Biohaven Pharmaceuticals

Protocol BHV3000-201

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

Statistical Analysis Plan

Version 6.0

Date: 29-July-2019

SIGNATURE PAGE

Protocol Title:	A Multicenter, Open Label Long-Term Safety Study of BHV-3000 in the Acute Treatment of Migraine
Sponsor:	Biohaven Pharmaceuticals, Inc
Protocol Number:	BHV3000-201
Document Version/Date:	Protocol Version 6.0/20-December-2018
Author:	PPD

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report (CSR).

Sponsor Signatories:

PPD

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ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic class
BMI	Body mass index
BUN	Blood urine nitrogen
CGI-C	Clinical Global Impression - Change
CGRP	Calcitonin gene-related peptide
CI	Confidence interval
CPK	Creatinine phosphokinase
CRF	Case report form
CSR	Clinical study report
CV	Cardiovascular
DILI	Drug-induced liver injury
ECG	Electrocardiogram
EOD	Every other day
EOT	End of treatment
HDL	High-density lipoprotein
ICH	International Conference on Harmonization
IP	Investigational product
IRB/EC	Institutional Review Board/Ethics Committee
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LFT	Liver function test
LTT	Long-term treatment period
MIDAS	Migraine Disability Assessment
MSQoL	Migraine Specific Quality of Life Questionnaire
OP	Observational period
PID	Patient identifier
PoM	Preference of medication
PRN	Pro re nata (“when necessary”)

Abbreviation	**Definition**
PT	Preferred term
PVD	Peripheral vascular disease
QD	Quaque Die (one daily)
S-STS	Sheehan-Suicidality Tracking Scale
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System Organ Class
SM	Satisfaction with Medication
TEAE	Treatment-emergent adverse event
TBL	Total bilirubin
TIA	Transient ischemic attack
TLF	Table listing figure
ULN	Upper limit of normal

REVISION HISTORY

Version	Description of Change
1.0	Original Issue
2.0	• Added "Revision History" table after "Abbreviations" table. • Section 2.3: Replaced "treatment-emergent" with "on treatment". • Section 2.3.3: Specified that MSQoL, MIDAS, CGI-C, PoM and SM questionnaire are outcomes research, whereas S-STS is safety. • Section 3.1: Added definition of follow-up subjects. • Section 4.2.6: Added a reference to Section 5.1.2. • Section 4.4: Added a table of populations for analyses. • Section 4.6: Specified how outcomes research questionnaires are assessed over time. • Section 4.6.1: Replaced "treatment-emergent" with "on-treatment". Added a reference to Section 5.1.2. Specified that clinically significant laboratory abnormalities will be graded according to CTCAE numeric laboratory test criteria if available, otherwise according to DAIDS. • Section 4.6.2: Replaced "treatment-emergent" with "on-treatment", and added "and follow-up" to concurrent LFT elevations. • Section 4.6.3.1: Added 2 tables of LFT elevations, one for treated subjects who did not participate in previous studies and one for follow-up subjects. Added mutually exclusive categories to the LFT elevation table. Specified that longitudinal LFT elevation plots will also display the starts of the on-treatment and follow-up safety analysis periods. Added the follow-up safety analysis period to the by-subject longitudinal plots and the fifth eDISH plot. Added a table of time to first on-treatment LFT elevations for treated subjects. Specified that for all analyses in this section, subjects must have non-missing LFT data in the safety analysis period to be included. • Section 4.6.3.2: Revised definition of concurrent to be generic across analysis period. Specified MedDRA PTs for AEs of special interest. • Sections 4.6.3.6, 4.6.3.10, 4.6.3.11: Removed "on-treatment". • Sections 4.6.3.8: Specified that values and changes from baseline will be summarized at baseline and at each scheduled visit in the on-treatment and follow-up safety analysis periods. • Section 4.8: Replaced "rating scales, questionnaires" with "S-STS". Specified how continuous safety endpoints are assessed over time in safety analysis periods. • Section 4.8.1: Specified 4-week intervals for Kaplan-Meier plot. • Section 4.8.2: Added AEs of special interest to overiew AE table. Specified that pre-treatment AEs for treated subjects include severity. Replaced "treatment-emergent" with "on-treatment" in numerous places. Replaced "on-treatment not TE" overview table with "TEAE" overview table. Added 2 tables of on-treatment AEs occurring in ≥ 2% of subjects in any enrollment group (all; related to study drug). Added 3 tables of follow-up AEs (overview; by severity; SAE). Updated definition of AE related to study drug to include "not reported" relationship. Specified that only AE start dates will be imputed. • Section 5.1: Renamed to "General". Moved existing text to new Section 5.1.1 "Output Layout". Added new Section 5.1.2 "Rounding Rules".

Version	Description of Change
	• Section 4.8.3: Marked select laboratory tests graded according to DAIDS. Specified that tables will present laboratory tests alphabetically within laboratory test group, as applicable. Removed "CTCAE" from fourth paragraph. Added 2 tables of worst follow-up laboratory abnormalities. Changed ALT/AST shift categories to be mutually exclusive. Specified that values and changes from baseline will be summarized at baseline and at each scheduled visit in the on-treatment and follow-up safety analysis periods. Removed listings of abnormal laboratory values. • Sections 4.8.4 and 4.8.5: Added Follow-up Week 2 as a scheduled visit. Specified that values and changes from baseline will be summarized at baseline and at each scheduled visit in the on-treatment and follow-up safety analysis periods. • Section 5.4: Changed definition of the on-treatment safety analysis period. Added definition of the follow-up safety analysis period. • Section 5.6.1.1: Removed "and End" from title. Changed the algorithm for imputing AE start dates. • Section 5.6.2: Changed the algorithm for imputing non-study medication start and stop dates by adding 2 new subsections 5.6.2.1 and 5.6.2.2, respectively.
3.0	• Signature page: Replaced PPD with PPD . • Abbreviations: Added CGRP. • All Sections: Changed "all subgroups" to "all subgroup of interest" throughout document as needed. • Section 1.1: Modified the protocol version and date. • Section 2.1: Specified that Protocol Version 5.0 was amended to Version 6.0 to re-open study enrollment in the 2-8 moderate to severe migraine attacks per month group to approximately 20 subjects at select sites in order to assess safety of rimegepant in combination with FDA-approved calcitonin gene-related peptide (CGRP) antagonist biologics (Aimovig™, Ajovy™, Emgality™). Patients at select sites with a history of 2-8 moderate to severe migraines/month taking a stable FDA-approved CGRP antagonist biologic will be instructed to take a maximum of one tablet per calendar day for 12 weeks to treat migraines of mild, moderate, or severe intensity. These subjects will follow the same study visit schedule as subjects in the 12-week EOD+PRN dosing group. • Section 2.2: Modified title of Figure 2. • Section 2.3.3: Updated "Variable" and "Pop. Summary" rows for PoM, S-STS, and SM in Table 3. • Section 4.2.1: Specified the subjects in the "PRN (2-8) Dosing" enrollment group. • Section 4.2.6: Removed triptan non-responder as a subgroup of interest. Specified that the triptan non-responder subgroup will be derived according to Section 5.2.1, included in the subgroup summary table, and excluded from subgroup tabulations by subgroup level and overall. • Section 4.5: Defined time since last migraine and imputation of partial and missing last migraine dates. Modified the definition of baseline. • Section 4.6.3.1: Added 1 table of exposure-adjusted on-treatment LFT elevations for treated subjects. • Section 4.6.3.5: Changed percent decrease category of "≤ 0" to "< 1". • Sections 4.6.3.7 and 4.6.3.9: Specified that results will be summarized at each scheduled visit and last visit.

