**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.

| | |
|---|---|
| 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 |

### *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.

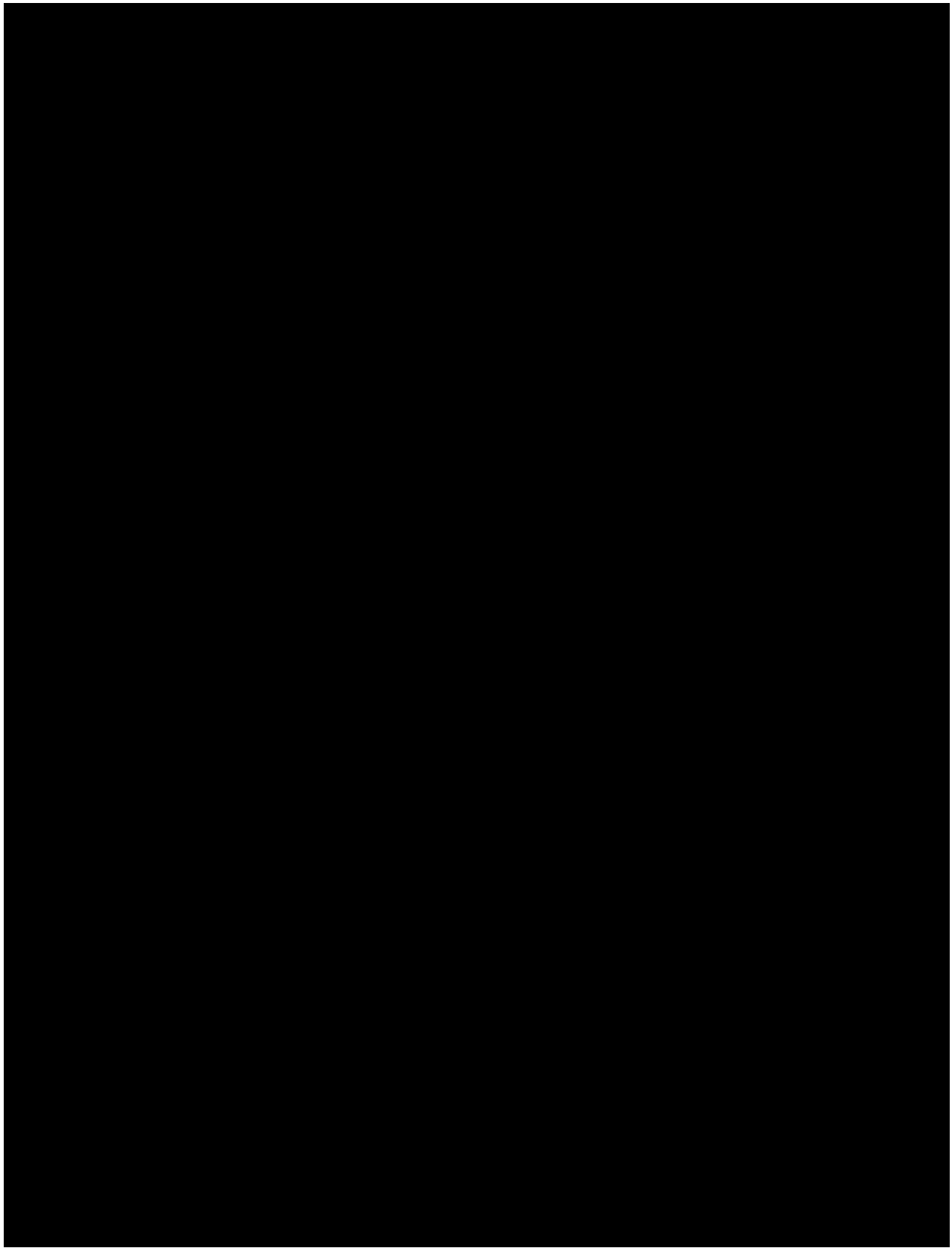
- To evaluate the safety and tolerability of rimegepant.

- 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.



## 3.4 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.

[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).

| **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** | **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] | | | | | | |

### *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]

- 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):

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.

# 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).

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;

# 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.

# 16 REFERENCES

1. Marcus R, Goadsby PJ, Dodick D, Stock D, Manos G, Fischer TZ. BMS-927711 for the acute treatment of migraine: a double-blind, randomized, placebo controlled, dose-ranging trial. *Cephalalgia.* 2014;34(2):114-125.

2. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia.* 2018;38(1):1-211.

