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

8.1.2 Collection and Reporting Serious Adverse Events

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specific procedures. All SAEs must be collected that occur during the observation phase and up to and including the 8-Week Follow-up. The investigator should report any SAE occurring after this time period that is believed to be related to study drug or protocol-specific procedures.

All SAEs should be followed to resolution or stabilization.

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

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

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

The Investigator is responsible for reporting all SAEs and all Other Important Medical Events to [redacted]

the Investigator, or designated staff, is responsible for entering the SAE information in the Electronic Data Capture (EDC) system (i.e.: event term, start stop dates, causality, severity).

Any serious adverse event must be reported immediately or no later than 24 hours after awareness of the event to [redacted]

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

[redacted]

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

The minimum information required for an initial SAE report is:

Sender of report (Site number, Investigator name)

Subject identification (subject number)

Protocol number

SAE term (if an SAE is being reported)

8.1.3 Overdose

An overdose is defined as the accidental or intentional administration of any dose of 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 subject 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 subject safety). Protocol-required procedures for the study discontinued and the follow-up must be performed on the subject unless contraindicated by the pregnancy (i.e., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

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 [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 subject 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 through the 2-Week Follow up Safety Visit. Non-serious AE information should also be collected from the start of a placebo lead-in phase or other observation period intended to establish a baseline status for a subject.

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

8.2.2 Laboratory Test Abnormalities

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

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

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

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

9 STATISTICS

Complete details on the statistical methods for this study may be found the Statistical Analysis Plan (SAP).

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 Populations for Analysis

The set of enrolled subjects consists of all subjects who signed the informed consent form and were assigned a subject identification number.

The set of randomized subjects consists of enrolled subjects who were assigned a randomized treatment group and prophylactic migraine medication use stratum.

The full analysis set (FAS) includes all randomized subjects who received at least one dose of double-blind study medication (rimegepant or placebo).

The efficacy analysis set is a subset of the FAS that includes subjects with at least 14 days of eDiary data in both the Observation Period and at least one 4-week interval during the double-blind treatment phase.

The safety analysis set consists of all enrolled subjects who received at least one dose of study medication (double-blind or open-label). For the double-blind phase, subjects in safety analyses will be analyzed based on their randomized treatment so long as they receive at least one dose of their randomized treatment. Otherwise, subjects will be analyzed based on the actual treatment received.

The rimegepant safety analysis set includes enrolled subjects who received at least one dose of rimegepant (double-blind or open-label).

9.3 Sample Size

With a sample size of roughly 800 subjects randomized, and 400 subjects per group, we expect roughly 370 subjects per group in the efficacy data set. Assuming rimegepant provides roughly a 1 day advantage over placebo on the primary endpoint, and a common standard deviation of 3.75 days, then the study will have roughly 95% power on the primary endpoint. The estimates for the change in migraine days per month and the standard deviation are consistent with publicly available information from another investigational oral CGRP antagonist for this indication.

9.4 Primary Endpoint

The change from baseline efficacy endpoint is analyzed using a generalized linear mixed effect model, that includes subject as a random effect, and has the baseline number of migraine days (i.e., during the Observation Period) as a covariate. The model includes fixed effects for: treatment group; stratification factor (use of prophylactic migraine medication); scheduled visit; and the visit by-treatment group interaction. Scheduled visits included in the model are nominally at 4, 8 and 12 weeks. Evaluation of migraine days per month is based on the data from the previous visit to the current visit (i.e., 4-week interval), and is prorated to account for missing migraine reports. A migraine days per month endpoint, prorated to 28 days, will be computed for subjects in the efficacy analysis set who provide at least 14 days of eDiary data during any reporting period (i.e., Observation Period or a 4-week interval during the double-blind treatment phase). The difference estimate (rimegepant - placebo), standard error, 95% confidence interval, and p-value will be reported for the last 4 weeks (Weeks 9 to 12) of the double-blind treatment phase.

9.5 Secondary Endpoint(s)

The number of subjects that experience at least a 50% reduction in the mean number of moderate or severe migraine days per month in the last 4 weeks of the double-blind treatment phase will be analyzed using a stratified Cochran-Mantel-Haenszel (CMH) test after the missing data are imputed as non-response.

The change from baseline in the mean number of migraine days per month over the entire double-blind treatment phase (Weeks 1 to 12) will be assessed with the same statistical model used to analyze the primary endpoint.

The use of rescue medications (mean number of days per month) in the last 4 weeks of the double-blind treatment phase will be assessed using a generalized linear mixed effects model that is similar in structure to that used for the primary analysis. Rescue medications are defined in Section 5.5.

The change from baseline in the mean number of migraine days per month in the first 4 weeks (Weeks 1 to 4) of the double-blind treatment phase will be assessed with the same statistical model used for to analyze the primary endpoint.