Version	Description of Change
	• Section 4.6.3.8: Added 1 table of worst on-treatment change from baseline category. • Sections 4.6.3.6, 4.6.3.7, 4.6.3.9, 4.6.3.10, 4.6.3.11, 4.8.3, and 4.8.5: Clarified the visit schedule for the 52-week PRN (2-8) and (9-14) dosing groups versus the 12-week EOD+PRN and PRN (2-8) dosing groups. • Section 4.8.1: Added 2 parameters to the eDiary exposure table: ≥ 8 tablets per 4 weeks for 4, 8, 12, 16, 20, ≥ 24, and ≥ 12 weeks; total rimegepant exposure summed across all subjects. • Section 4.8.2: Added 4 tables: pre-treatment AEs leading to study drug discontinuation for treated subjects; exposure-adjusted AEs for treated subjects; exposure-adjusted SAEs for treated subjects; follow-up AEs leading to study drug discontinuation for follow-up subjects. • Section 4.8.3: Aligned laboratory tests with the clinical database. • Section 5.1.1: Specified that a list of tables, listings, and figures and corresponding templates will be presented separately in the Mock TLF document. • Section 5.3: Specified that EOT visit date/time is derived only for subjects who have non-missing completion status on the Study Exit Status CRF. • Section 5.4: Modified titles and column 1 headers of Tables 6 and 7. • Section 5.6.1.3: New section added to define exposure-adjusted AEs.
4.0	• Section 3: Renamed section as "Populations for Analyses". Removed Sections 3.1 and 3.2. Specified a table of populations for analyses. Added a by-subject listing of populations for analyses for screened subjects. • Section 3.2: Moved text to new Section 4.4.2. • Section 4.4: Renamed section as "Study Population". Restructured subsections for subject disposition (Section 4.4.1) and protocol deviations (Section 4.4.2). Added a table of significant protocol deviations for treated subjects. • Section 4.5: Modified derivation of time since last migraine. • Section 4.6.3.1: Specified that the eDISH plot is a scatter plot. • Section 4.6.3.5: Added percent changes to the tables of values and changes over time. Added longitudinal analyses to the tables of decrease categories. Specified that percent change/decrease analyses must also be on subjects with ≥ 1 total number of migraine days during the OP. Specified the by-subject listing of migraine attacks and severity. Added a by-subject listing of migraine days during 4-week intervals in LTT for treated subjects. • Section 4.8: Specified the by-subject listing of procedures for screened subjects. Added a by-subject listing of safety narrative subject identifiers for treated subjects. • Section 4.8.1: Added new categorical parameters to exposure tables. Specified by-subject listings of eDiary exposure and drug accountability, and batch numbers for treated subjects. Added a by-subject listing of eDiary exposure over 4-week intervals during LTT for treated subjects. Added a table of eDiary compliance during OP and LTT, and defined compliance. • Section 4.8.2: Added listings of AEs of special interest. • Section 4.8.3: Removed urine choriogonadotropin beta as a test of interest. Moved text on handling bi-directional tests from shift from baseline tables to worst toxicity tables. Added text to describe how subjects with low, normal, and high values are counted in shift from baseline tables. Specified select laboratory test groups for listings. Added by-subject listings of endocrinology, serology, and miscellaneous lab test results, and LFT values and ratios to ULN for screened subjects. • Sections 4.8.4 and 4.8.5: Specified by-subject listings for screened subjects.

Version	Description of Change
	• Section 4.9: Replaced "PT" with "preferred name". • Section 5.1.3: New section added to describe conventions for handling duplicate subjects. • Section 5.6.1.2: Modified algorithm for euphoria-related AEs under drug abuse AEs.
5.0	• Table 3: Specified that MSQoL, MIDAS, CGI-C will also be assessed at the last visit. Modified text on S-STS to be consistent with Section 4.6.3.8. • Section 4.4.1: Added 1 listing of eligibility of inclusion and exclusion criteria. • Section 4.6.1: Replaced toxicity grading criteria with a reference to the BHV3000 Core SAP. • Section 4.6.3.1: Specified that exposure-adjusted on-treatment cumulative LFT elevations be assessed. Specified that rates of multiple on-treatment, cumulative and mutually exclusive LFT elevations will be assessed. Added "ALP > 2 x ULN" as a criterion to the by-subject LFT longitudinal plot. For eDISH plots, specified that ratios < 0.1 x ULN will be set to 0.1, and that sample sizes in the legend will represent subjects with paired ratios. • Sections 4.6.3.6, 4.6.3.10, and 4.6.3.11: Specified that results will also be shown at the last visit. • Section 4.6.3.8: Replaced existing tables with 2 tables of worst score change from baseline category. • Section 4.8.1: Added 2 new compliance categories and PoM and SM as subject sources to the eDiary compliance table. Added 1 table of drug accountability compliance. • Section 4.8.2: Added 3 tables (TEAEs occurring in ≥ 2% of subjects in any enrollment group after rounding; AEs leading to study drug discontinuation and hepatic-related AEs leading to study drug discontinuation across all safety analysis periods combined). Removed 2 tables of AEs leading to study drug discontinuation during pre-treatment and follow-up. Changed "drug abuse" to "potential drug abuse". Specified reference dates for exposure-adjusted AE calculations. Specified that potential drug abuse AEs will be displayed in alphabetical order by severity and PT without SOC. • Section 4.8.3: Replaced list of laboratory tests with a reference to the BHV3000 Core SAP. Added 2 tables of laboratory test toxicity grade shifts from baseline. • Section 4.8.4: Added 2 tables of vital sign, physical measurement and ECG abnormalities. • Section 4.8.5: Added QTcB to list of ECG parameters. • Section 5.1.1: Removed Table 4. • Sections 5.1.2 and 5.6: Removed these sections, and replaced references to this section with references to the BHV3000 Core SAP throughout this SAP. • Section 5.1.3: Renumbered as Section 5.1.2. • Section 5.2.1: Renumbered Table 5 as Table 4. • Section 5.5: Renumbered Tables 6 and 7 as Tables 5 and 6, respectively.
6.0	• Signature page: Removed "Summary of Changes" because it was blank and not needed. • Section 2.3.3: Modified Table 3: (1) replaced "last visit" with "last post-baseline visit" for MSQoL, MIDAS, CGI-C, PoM and SM; (2) replaced "3" with "5" preference categories for PoM; (3) removed references to MIDAS total score; (4) updated definition of CGI-C to be consistent with protocol. • Section 4.2.6: Added 3 subgroups: (1) prophylactic migraine medication use on or after study drug start; (2) treated subjects who took ≥ 20 tablets per 4 weeks for ≥ 4 weeks; and (3) treated subjects with near-daily dosing.

Version	Description of Change

- Section 4.6.3.1: Added 2 on-treatment eDISH plots by enrollment group for treated subjects (1) who took ≥ 20 tablets per 4 weeks for ≥ 4 weeks and (2) with near-daily dosing.
- Section 4.6.3.6: Specified that MSQoL will also be evaluated at early termination. Replaced algorithm for deriving transformed scores with a reference to the BHV3000 Core SAP. Replaced "dimension" with "domain" and "preventative" with "preventive". Specified that two-sided normal 95% CIs for mean changes from baseline will be also be presented. Replaced "last visit" with "last post-baseline visit".
- Section 4.6.3.7: Replaced last sentence with a reference to the BHV3000 Core SAP about additional combined categories. Replaced "last visit" with "last post-baseline visit".
- Section 4.6.3.8: Replaced algorithm for deriving scores with a reference to the BHV3000 Core SAP.
- Sections 4.6.3.9 and 4.6.3.11: Specified that percentages will also be displayed with two-sided Agresti-Coull 95% CIs. Added a referece to the BHV3000 Core SAP about additional combined categories. Replaced "last visit" with "last post-baseline visit".
- Section 4.6.3.10: Added a reference to the BHV3000 Core SAP about deriving total, absenteeism, presenteeism, and item scores. Specified that two-sided normal 95% CIs for mean changes from baseline will be also be presented. Replaced "last visit" with "last post-baseline visit".
- Section 4.8.1: Added (1) "≥ 4 weeks" category to exposure over time, and (2) total rimegepant exposure (patient-years) to eDiary exposure tables.
- Section 4.8.2: Removed tables of CV and suicidality AEs by subgroups due to very low frequency.
- Section 4.8.3: Specified that LDL cholesterol and triglycerides will be analyzed as separate laboratory test parameters by 8-hour fasting status with a reference to the BHV3000 Core SAP.
- Section 5.3: Modified "EOT visit date/time" as "EOT visit date" and "Last contact date/time" as "Last contact date".
- Section 5.4: Removed "/time" from derivations of post-enrollment, follow-up, on-treatment safety, and follow-up safety analysis periods.

1 INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1 Introduction

This document presents the statistical analysis plan (SAP) for Biohaven Pharmaceuticals, Protocol BHV3000-201: A Multicenter, Open Label Long-Term Safety Study of BHV-3000 in the Acute Treatment of Migraine.

This SAP is based on Version 6 of the BHV3000-201 protocol dated 20-DEC-2018. It contains the analysis details and methodology to answer the study objectives, including planned summary tables, by-subject listings, and figures, which will provide the basis for the results section of the clinical study report (CSR). Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analyses.

1.2 Study Objectives

1.2.1 Primary Objectives

To evaluate the safety and tolerability of rimegepant.

1.2.2 Secondary Objectives

- To evaluate the frequency of elevations in Alanine Transaminase (ALT) or Aspartate Transaminase (AST) > 3 x the Upper Limit of Normal (ULN) with concurrent elevations in bilirubin > 2 x ULN in subjects treated with rimegepant.

- To evaluate the frequency and severity of hepatic-related adverse events (AEs) and the frequency of hepatic-related treatment discontinuations.

1.2.3 Exploratory Objectives

- To evaluate the frequency of subjects with elevated liver function tests (LFTs); AST, ALT or total bilirubin (TBL).

- To evaluate the frequency of subjects with ALT or AST elevations > 3 x ULN in temporal association with nausea, vomiting, anorexia, abdominal pain or fatigue.

- To explore the contributions of gender, age and exposure to rimegepant to abnormalities in AST, ALT, or bilirubin.