3. CN170003. A Phase 2b, adaptive, double-blind, randomized, multi-center outpatient, dose-ranging trial to evaluate the efficacy and safety of BHV-92771 for the acute treatment of moderate or severe migraine.

4. CN170002. *Effect of BMS-927711 on the Pharmacokinetics of a Combined Oral Contraceptive Containing Ethinyl Estradiol and Norgestimate in Healthy Female Subjects.* Bristol-Myers Squibb Company;2012.

5. CN170004. *Phase 1 open-label, randomized single sequence study with two dose groups to compare the pharmacokinetics of BMS-927711 in migraine subjects during an acute migraine attack and during nonmigraine period.* Bristol-Myers Squibb Company;2012.

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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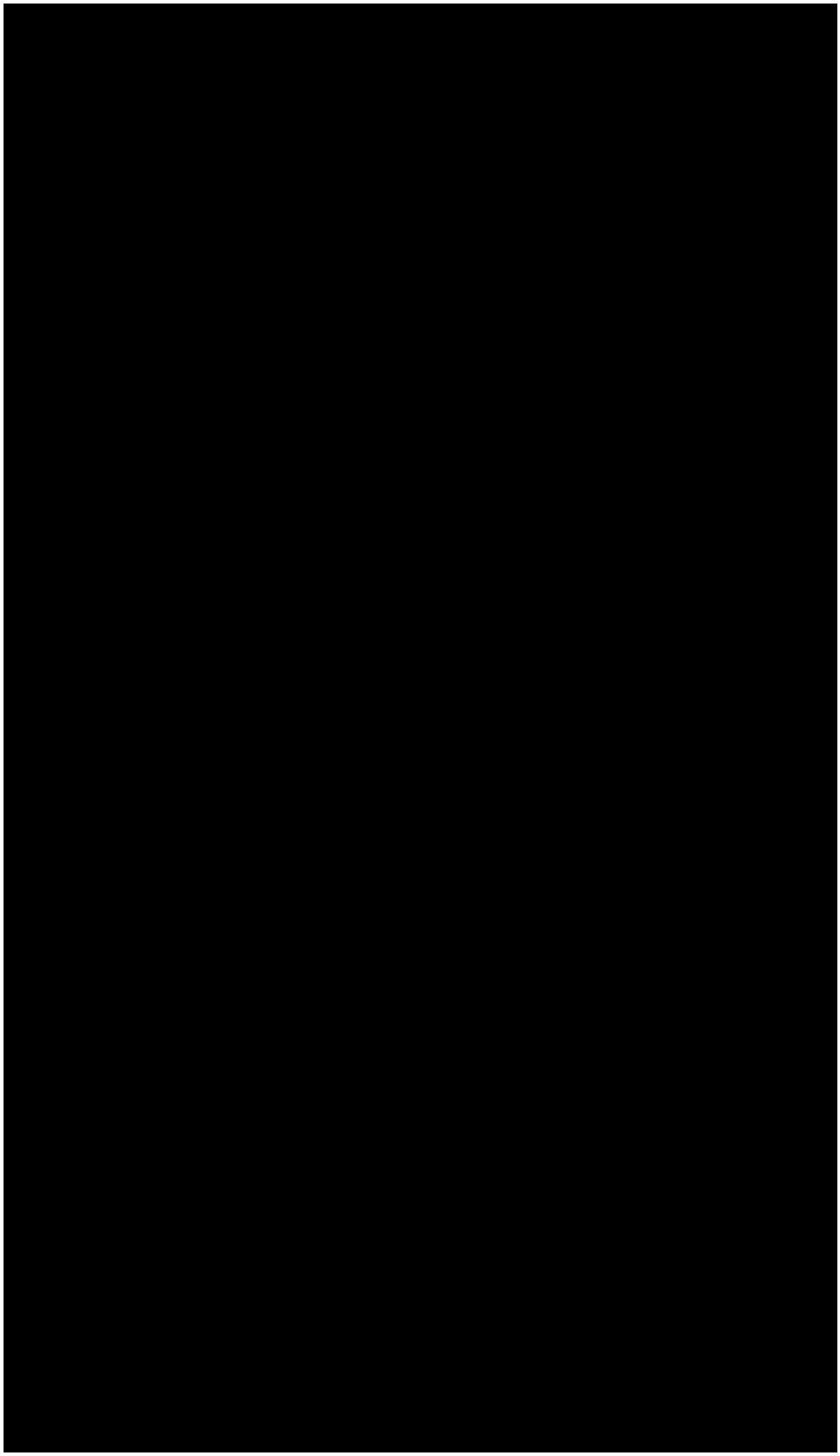


| | |
|---|---|
| min | Minute |
| mmHg | Millimeters Mercury |
| NOEL | No Observed Effect Level |
| NOAEL | No Observed Adverse Event Level |
| O-L | Open-label |
| PK | Pharmacokinetic |
| PO | By Mouth, Orally |
| [redacted] | |
| QD | Once Daily |
| QTc | Interval between Q-wave and T-wave in the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