The investigators will determine the severity 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 severities over time, then only the worst severity will be reported. Tabulations will be made for the frequency of unique subjects with adverse events (by severity, by relationship to study drug, and overall), serious adverse events, adverse events leading to treatment discontinuation, hepatic-related adverse events (by severity, by relationship to study drug, and overall), and hepatic-related adverse events leading to treatment discontinuation from case report forms.

The frequency of unique subjects with clinically significant laboratory test abnormalities will be tabulated based on Grade 3 - 4 clinical laboratory evaluations graded using the latest version of Common Terminology Criteria for Adverse Events (CTCAE).

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

The frequency of unique subjects that have ALT or AST that exceed 3x the ULN concurrently (on the same laboratory test occasion) with total bilirubin that exceeds 2x the ULN will be tabulated and presented with descriptive statistics and exact confidence intervals.

Safety endpoints will be assessed separately for the following phases and populations:

- Double-blind treatment for the safety analysis set;
- Rimegepant treatment (double-blind or open-label) for the rimegepant safety analysis set.

The changes from baseline in MSQ role function - restrictive domain score and MIDAS total score at Week 12 will be analyzed using generalized linear models that include the baseline score as a covariate, and fixed effects for treatment group and stratification factor (use of prophylactic migraine medication). The Week 12 difference estimate (rimegepant - placebo), standard error, 95% confidence interval, and p-value will be reported for each endpoint.

9.6 Multiplicity Correction

Type 1 error is controlled through the use of hierarchical testing. The significance of the primary endpoint is evaluated at the 0.05 level. If the primary endpoint is significant, then the following secondary endpoints will be tested hierarchically in the following order, each at the 0.05 level:

- proportion of subjects with a 50% reduction in the mean number of moderate or severe migraine days per month in the last 4 weeks of the double-blind treatment phase;

- change from baseline in the mean number of migraine days per month over the entire course of the double-blind treatment phase;

- use of rescue medications (mean number of days per month) in the last 4 weeks of the double-blind treatment phase;

- change from baseline in the mean number of migraine days per month in the first 4 weeks of the double-blind treatment phase;

- change from baseline in MSQ role function - restrictive domain scores at Week 12 of the double-blind treatment phase;

- change from baseline in MIDAS total score at Week 12 of the double-blind treatment phase.

Thus, a secondary endpoint will be tested only if the preceding secondary endpoint in the hierarchy is determined to be significant. Descriptive p-values will be provided for any non-significant secondary endpoints and comparative exploratory endpoints.

9.7 Demographic and Baseline Characteristics

Tabulations of demographic and baseline characteristics are made for FAS subjects. Separate tabulations are made for subjects enrolled but not in FAS.

9.8 Schedule of Analyses

The data from this study may be locked and analyzed at any point after the last subject completes their last visit in the double-blind phase of the study, and adequate time has been allowed for follow-up. Analyses of the data may be conducted after the double-blind phase, and at any point in, or after, the open-label phase.

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 Independent Ethics Committee (IEC) requirements relative to clinical studies. The study will also be conducted in compliance with the recommendations laid down in the most recent version of the Declaration of Helsinki, with the exception that registration of such Phase 1 trials in a publicly accessible database is not mandatory.

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

All serious breaches must be reported to 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 subjects of the study or the scientific value of the study.

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

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

10.2 Data and Safety Monitoring Committee

This study will not make use of a Data 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 and an Institutional Review Board/Independent Ethics Committee.

10.3 Informed Consent

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

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

Before the potential subject has undergone any study-related screening procedures, the nature of the study and the potential risks associated with it will be explained to the subject, and the subject will be given an opportunity to ask questions to his or her satisfaction. After the questions are answered, but before proceeding further, the subject must read and sign a written informed consent form for study participation and CTS database participation. These signed informed consent forms 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 forms.

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

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

The 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.

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

10.4 Case Report Forms

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

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

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

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

10.5 Records Management and Retention

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

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

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

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

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

1. amount of study drug received and placed in storage area

2. label ID number or batch number or Kit number as specified for the protocol

3. amount dispensed to and returned from each subject

4. amount transferred to another area or site for dispensing or storage if applicable

5. amount of drug lost or wasted
6. amount destroyed at the site, if applicable
7. amount returned to sponsor, if applicable
8. retain sampled for bioavailability/bioequivalence, if applicable
9. record of dates and initials of personnel responsible for IM dispensing and accountability

10.6 Source Documentation

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

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

10.7 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.