- To investigate the time on treatment and cumulative exposure associated with: (1) hepatic related serious AEs (SAEs) and treatment discontinuations; (2) elevations in ALT or AST > 3 x ULN with concurrent elevations in bilirubin > 2 x ULN.

- To evaluate the number of headache days and severity of migraine attacks while subjects are treated with rimegepant relative to the observational period (OP).

- To evaluate the effect of rimegepant treatment compared to baseline on the 20-Item Migraine-Specific Quality of Life Questionnaire (MSQoL) version 2.1.

- To evaluate the effect of rimegepant treatment compared to baseline on the Migraine Preference of Medication (PoM).

- To examine the scores on the Sheehan Suicidality Tracking Scale (S-STS).

- To evaluate the effect of rimegepant treatment compared to baseline on the Satisfaction with Medication (SM) Survey.

- To evaluate the effect of rimegepant treatment compared to baseline on the Migraine Disability Assessment (MIDAS).

- To evaluate the effect of rimegepant treatment compared to baseline on the Clinical Global Impression – Change (CGI-C) scale.

2 STUDY DESIGN

2.1 Synopsis of Study Design

BHV3000-201 is a Phase IIb, multicenter, open-label study designed to assess the safety and tolerability of long-term use of rimegepant, taken up to one tablet per calendar day, in patients with migraine.

The Screening phase includes a Screening Visit and a 30-day Observation Period (OP). For subjects to be eligible for the study, they must have 2-14 migraine attacks of moderate to severe intensity per month in the 3 months prior to the Screening Visit. Patients enrolled in the every other day (EOD) dosing group must have had 4-14 migraine attacks of moderate to severe intensity per month within the 3 months prior to the Screening Visit. Enrollment into this study will initially be open to patients with 2-8 moderate to severe migraine attacks per month (primarily the patients from BHV3000-301 and BHV-3000-302) for approximately 3 months. After approximately 3 months, study enrollment will open for patients with a history of 9-14 migraine attacks of moderate to severe intensity per month within the 3 months prior to the Screening Visit. Lastly, study enrollment will open for subjects (including patients from BHV3000-303) in the EOD dosing group (4-14 moderate to severe migraines per month).

After providing informed consent, patients will first participate in the Screening phase to determine eligibility for the study. At the Screening Visit, patients will be given an electronic diary (eDiary) to document on each day of the OP if a migraine occurred, intensity, and if it was treated. They will also be given a paper diary to record the standard of care migraine treatment.

After completing the OP, patients will return to the clinic for their Baseline Visit, where enrollment into the Long-Term Treatment (LTT) phase will commence and eligibility for continued participation in the study will be determined before study medication is dispensed. After the investigator reviews the results of the baseline laboratory assessments and determines continued eligibility, the site staff will inform the patient whether or not they are eligible to start

dosing in the Long-Term Treatment (LTT) phase in the 2-8 or 9-14 moderate to severe migraines/month group followed for 52 weeks, or the 4-14 moderate to severe migraines/month group followed for 12 weeks.

If in the 2-8 or 9-14 moderate to severe migraines/month group, patients will be instructed to take study medication at the onset of a migraine (of mild to severe intensity), with a maximum of one tablet per day. If in the 4-14 moderate to severe migraines/month group, patients will be instructed to take study medication every other calendar day, regardless of whether the patient has a migraine. However, they may take a tablet at the onset of a migraine (of mild to severe intensity), even if the migraine begins on a day they are not scheduled to dose.

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

Study visits will be roughly every 2 weeks during the first month and then every 4 weeks until Week 52 (or Week 12 for patients in the EOD+PRN dosing group).

Patients will return to the study site at the end of Week 52 (or Week 12 for patients in the EOD+PRN dosing group) for the End of Treatment (EOT) Visit. There is also a Follow-Up Visit 14 days after the Week 12/Week 52/EOT Visit.

Protocol Version 5.0 was amended to Version 6.0 to re-open study enrollment in the 2-8 moderate to severe migraine attacks per month group to approximately 20 subjects at select sites in order to assess safety of rimegepant in combination with FDA-approved calcitonin gene-related peptide (CGRP) antagonist biologics (Aimovig™, Ajovy™, Emgality™). Patients at select sites with a history of 2-8 moderate to severe migraines/month taking a stable FDA-approved CGRP antagonist biologic will be instructed to take a maximum of one tablet per calendar day for 12 weeks to treat migraines of mild, moderate, or severe intensity. These subjects will follow the same study visit schedule as subjects in the 12-week EOD+PRN dosing group.

2.2 Randomization Methodology

There is no randomization in this open-label trial. Subject numbers, enrollment group, and study medication will be assigned via the Interactive Web Response System (IWRS). Note that enrollment group will be assigned at screening by IWRS based on migraine history in the 3 months prior to the Screening Visit (see Section 2.1).

Figure 1: Study Schematic (Up to 52 Weeks Treatment for 2-8 and 9-14 Moderate to Severe Migraines/Month Groups)

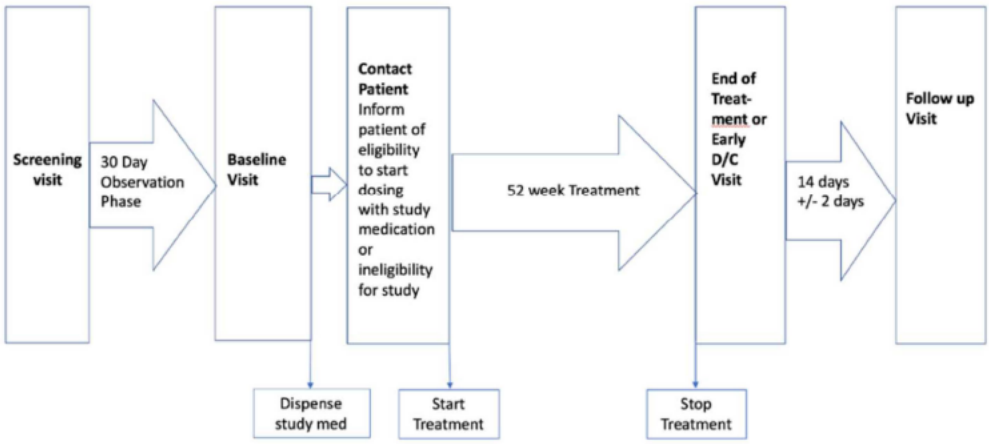
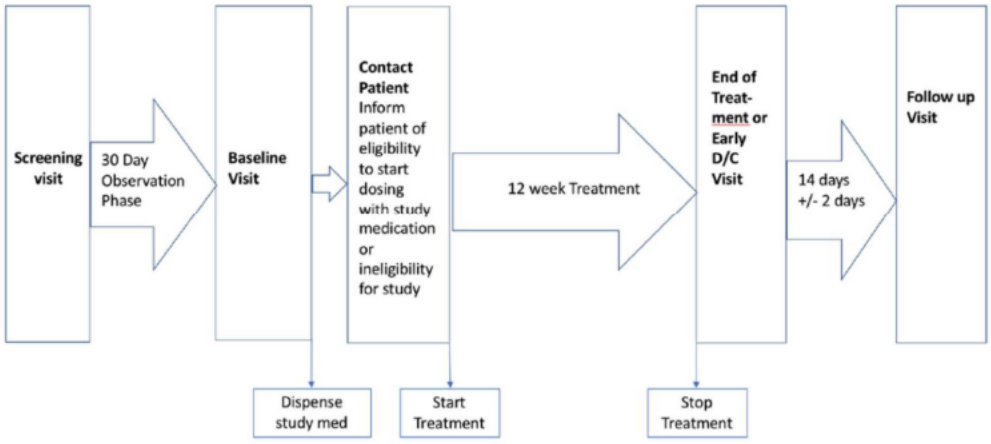


Figure 2: Study Schematic (Up to 12 Weeks Treatment for 4-14 Moderate to Severe Migraines/Month, EOD Dosing Group and Subjects Receiving FDA-Approved CGRP Antagonist Biologics in the 2-8 Moderate to Severe Migraines/Month Group)



2.3 Study Estimands

The tables that follow present the estimands corresponding to the study objectives.

Estimands are not adjusted for intercurrent events. Subjects that discontinue the study are tracked until they are no longer available.

2.3.1 Primary Estimands

The estimands corresponding to the primary endpoint for this study are shown in Table 1.

Table 1: Estimands for the Primary Objective

Objective	**Safety and Tolerability**
Population	All treated subjects
Variables	Number and percentage of subjects with AEs occurring in ≥ 5% of treated subjects by severity, SAEs, AEs leading to study drug discontinuation on treatment, and clinically significant laboratory abnormalities on treatment
Pop. Summary	Frequency by enrollment group and overall

2.3.2 Secondary Estimands

The estimands corresponding to the secondary objectives are shown in Table 2.