# 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

# 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.

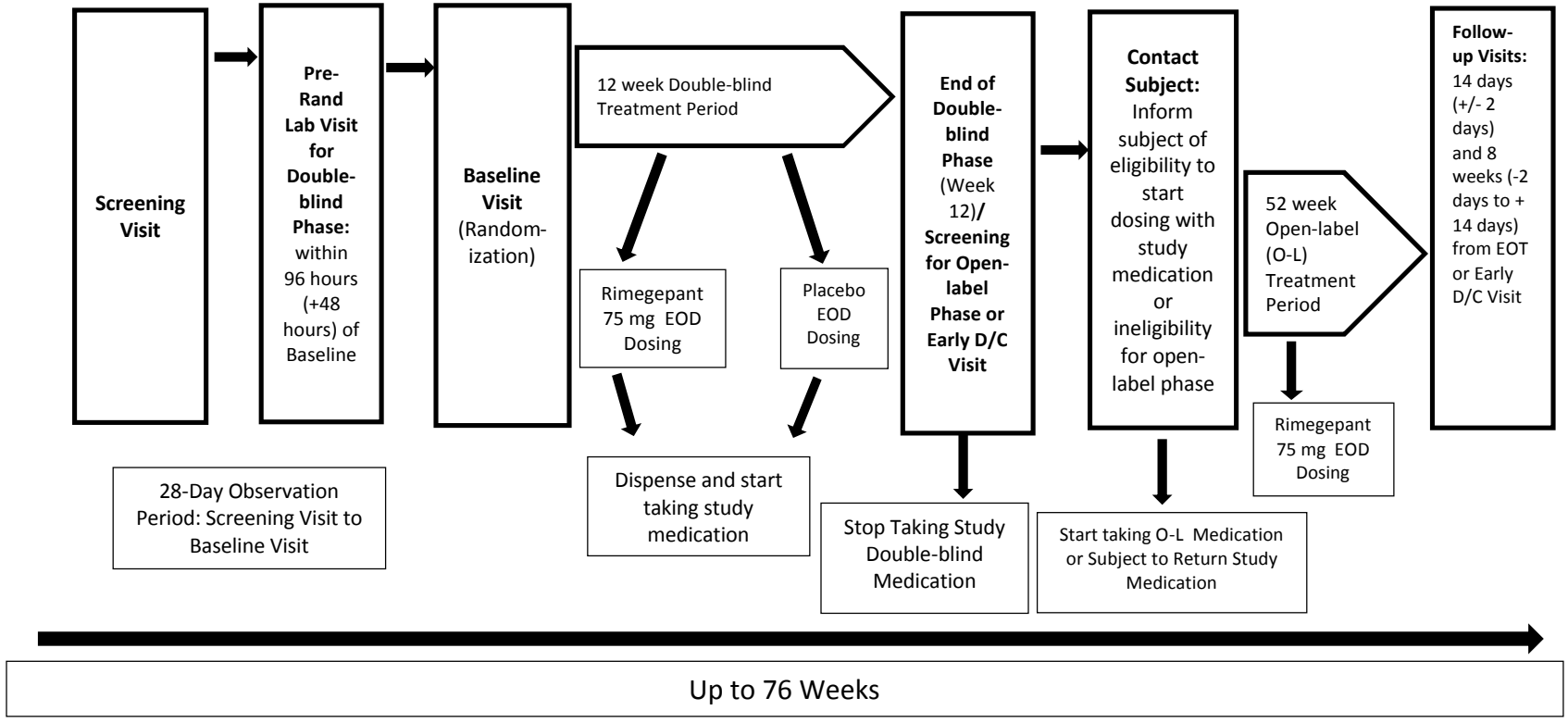
At the Baseline Visit, eligibility for continued participation in the study will be assessed before randomization occurs and study medication will be dispensed. Subjects will be instructed that they must take one tablet of blinded study drug every other calendar day. If subjects have a migraine during 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]

## 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**



| **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.

| **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.

# 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.

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]

### *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)

## 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.

- 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.

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.

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