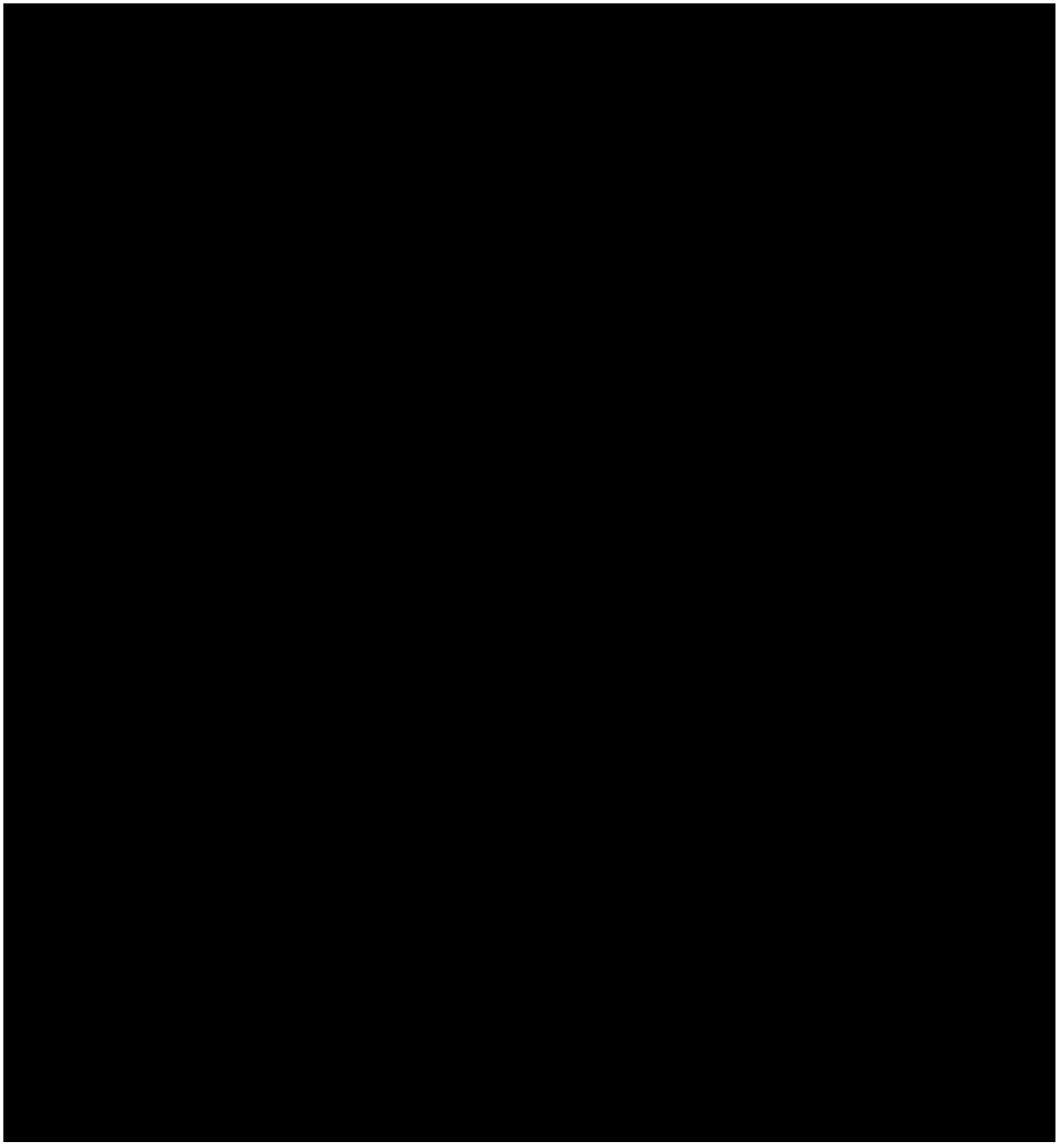
14 CONFIDENTIALITY

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

15 APPENDICES

15.1 APPENDIX 1 - Names of Study Personnel



15.2 Appendix 2 – Inhibitors and Inducers of CYP3A4 or CYP2C9 (Not all-inclusive)

The following text presents some of the inhibitors and inducers of CYP3A or CYP2C9. This list should not be considered all-inclusive. Individual drug labels should be reviewed for specific information on propensity to inhibit or induce CYP450 enzymes for a specific compound.

As described in the study protocol, concomitant use of strong CYP3A4 inhibitors is prohibited.