Table 2: Estimands for the Secondary Objectives

Objective	**Concurrent LFT elevations – Safety**
Population	All treated subjects
Variables	Number and percentage of subjects with ALT or AST > 3 x ULN concurrent with TBL > 2 x ULN on treatment
Pop. Summary	Frequency by enrollment group and overall
Objective	**Hepatic-related AEs – Safety**
Population	All treated subjects
Variables	Number and percentage of subjects with hepatic-related AEs by severity, and hepatic-related AEs leading to study drug discontinuation on treatment
Pop. Summary	Frequency by enrollment group and overall

2.3.3 Exploratory Estimands

The estimands corresponding to the exploratory objectives are shown in Table 3.

Table 3: Estimands for the Exploratory Objectives

Objective	**LFT elevations – Safety**
Population	All treated subjects
Variables	Number and percentage of subjects with LFT elevations (ALT, AST or TBL) on treatment
Pop. Summary	Frequency by enrollment group and overall
Objective	**LFT elevations > 3 x ULN in temporal association with AEs – Safety**
Population	All treated subjects
Variables	Number and percentage of subjects with ALT or AST > 3 x ULN concurrent with nausea, vomiting, anorexia, abdominal pain or fatigue on treatment
Pop. Summary	Frequency by enrollment group and overall
Objective	**LFT abnormalities and elevations by subgroups – Safety**
Population	All treated subjects
Variables	Number and percentage of subjects with LFT abnormalities and elevations on treatment by sex, age, exposure to rimegepant
Pop. Summary	Frequency by subgroup level
Objective	**Hepatic-related AEs and concurrent LFT elevations by rimegepant exposure – Safety**
Population	All treated subjects
Variables	Number and percentage of subjects with hepatic-related SAEs, hepatic-related AEs leading to study drug discontinuation, and ALT or AST > 3 x ULN concurrent with total bilirubin > 2 x ULN on treatment
Pop. Summary	Frequency by time on rimegepant, cumulative rimegepant exposure, and average rimegepant exposure
Objective	**Migraine Days and Severity – Outcomes Research**
Population	All treated subjects
Variables	Change from OP in the number of migraine days per 4 weeks during LTT(1) over time by 4-week intervals and (2) overall average, by severity (total; moderate or severe)
Pop. Summary	Change from OP by enrollment group and overall
Objective	**Migraine-Specific Quality of Life (MSQoL) Questionnaire – Outcomes Research**
Population	All treated subjects
Variable	Change from baseline in the MSQoL score over time for each dimension
Pop. Summary	Change in MSQoL score from baseline by enrollment group and overall at each post-baseline visit and the last post-baseline visit for each dimension

Table 3: Estimands for the Exploratory Objectives (Continued)

Objective	**Preference of Medication (PoM) – Outcomes Research**
Population	All treated subjects
Variable	Number and percentage of subjects in each of 5 preference categories (much better to much worse) of study medication relative to previous migraine medications over time
Pop. Summary	Frequency by enrollment group and overall at each post-baseline visit and last post-baseline visit
Objective	**Sheehan-Suicidality Tracking Scale (S-STS) – Safety**
Population	All treated subjects
Variable	Worst change from baseline in S-STS total score and subscale scores
Pop. Summary	Change from baseline to worst (highest) score on-treatment and follow-up by enrollment group and overall; number and percentage of subjects in each of 5 worst change from baseline score categories (< -1, -1, no change, 1, > 1) on-treatment and follow-up by enrollment group and overall
Objective	**Satisfaction with Medication (SM) – Outcomes Research**
Population	All treated subjects
Variable	Number and percentage of subjects in each of 7 satisfaction categories (completely satisfied to completely dissatisfied) of study medication over time
Pop. Summary	Frequency by enrollment group and overall at each post-baseline visit and last post-baseline visit
Objective	**Migraine Disability Assessment (MIDAS) – Outcomes Research**
Population	All treated subjects
Variable	Change from baseline in MIDAS scores over time
Pop. Summary	Change in MIDAS scores from baseline by enrollment group and overall at each post-baseline visit and last post-baseline visit
Objective	**Clinical Global Impression - Change (CGI-C) – Outcomes Research**
Population	All treated subjects
Variable	Number and percentage of subjects in each of 7 improvement categories (very much improved to very much worse) relative to investigator's past experience with other patients with the same diagnosis over time
Pop. Summary	Frequency by enrollment group and overall at each post-baseline visit and last post-baseline visit

3 POPULATIONS FOR ANALYSES

The following populations for analyses will be evaluated and used for presentation and analysis of the data:

- Screened subjects: Subjects who sign an informed consent form and are assigned a subject identification number and enrollment group by IWRS.
- Enrolled subjects: Screened subjects who have a non-missing enrollment date (i.e., enrolled in the LTT period).
- Treated subjects: Enrolled subjects who take any amount of rimegepant.
- Follow-up subjects: Treated subjects whose last contact date is in the follow-up safety analysis period (see Sections 5.3 and 5.4).

The number of subjects in each population will be presented by enrollment group and overall. A by-subject listing of populations for analyses will be provided for screened subjects.

4 STATISTICAL METHODS

4.1 Sample Size Justification

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

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

4.2 General Statistical Methods and Data Handling

4.2.1 General Methods

Tabulations will be produced by enrollment group (PRN Dosing (2-8), PRN Dosing (9-14), EOD+PRN Dosing (4-14)) and overall, unless specified otherwise. Note that "enrollment group" refers to the dosing groups assigned at screening based on migraine history during the 3 months prior to the Screening Visit (see Sections 2.1 and 2.2). The "PRN Dosing (2-8)" enrollment group will include subjects with a history of 2-8 moderate to severe migraines per month receiving rimegepant PRN for 52 weeks (i.e., "52-week PRN (2-8)") and subjects receiving rimegepant PRN with FDA-approved CGRP antagonist biologics for 12 weeks (i.e., "12-week PRN (2-8)").

Refer to the BHV3000 Core SAP for descriptive statistics, counting rules, rounding rules, dictionaries for coding AEs, medical history, and non-study medications, and examples of complete dates.

See Section 5 for conventions.

4.2.2 Computing Environment

All statistical analyses will be performed using SAS statistical software (Version 9.4 or higher).

4.2.3 Methods of Pooling Data

Enrollment groups are pooled for analysis of endpoints of interest by all subgroups of interest (see Section 4.2.6).

4.2.4 Adjustments for Covariates and Stratification

This is not applicable to this study.

4.2.5 Multiple Comparisons

This is not applicable to this study.

4.2.6 Subpopulations

The subgroups of interest for this study are the following:

- Intrinsic factors
  - Age: categorized as < 40, ≥ 40, < 65, ≥ 65
  - Sex: female, male
  - Sex and age: female < 40, female ≥ 40, male < 40, male ≥ 40
  - Race: white, black or African American, other including Asian, Asian
  - Ethnicity: Hispanic or Latino, not Hispanic or Latino
- Extrinsic disease-related factors
  - CV risk contraindicating triptans: yes, no (see Section 5.2.2)
  - Baseline body mass index (BMI; kg/m^2): categorized as < 25, ≥ 25 to < 30, ≥ 30
  - Prophylactic migraine medication use on or after study drug start: yes, no (see Section 4.9)
- Extrinsic exposure factors
  - Time on rimegepant (weeks): categorized as quintiles for treated subjects (see Sections 4.8.1 and 5.2.3)

- Cumulative rimegepant exposure (tablets): categorized as quintiles for treated subjects (see Sections 4.8.1 and 5.2.3)
- Key factors
  - Average rimegepant exposure (tablets per 4 weeks): categorized as < 2, ≥ 2 to < 8, ≥ 8 to < 14, < 14, ≥ 14 for treated subjects (see Section 4.8.1)
  - Average rimegepant exposure (tablets per 4 weeks) for EOD+PRN treated subjects: categorized as < 14, ≥ 14 (see Section 4.8.1)
  - Treated subjects who took ≥ 14 tablets per 4 weeks for ≥ 12 weeks: categorized by enrollment group (see Section 4.8.1)
  - Treated subjects who took ≥ 20 tablets per 4 weeks for ≥ 4 weeks: categorized by enrollment group (see Section 4.8.1)
  - Treated subjects with near-daily dosing, defined as those in the (1) PRN dosing groups who took ≥ 14 tablets per 4 weeks for ≥ 12 weeks (see previous bullet), or (2) EOD+PRN dosing group: categorized by enrollment group.

Subgroup levels may be combined or redefined based on the availability of the data.

Subgroup tabulations will be by subgroup level and overall for treated subjects with non-missing subgroup level data. Refer to the BHV3000 Core SAP for rounding rules.

The triptan non-responder (yes, no) subgroup will be derived according to Section 5.2.1, included in the subgroup summary table (see Section 4.5), and excluded from subgroup tabulations by subgroup level and overall.

4.2.7 Withdrawals, Dropout and Loss to Follow-Up

Subjects who withdrew from the study were not replaced.

4.2.8 Missing, Unused and Spurious Data

Analyses will be based on observed data only.

4.3 Planned Analyses

During the course of this study, laboratory, safety and exposure data will be monitored on an ongoing basis. The analyses planned for endpoints that use data from this study may be conducted after an interim database lock, prior to last patient last visit. The CSR will be produced after last patient last visit and final database lock.

4.4 Study Population

4.4.1 Subject Disposition

Subject disposition will be summarized for screened subjects by enrollment group and overall as the number and percentage of subjects in the following categories:

- Screened (identified as subjects with non-missing informed consent date and enrollment group)
- Did not enroll in the LTT period (identified as screened subjects with missing IWRS enrollment date)
    - Did not enter the OP (identified as a subset with missing OP start date)
        - Reasons for discontinuation, including not reported*
    - Entered the OP (identified as a subset with non-missing OP start date)
        - Reasons for discontinuation, including not reported*
- Enrolled in the LTT period (identified as screened subjects with non-missing IWRS enrollment date)
    - Not treated (identified as enrolled subjects with missing study drug dose start date)
        - Reasons for discontinuation, including not reported*
    - Treated (identified as enrolled subjects with non-missing study drug dose start date)
        - Ongoing (identified as treated subjects with missing study drug last dose date)
        - Completed* (identified as treated subjects with non-missing study drug last dose date who completed)
        - Discontinued* (identified as treated subjects with non-missing study drug last dose date who discontinued)
            - Reason for discontinuation, including not reported*

The categories marked in with "*" will be based on the Study Exit Status CRF.

Subject disposition will be also be summarized for treated subjects by all subgroups of interest defined in Section 4.2.6.

Participation in previous Studies BHV3000-301/302/303 will be summarized by enrollment group and overall for the following populations: screened; enrolled; treated. The number and percentage of subjects in each previous study (total; 301; 302; 303) and treatment group (rimegepant, placebo) will be presented for each population. Note that subjects may participate in multiple studies and be in both treatment groups.

A by-subject listing of subject disposition information, including the reason for discontinuation and previous study participation, will be presented based on the Study Exit Status CRF for screened subjects.

A by-subject listing of eligibility with inclusion and exclusion criteria will be provided for all screened subjects, not just those who have non-missing criteria.

4.4.2 Protocol Deviations

A protocol deviation is any variance from the approved protocol, either intentional or unintentional. The possible categories for all protocol deviation are as follows:

- Informed Consent
- Inclusion/Exclusion Criteria (specify #)
- Concomitant Medication
- SAE Reporting
- Regulatory
- Drug Storage/Preparation
- Drug Administration
- Visit Schedule
- EPro Diary Noncompliance
- Noncompliance (i.e., trends, missed assessments).

A significant protocol deviation is any deviation that could impact subject safety or the integrity of the trial. For the purposes of this study, significant protocol deviations will be defined as the following:

- Inadequate informed consent or initiation of study procedures prior to completing the informed consent
- Subjects receiving an enrollment date in IWRS, but not meeting the inclusion/exclusion criteria
- Unreported SAEs
- Use of prohibited medication as defined by the protocol
- eDiary non-compliance
- Repeated deviations of the same nature for a given site or subject

The sponsor or designee will be responsible for producing the final significant protocol deviation file (formatted as a Microsoft Excel file). This file will include site, subject ID, deviation date, deviation type, and a description of the protocol deviation.

The number and percentage of treated subjects with significant protocol deviations will be summarized by deviation type and by enrollment group and overall. Deviation types will be presented in descending order of overall frequency.

A by-subject listing of significant protocol deviations will be provided for screened subjects.

4.5 Pre-Treatment Characteristics

The following pre-treatment characteristics will be summarized descriptively by enrollment group and overall for treated subjects:

- Demographics and baseline characteristics*#: age (years), continuous and categorical in the subgroups specified in Section 4.2.6; sex; race; ethnicity; height (cm); weight (kg); body mass index (BMI; kg/m^2), continuous and categorical in the subgroups specified in Section 4.2.6.

- Medical history by system organ class (SOC) and preferred term (PT)

- Migraine history#: age (years) at migraine onset; time since last migraine (days); number of moderate to severe migraines per month; average duration of untreated migraine attacks (hours); primary migraine type (migraine without aura, migraine with aura); history of migraine without aura; migraine symptoms (e.g., headache attacks lasting 4-72 hours, unilateral location); history of migraine with aura; aura symptoms (e.g., visual, sensory); migraine with aura type (migraine with typical aura, typical aura with headache, typical aura without headache)

- Cardiac and other risk factors*: ischemic coronary artery disease (e.g., angina pectoris, myocardial infarction); other significant underlying cardiovascular disease, etc.

- Prior triptan response by historically discontinued triptan, route (e.g., intravenous, nasal), and reason for discontinuation (e.g., took too long to relieve headache pain) subcategorized as most or all of the time, some of the time, rarely, or never

- Current triptan response by currently used triptan, route (e.g., intravenous, nasal), and durability of effect (e.g., freedom from pain within 2 hours, often satisfied with speed of pain relief) subcategorized as never, rarely, some of the time, most of the time, or all of the time.

Endpoints marked with "*" will be also be summarized by subgroup level and overall for treated subjects by all subgroups of interest defined in Section 4.2.6. Endpoints marked with "#" will also be summarized by enrollment group and overall for screened subjects who were not treated.

The number and percentage of subjects in all subgroups specified in Section 4.2.6 will be tabulated for treated subjects by enrollment group and overall.

These data will also be provided in by-subject listings.

For screened subjects who were not enrolled, baseline is defined as the last non-missing value available. For enrolled subjects who were not treated, baseline is defined as the last non-missing value on or before the IWRS enrollment date/time. For treated subjects, baseline is defined as

the last non-missing value on or before the study drug first dose date/time (i.e., in the pre-treatment analysis period; see Sections 5.3 and 5.4).

Age (years) at informed consent is calculated as: (informed consent date - birth date + 1) / 365.25.

For migraine history, time since last migraine (days) is calculated as informed consent date – imputed last migraine date for subjects with imputed last migraine date up to 1 year before informed consent date. Last migraine dates will be imputed for partial and missing dates using the same methodology as for imputation of AE start dates, but using the informed consent date as the surrogate date. Refer to the BHV3000 Core SAP for AE start date imputation.

For each subject, multiple medical histories of the same SOC or PT will be counted only once within each SOC and PT. Medical histories will be presented in descending order of overall frequency within SOC and PT.

4.6 Safety, Tolerability and Other Evaluations

Unless otherwise noted, all primary, secondary and exploratory analyses will be conducted using all treated subjects. All data will also be included in by-subject listings that will include enrollment group and time point (as applicable). The terms "on-treatment" and "follow-up" will apply to the on-treatment and follow-up safety analysis periods, respectively (see Section 5.4) unless specified otherwise.

Outcomes research (non-safety) questionnaires and rating scales are MSQoL, MIDAS, CGI-C, PoM, and SM (see Section 2.3.3). MSQoL, MIDAS, and CGI-C will be summarized as continuous parameters at baseline and each scheduled visit over time. Post-baseline measurements will be slotted into analysis visit windows in the post-enrollment and follow-up analysis periods (see Section 5.4). If a subject has multiple values in an analysis visit window, then the non-missing value closest to the target date for the visit will be used; in the case of a tie, the latest value collected will be used. See Sections 4.5, 5.4 and 5.5 for definitions of baseline, analysis periods, and analysis visit windows, respectively.

4.6.1 Primary Safety Endpoints

The following primary endpoints to examine safety and tolerability are summarized by enrollment group and overall: frequency and severity of AEs occurring in ≥ 5% of treated subjects, SAEs, AEs leading to study drug discontinuation, and clinically significant laboratory abnormalities.

On-treatment AEs as described above will be shown in separate tables by SOC and PT for each endpoint (AEs occurring in ≥ 5% of subjects in any enrollment group by severity [mild, moderate, severe, moderate or severe, not reported, total], SAEs, AEs leading to study drug discontinuation). The 5% cut applies to the percentage of subjects with a PT in any enrollment group, regardless of severity. See Section 4.8.2 for additional details about AEs, and a comprehensive list of AE tables. Refer to the BHV3000 Core SAP for rounding rules.

4.6.2 Secondary Safety Endpoints

The following secondary endpoints will be summarized by enrollment group and overall: frequency of on-treatment elevations of AST or ALT > 3 x ULN concurrent with TBL > 2 x ULN; frequency and severity of on-treatment hepatic-related AEs; and frequency of on-treatment hepatic-related AEs leading to study drug discontinuation.

AST or ALT > 3x ULN concurrent with TBL > 2 x ULN is defined as elevations on the same collection date, and will be summarized as the number and percentage of subjects experiencing these elevations concurrently on treatment and during follow-up. This will include two-sided Agresti-Coull 95% CIs for each percentage. These will be summarized together in the same table as other LFT elevation endpoints (see Section 4.6.3.1).