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

The following medications and supplements are some of the strong inducers of CYP3A4. As described in the study protocol, concomitant use of strong CYP3A4 inducers is prohibited. Individual product labels should be reviewed for specific information on

CYP3A inducers
Carbamazepine, phenytoin, rifampin, St. John's wort

The following medications and medication combinations are some of the inhibitors of CYP2C9. As described in the study protocol, concomitant use of CYP2C9 inhibitors is prohibited. Individual drug labels should be reviewed for specific information on

CYP2C9 inhibitors
amiodarone, felbamate, fluconazole, miconazole, piperine, diosmin, disulfiram, fluvastatin, fluvoxamine, voriconazole

The following medications and supplements are some of the inducers of CYP2C9. As described in the study protocol, concomitant use of CYP2C9 inducers is prohibited. Individual product labels should be reviewed for specific information on propensity to

CYP2C9 inducers
aprepitant, carbamazepine, enzalutamide, rifampin, ritonavir

Resources:

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

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

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

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

15.3 Appendix 3 – Definition of Migraine Days

Migraine Day: Any calendar day in which the subject experiences a qualified migraine headache (onset, continuation, or recurrence of the migraine headache). A qualified migraine headache is defined as a migraine with or without aura, lasting for ≥ 30 minutes, and meeting at least one of the following criteria (a and/or b)

a) ≥ 2 of the following pain features:

- Unilateral location,
- Pulsating quality (throbbing),
- Moderate or severe pain intensity,
- Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)

b) ≥ 1 of the following associated symptoms:

- Nausea and/or vomiting
- Photophobia and phonophobia

If the subject took a migraine-specific medication (i.e., study medication [open-label, extension phase only], triptan or ergotamine) during aura or to treat headache on a calendar day, then it will be counted as a migraine day regardless of the duration and pain features/associated symptoms. The use of study medication on non-scheduled dosing days is only permitted during the open-label, extension phase; **dosing with study medication on non-scheduled dosing days is not permitted during the double-blind, treatment phase**.

A moderate to severe migraine day is a migraine day with a migraine reported with moderate or severe pain intensity.

Headache Day: Any calendar day in which the subject experiences a qualified headache (initial onset, continuation, or recurrence of the headache). A qualified headache is defined as:

- a qualified migraine headache (including an aura-only event that is treated with acute migraine-specific medication), or
- a qualified non-migraine headache, which is a headache that lasts ≥ 30 minutes and is not a qualified migraine headache, or
- a headache of any duration for which acute headache treatment is administered.

Acute Migraine-specific Medication Treatment Day: Any calendar day during which the subject took a migraine-specific medication (i.e., study medication [open-label, extension phase only], triptan or ergotamine). The use of study medication on non-scheduled dosing days is only permitted during the open-label, extension phase; **dosing with study medication on non-scheduled dosing days is not permitted during the double-blind, treatment phase**.

Monthly eDiary Data: Data collected by the eDiary based on the subject's monthly investigational product dosing schedule when at least 14 days of eDiary data are collected within that interval. Monthly frequency measurements will be prorated to 28-day equivalents.

Migraine Attack: An episode of any qualified migraine headache. The following rules will be used to distinguish an attack of long duration from two attacks, or to distinguish between attacks and relapses:

a) A migraine attack that is interrupted by sleep, or temporarily remits, and then recurs within 48 hours (i.e., ≤ 48 hours between the start of the migraine attack to the time of the recurrence) will be considered as one attack and not two.

b) An attack treated successfully with medication but with relapse within 48 hours (i.e., ≤ 48 hours between the start of the migraine attack to the time of the recurrence) will be considered as one attack.

15.4 Appendix 4 – Categories of Migraine Prevention Medications

No therapeutic response with > 2 of the following 8 medication categories for prophylactic treatment of migraine after an adequate therapeutic trial. These medication categories are:

- **Category 1**: Divalproex sodium, sodium valproate
- **Category 2**: Topiramate, carbamazepine, gabapentin
- **Category 3**: Beta blockers (for example: atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol)
- **Category 4**: Tricyclic antidepressants (for example: amitriptyline, nortriptyline, protriptyline)
- **Category 5**: Serotonin-norepinephrine reuptake inhibitors (for example: venlafaxine, desvenlafaxine, duloxetine, milnacipran)
- **Category 6**: Flunarizine, verapamil
- **Category 7**: Lisinopril, candesartan
- **Category 8**: Botox®

No therapeutic response is defined as no reduction in headache frequency, duration, or severity after administration of the medication for at least 6 weeks at the generally-accepted therapeutic dose(s) based on the investigator's assessment.

The following scenarios ***do not*** constitute lack of therapeutic response:

- Lack of sustained response to a medication
- Failure to tolerate a therapeutic dose

16 REFERENCES

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6. CN170006. *Phase 1 Mass Balance Recovery Study - Rimegepant oral dosing and infusion.* Bristol-Myers Squibb Company

7. CN170007. *DDI with Midazolam (CYP3A4 substrate) to study the changes of midazoloam pharmacokinetics with or without BMS-92771.* Bristol-Myers Squibb Company.

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