Refer to the BHV3000 Core SAP for hepatic-related AEs.

See also Section 4.8.2 for additional details about AEs, and a comprehensive list of AE tabulations.

4.6.3 Exploratory Safety and Other Endpoints

4.6.3.1 LFT Elevations

The number and percentage of subjects with LFT elevations will be summarized separately for the following populations and safety analysis periods:

- Screened subjects during pre-treatment by enrollment group, and overall
- Treated subjects during pre-treatment by enrollment group and overall
- Treated subjects on-treatment by enrollment group and overall
- Treated subjects on-treatment by subgroup level and overall for all subgroups of interest specified in Section 4.2.6
- Treated subjects on-treatment by enrollment group and overall for subjects who did not participate in previous Studies BHV3000-301/302/303
- Follow-up subjects during follow-up by enrollment group and overall.

LFT elevations include the following endpoints:

- Cumulative elevations:
  - ALT > 1 x, > 3 x, > 5 x, > 10 x, and > 20 x ULN
  - AST > 1 x, > 3 x, > 5 x, > 10 x, and > 20 x ULN
  - ALT or AST > 1 x, > 3 x, > 5 x, > 10 x, and > 20 x ULN
  - TBL > 1 x, 1.5 x, and > 2 x ULN
  - Alkaline phosphatase (ALP) > 1 x, > 1.5 x, and > 2 x ULN

- Mutually exclusive elevations:
  - ALT > ULN to ≤ 3 x ULN, > 3 x ULN to ≤ 5 x ULN, > 5 x ULN to ≤ 10 x ULN, > 10 x ULN to ≤ 20 x ULN, and > 20 x ULN
  - AST > ULN to ≤ 3 x ULN, > 3 x ULN to ≤ 5 x ULN, > 5 x ULN to ≤ 10 x ULN, > 10 x ULN to ≤ 20 x ULN, and > 20 x ULN
  - ALT or AST > ULN to ≤ 3 x ULN, > 3 x ULN to ≤ 5 x ULN, > 5 x ULN to ≤ 10 x ULN, > 10 x ULN to ≤ 20 x ULN, and > 20 x ULN
- Composite elevations:
  - ALT or AST > 3 x ULN and TBL > 1.5 x ULN
  - ALT or AST > 3 x ULN and TBL > 2 x ULN
  - ALT or ALT > 3 x ULN concurrent with TBL > 2 x ULN with Agresti-Coull 95% CIs (see Section 4.6.2)
  - ALT or ALT > 3 x ULN concurrent with TBL > 2 x ULN and ALP ≤ 2 x ULN with Agresti-Coull 95% CIs (see Section 4.6.2)
  - ALT or AST > 3 x ULN concurrent with AEs of interest (nausea, vomiting, anorexia, abdominal pain, fatigue; see Section 4.6.3.2).

Exposure-adjusted on-treatment cumulative LFT elevations will also be summarized for treated subjects with the number and percentage of subjects with LFT elevations, along with patient-years and exposure-adjusted rates based on exposure up to time of first LFT elevation (see Section 4.8.2).

By-subject longitudinal LFT plots will display all normalized results (i.e., LFT ratio of value to ULN) regardless of study period for AST, ALT, ALP and TBL on the y-axis versus study week of laboratory result on the x-axis for treated subjects with any of the following LFT elevations during a safety analysis period (pre-treatment, on-treatment, follow-up): ALT > 3 x ULN; AST > 3 x ULN; TBL > 2 x ULN; ALP > 2 x ULN. Study week is defined as study day/7 (see Section 5.5). Each figure will also display treated migraine onsets, start of the on-treatment safety analysis period, and start of the follow-up safety analysis period.

Additionally, an evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) scatter plot will display the maximum TBL ratio of value to ULN on the y-axis versus the maximum ALT ratio of value to ULN on the x-axis, where the maxima will be in the same safety analysis period but not necessarily concurrent. Both axes will be on the $\log_{10}$ scale. Ratios < 0.1 x ULN will be set to 0.1. Sample sizes in the legend will represent subjects with paired ratios. A horizontal reference line will be placed at 2 x ULN, and a vertical reference line will be placed at 3 x ULN. The lower left quadrant will be labeled “Normal Range”, the upper left quadrant will be labeled “Hyperbilirubinemia”, the lower right quadrant will be labeled “Temple’s Corollary”, and the upper right quadrant will be labeled “Possible Hy’s Law Range.” The following eDISH scatter plots will be produced for treated subjects: (1) on-treatment by enrollment group; (2) on-treatment by average rimegepant exposure; (3) on-treatment by average rimegepant exposure for the EOD+PRN dosing group; (4) on-treatment by enrollment group for treated subjects who

took ≥14 tablets per 4 weeks for ≥ 12 weeks; (5) by safety analysis period (pre-treatment, on-treatment, follow-up) across enrollment groups pooled; (6) on-treatment by enrollment group for treated subjects who took ≥ 20 tablets per 4 weeks for ≥ 4 weeks; (7) on-treatment by enrollment group for treated subjects with near-daily dosing.

Rates of multiple on-treatment, cumulative and mutually exclusive LFT elevations will be summarized using descriptive statistics for treated subjects (1) enrollment group and overall, and (2) subgroup level and overall for key extrinsic exposure factors. For each subject and LFT elevation endpoint, the rate is defined as total number of elevations/total number of non-missing values during the on-treatment period. Multiple values on the same collection date will be counted only once.

The number and percentage of subjects with time to first on-treatment LFT elevations (ALT > 3 x ULN; AST > 3 x ULN; ALT or AST > 3 x ULN) will be presented by enrollment group and overall for treated subjects with on-treatment LFT elevations in the following categories: ≤ 2, > 2 to ≤ 4, > 4 to ≤ 8, …, > 48 to ≤ 52, > 52 weeks. Time to elevation is calculated as (LFT collection date – study drug first dose + 1)/7.

In all of these analyses described in this section, subjects must have non-missing LFT data (i.e., ALT, AST, TBL, or ALP) in the safety analysis period to be included.

4.6.3.2 ALT or AST > 3 x Upper Limit of Normal (ULN) Concurrent with Nausea, Vomiting, Anorexia, Abdominal Pain or Fatigue

AST or ALT > 3 x ULN elevations that are concurrent with nausea, vomiting, anorexia, abdominal pain or fatigue will be summarized, as the number and percentage of subjects experiencing this concurrently, in the same table as other LFT elevation endpoints described in Section 4.6.3.1. For a given safety analysis period (pre-treatment, on-treatment, follow-up), an LFT elevation is concurrent with an AE of interest if the imputed AE start date is +/- 7 days inclusive of the LFT collection date; both the LFT collection date and the imputed AE start date must also be in the safety analysis period. Refer to the BHV3000 Core SAP for AE start date imputation. The following will be used to identify the AEs of interest: nausea, vomiting, anorexia, fatigue, and those containing "abdominal pain".

4.6.3.3 LFT Elevations by Gender, Age, and Rimegepant Exposure

See Section 4.6.3.1.

4.6.3.4 Secondary Safety Endpoints by Rimegepant Exposure

Secondary safety endpoints as described in Section 4.6.2 will be assessed by several study drug exposure groups for treated subjects. The number and percentage of subjects with hepatic-related SAEs by SOC, PT and severity, hepatic-related AEs leading to study drug discontinuation by SOC and PT, and concurrent elevations of AST or ALT > 3 x ULN with TBL > 2 x ULN will be shown by subgroup level and overall for extrinsic exposure subgroups (see Section 4.6.2). Only treatment-emergent AEs and on-treatment laboratory test values will be included.

4.6.3.5 Number and Severity of Migraine Days per Month

Subjects are instructed to report migraine status (yes, no, unable to recall) and severity (mild, moderate, severe, unable to recall) in their diaries every day.

Migraine days per month will be assessed as "migraine days per 4 weeks" to correspond with the 4-week visit schedule. Analyses will be based on the OP and LTT analysis periods for evaluable treated subjects, i.e., treated subjects who had ≥ 14 days of data (not necessarily consecutive) in both the OP analysis period and at least one 4-week interval in the LTT analysis period.

- A day of data is defined as an eDiary record with complete date and {yes or no} response to having a migraine. If a subject has multiple responses or migraine severities on the same date, then the most severe migraine last sequenced chosen. Only days of data are included in analyses.
- A migraine day is defined as a day of data with a "yes" response to having a migraine.
- 4-week (28-day) intervals are defined from LTT start as: interval 1 (≤ 4 weeks; LTT study days 1 to 28), interval 2 (> 4 to ≤ 8 weeks; LTT study days 29 to 56), …, interval 13 (> 48 to ≤ 52 weeks; LTT study days to 336 to 364), interval 14 (> 52 to ≤ 56 weeks; LTT study days to 365 to 392). See Section 5.5 for the definition of LTT study days.

Thus, the total numbers of days of data and migraine days are calculated for the OP analysis period and for each 4-week interval in the LTT analysis period.

OP records will come from the screening epoch, whereas LTT records will be come from the treatment epoch.

Tables will present results by enrollment group and overall separately for (1) evaluable treated subjects, (2) evaluable treated subjects with ≥ 14 migraine days per 4 weeks in the OP, (3) evaluable treated subjects with ≥ 20 migraine days per 4 weeks in the OP, and (4) evaluable treated subjects taking concomitant prophylactic migraine medication (see Section 4.9). In addition, tables will present results by average rimegepant exposure and overall for evaluable EOD+PRN treated subjects (see Section 4.2.6).

The number of migraine days per 4 weeks in the LTT period will be examined relative to the number of migraine days per 4 weeks in the OP by severity (total [mild, moderate, severe, unable to recall, not reported]; moderate or severe). The following tables will be produced:

- Values and changes (both absolute and percent) from the OP in the number of migraine days per 4 weeks in 4-week intervals during LTT and overall LTT average will be summarized using descriptive statistics by severity (including two-sided 95% normal CIs for mean change). The number of migraine days per 4 weeks will be prorated to 28 days and derived as follows:
  - OP: 28*(total number of migraine days in the OP analysis period)/(total number of data days in the OP analysis period).

- 4-week interval during LTT: 28*(total number of migraine days in the interval)/(total number of data days in the interval). In addition, subjects must have ≥ 14 days of data (not necessarily consecutive) in an interval to be evaluable for that interval.
- Overall LTT average: 28*(total number of migraine days in the LTT analysis period) / (total number of data days in the LTT analysis period).

- Number and percentage of subjects with < 1, ≥ 1, ≥ 2, ≥ 3, ≥ 4 and ≥ 5 decrease from the OP and ≥ 20%, ≥ 25%, ≥ 30%, ≥ 35%, ≥ 40%, ≥ 45%, and ≥ 50% decrease from the OP in the number of migraine days per 4 weeks in 4-week intervals during LTT and overall LTT average by severity.

A scatter plot by enrollment group will display the decrease in the number of migraine days per 4 weeks in the overall LTT average from the OP (y-axis) versus number of migraines per 4 weeks in the OP (x-axis). Another scatter plot by enrollment group will display the percent decrease in the number of migraine days per 4 weeks in the overall LTT average from the OP (y-axis) versus number of migraine days per 4 weeks in the OP (x-axis). Plots will include a horizontal reference line at 0. These scatter plots will also be produced by average rimegepant exposure for evaluable EOD+PRN treated subjects (see Section 4.2.6).

In the percent change/decrease analyses, subjects must also have ≥ 1 total number of migraine days during the OP to be included.

A by-subject listing will present migraine attacks and severity for screened subjects. Another by-subject listing will present the number of migraine days per 4 weeks during the OP, overall LTT average, and in 4-week intervals during the LTT for treated subjects.

4.6.3.6 Migraine-Specific Quality of Life

Impact of treatment on patient-reported quality of life is assessed using the MSQoL, which is a 14-item questionnaire that has been validated in migraine patients to assess the effects of migraines on their daily activities over the past 4 weeks. The MSQoL will be evaluated at early termination and the following visits: Baseline; Weeks 12, 24, 36 and 52 for the 52-week PRN (2-8) and (9-14) dosing groups; and Week 12 for the 12-week EOD+PRN and PRN (2-8) dosing groups.

The MSQoL consists of the following 3 domains: (1) restrictive role function, (2) preventive role function and (3) emotional function. Values and changes from baseline in transformed scores for each domain will be summarized using descriptive statistics (including two-sided 95% normal CIs for mean change) at baseline, each scheduled visit, and the last post-baseline visit by enrollment group and overall. Refer to the BHV3000 Core SAP for deriving transformed scores for each domain.

4.6.3.7 Preference of Medication (PoM)

The PoM is a 5-point rating scale that measures the patient's preference of study medication to previous medications to treat migraine pain. The 5 preference categories are: much better, I prefer this medication; slightly better than the previous medication; about the same as the previous medication; slightly worse than the previous medication; much worse, I prefer my previous medication. The PoM will be evaluated with the eDiary at early termination and the following visits: Weeks 24 and 52 for the 52-week PRN (2-8) and (9-14) dosing groups; Week 12 for the 12-week EOD+PRN and PRN (2-8) dosing groups.

The number and percentage of subjects with PoM data and in each category will be tabulated at each scheduled visit and the last post-baseline visit by enrollment group and overall. Percentages for categories will be based on subjects with PoM data at each visit, along with two-sided Agresti-Coull 95% CIs for each percentage. Refer to the BHV3000 Core SAP for additional combined categories.

4.6.3.8 Sheehan-Suicidality Tracking Scale (S-STS)

The S-STS is a prospective, self-reported rating scale that contains 16 questions to track both treatment-emergent suicidal ideation and behaviors. In the event the subject is unavailable, the S-STS clinician-administered rating scale will be completed that contains 6 yes/no questions. The S-STS will be evaluated at Screening, Baseline, all subsequent visits during the treatment period, and early termination for all enrollment groups.

Refer to the BHV3000 Core SAP for calculating self-reported S-STS ideation subscale, behavior subscale, and total scores.

Values and changes from baseline in the self-reported S-STS ideation subscale, behavior subscale, and total score will be summarized as continuous parameters at baseline and the worst (highest) score in safety analysis periods by treatment group and overall. The table will also present the number and percentage of subjects in the worst (highest) score change from baseline category (i.e., < -1, -1, no change, 1, > 1) in safety analysis periods by treatment group and overall for the ideation subscale, behavior subscale, and total score.

Results will be summarized on-treatment for treated subjects, and follow-up for follow-up subjects. Subjects have a non-missing measurement in the safety analysis period (plus baseline for worst score change) to be included for a given parameter.

4.6.3.9 Satisfaction with Medication (SM)

The SM is a 7-point rating scale that captures the subjects' perception of whether they are satisfied with their headache medication. The 7 satisfaction categories are: completely satisfied, could not be better; very satisfied; somewhat satisfied; neither satisfied nor dissatisfied; somewhat dissatisfied; very dissatisfied; completely dissatisfied, could not be worse. The SM will be evaluated with the eDiary at early termination and the following visits: Weeks 24 and 52 for the 52-week PRN (2-8) and (9-14) dosing groups; Week 12 for the 12-week EOD+PRN and PRN (2-8) dosing groups.

The number and percentage of subjects with survey data and in each category will be tabulated at each scheduled visit and the last post-baseline visit by enrollment group and overall. Percentages for categories will be based on subjects with survey data at each visit, along with two-sided Agresti-Coull 95% CIs for each percentage. Refer to the BHV3000 Core SAP for additional combined categories.

4.6.3.10 Migraine Disability Assessment (MIDAS)

The MIDAS is a retrospective, patient-administered, 5-item questionnaire that measures headache-related disability as lost time due to headache from paid work or school, household work and non-work activities. The MIDAS will be evaluated at early termination and the following visits: Baseline; Weeks 12, 24, 36 and 52 for the 52-week PRN (2-8) and (9-14) dosing groups; Week 12 for the 12-week EOD+PRN and PRN (2-8) dosing groups.

Values and changes from baseline in the total, absenteeism, presenteeism, and item scores will be summarized using descriptive statistics (including two-sided 95% normal CIs for mean change) at baseline, each scheduled visit and the last post-baseline visit by enrollment group and overall. Refer to the BHV3000 Core SAP for calculating the total, absenteeism, presenteeism, and item scores.

4.6.3.11 Clinical Global Impression of Change (CGI-C)

CGI-C is an observer-rated 7-point scale that measures patient total improvement relative to the investigator's past experience with other patients with the same diagnosis, with or without collateral information. The 7 improvement categories are: very much improved; much improved; minimally improved; no change; minimally worse; much worse; very much worse. The CGI-C will be evaluated at early termination and the following visits: Weeks 12, 24, 36 and 52 for the 52-week PRN (2-8) and (9-14) dosing groups; Week 12 for the 12-week EOD+PRN and PRN (2-8) dosing groups.

The number and percentage of subjects in each category will be tabulated at each scheduled visit and the last post-baseline visit by enrollment group and overall. Percentages for categories will be based on subjects with non-missing data at each visit, along with two-sided Agresti-Coull 95% CIs for each percentage. Refer to the BHV3000 Core SAP for additional combined categories.

4.7 Pharmacokinetic Evaluations

No pharmacokinetic data were collected in this study.

4.8 Safety Analysis

Safety analyses will be conducted on treated subjects by enrollment group and overall, unless otherwise noted. Safety outcome measures include: AEs, laboratory assessments including liver toxicity, vital signs, physical measurements, electrocardiograms (ECGs), and S-STS.

Select safety parameters will be summarized as continuous parameters at baseline and each scheduled visit over time during the on-treatment and follow-up safety analysis periods. Post-

baseline measurements will be first slotted into analysis visit windows in the post-enrollment and follow-up analysis periods (see Section 5.4). Post-baseline measurements will then be slotted into safety analysis periods (on-treatment and follow-up). If a subject has multiple values in an analysis visit window during a safety analysis period, then the non-missing value closest to the target date for the visit will be used; in the case of a tie, the latest value collected (from the central laboratory, if applicable) will be used. In these tables, the latest non-missing value collected (from the central laboratory, if applicable) among those at analysis visits Weeks 2 to 56 that fall in the follow-up safety analysis period will be summarized under the "Follow-up EOT" visit. See Sections 4.5, 5.4 and 5.5 for definitions of baseline, analysis periods, and analysis visit windows, respectively.

By-subject listings of safety data are described in subsections. In addition, a by-subject listing of procedures will be provided for screened subjects.

A by-subject listing of safety narrative subject identifiers will be provided for screened subjects with select events, as described in the BHV3000 Core SAP. The listing will flag subjects with select events.

4.8.1 Extent of Exposure

Study medication is rimegepant 75 mg tablet. This is dispensed in bottles containing 30 tablets of 75 mg rimegepant at the baseline visit and at study visits as needed; subjects should finish a bottle of study medication (containing 30 tablets of drug) prior to starting a new bottle.

Subjects are instructed to provide study drug taken status (yes, no) and number of tablets in their eDiaries every day after they are determined to be eligible to take study drug. If a subject did not report any study drug data in the eDiary on a given day, then it is assumed that the subject did not take study drug that day. Study drug records will come from the treatment epoch.

Drug accountability is provided by the site on the Drug Accountability CRF.

A by-subject listing will present eDiary exposure (i.e., number of tablets taken) and drug accountability for treated subjects.

Another by-subject listing will present eDiary exposure (i.e., total number of tablets taken) in 4-week intervals during the LTT for treated subjects. This will also display cumulative rimegepant exposure from both sources (i.e., eDiary and drug accountability), and flag subjects with ≥ 10 cumulative tablet difference between the 2 sources.

Another by-subject listing will present batch numbers for treated subjects.

eDiary Exposure

eDiary exposure will be summarized descriptively for treated subjects by enrollment group and overall, and will include the following parameters:

- Time in the OP (weeks), defined as (OP end date – OP start date + 1)/7
- Time from enrollment to last contact (weeks), defined as (last contact date – IWRS enrollment date + 1)/7
- Time in the LTT period (weeks), derived as (LTT end date – LTT start date + 1)/7
- Time on rimegepant (weeks), derived as (study drug end dose date – study drug first dose date + 1)/7.*
- Cumulative rimegepant exposure (tablets), derived by summing number of tablets across records with complete dates for subjects who reported taking study medication during the treatment epoch in the eDiary.*
- Average rimegepant exposure (tablets per 4 weeks), derived as 4*cumulative rimegepant exposure/time in the LTT period.*
- Number and percentage of subjects in the average rimegepant exposure (tablets per 4 weeks) categories defined in Section 4.2.6, and also in the following categories:
  - ≥ 12.6 (≥ 90% compliant with EOD dosing)
  - ≥ 11.2 (≥ 80% compliant with EOD dosing)
- Number and percentage of subjects who took more than 1 tablet per day on any day. This could be from the same bottle or different bottles due to an unscheduled visit.
- Exposure over time, as defined by the number and percentage of subjects who took
  - ≥ 8 tablets per 4 weeks for 4, 8, 12, 16, 20, ≥ 24, ≥ 12, and ≥ 4 weeks. These categories correspond respectively to 1, 2, 3, 4, 5, ≥ 6, and ≥ 3 4-week intervals that are not necessarily consecutive (see below)
  - ≥ 12 tablets per 4 weeks for 4, 8, 12, 16, 20, ≥ 24, ≥ 12, and ≥ 4 weeks
  - ≥ 13 tablets per 4 weeks for 4, 8, 12, 16, 20, ≥ 24, ≥ 12, and ≥ 4 weeks
  - ≥ 14 tablets per 4 weeks for 4, 8, 12, 16, 20, ≥ 24, ≥ 12, and ≥ 4 weeks (the "≥ 12 weeks" category will support the subgroup "treated subjects who took ≥ 14 tablets per 4 weeks for ≥ 12 weeks" specified in Section 4.2.6)
  - ≥ 20 tablets per 4 weeks for 4, 8, 12, 16, 20, ≥ 24, ≥ 12, and ≥ 4 weeks
  - ≥ 25 tablets per 4 weeks for 4, 8, 12, 16, 20, ≥ 24, ≥ 12, and ≥ 4 weeks
- Total rimegepant exposure (tablets) summed across all subjects, derived by summing cumulative exposure across all subjects
- Total rimegepant exposure (patient-years), derived by summing (study drug end dose date – study drug first dose date + 1)/365.25 across all subjects.

This summary will also display quintiles (e.g., P20, P40, P60, P80, where "PX" denotes X^{th} percentile) for asterisked ("*") continuous parameters to support the derivation of rimegepant exposure subgroups (see below). See Section 5.3 for derived dates.

eDiary exposure over time will assess the number of 4-week (28-day) intervals in which a subject exceeded select tablet counts in the LTT analysis period (see Section 5.4), where the number of 4-week intervals are not necessarily consecutive. For example, suppose a subject takes 20 tablets through 4 weeks (interval 1; LTT study days 1 to 28), 10 tablets after 4 weeks to 8 weeks (interval 2; LTT study days 29 to 56), 25 tablets after 8 weeks to 12 weeks (interval 3; LTT study days 57 to 84), and 15 tablets after 12 weeks to 16 weeks (interval 4; LTT study days 85 to 112). Thus, this subject is considered to have taken ≥ 14 tablets per 4 weeks for 12 weeks (i.e., intervals 1, 3 and 4), ≥ 20 tablets per 4 weeks for 8 weeks (i.e., intervals 1 and 3), and ≥ 25 tablets per 4 weeks for 4 weeks (i.e., interval 3). See Section 5.5 for the definition of LTT study days.

eDiary exposure will also be summarized by subgroup level and overall for treated subjects for all subgroups of interest described in Section 4.2.6.

Kaplan-Meier mortality tables will summarize time to rimegepant discontinuation and time to study discontinuation in 4-week intervals (i.e., ≤ 4, > 4 to ≤ 8, …, > 52) by enrollment group and overall. A Kaplan-Meier mortality plot by enrollment group will display the percentage of subjects on rimegepant (y-axis) versus weeks (x-axis). Time to rimegepant discontinuation is defined as time from study drug first dose to study drug end dose. Time to study discontinuation is defined as time from enrollment to last contact. Subjects who have non-missing completion status on the Study Exit Status CRF will be considered to have discontinued both rimegepant and the study; otherwise, in an interim analysis, subjects will be censored at the study drug end date or the last contact date.

Drug Accountability Exposure

Drug accountability exposure will be summarized descriptively by enrollment group and overall for treated subjects, and will include the following:

- Time from first kit dispensed to last kit returned (weeks), derived as (latest kit return date – earliest kit dispense date + 1)/7. Subjects who were dispensed at least one kit but never returned any kit will be credited with 1 day.
- Cumulative rimegepant exposure (tablets) based on kits dispensed and returned, derived as summing (30 - number of tablets remaining) across records with non-missing kit dispense and return dates.
- Average rimegepant exposure (tablets per 4 weeks) based on kits dispensed and returned, derived as 4*cumulative rimegepant exposure based on kits dispensed and returned/time from first kit dispensed to last kit returned.

eDiary Compliance

eDiary compliance during the OP and LTT periods will be summarized descriptively by enrollment group and overall for treated subjects, for each source (subject; subject or site). Data days are records with complete eDiary dates. Compliance will be derived as:

- Last 30 days before enrollment: 100*(total number of data days from the IWRS enrollment date – 30 days to the IWRS enrollment date – 1 day)/30
- OP: 100*(total number of data days in the OP analysis period)/total number of days in the OP analysis period
- LTT: 100*(total number of data days in the LTT analysis period)/total number of days in the LTT analysis period.
- Enrollment to last visit during LTT: 100*(total number of data days from the IWRS enrollment date to the last visit date during LTT)/(Last visit date during LTT – IWRS enrollment date +1). Last visit date during LTT is same as EOT visit date, but derived for all treated subjects (see Section 5.3).

eDiary compliance will be summarized as a continuous parameter and as the number and percentage of subjects in the following categories: ≥ 90% compliance; ≥ 80% compliance. Subject sources are the evening report, PoM, and SM. The site source is the medication reconciliation form.

Drug Accountability Compliance

Drug accountability compliance will be summarized by enrollment group and overall with the number and percentage of enrolled subjects in the following categories:

- At least one kit dispensed
- Did not return at least one kit dispensed and discontinued the study
- Did not return any kit dispensed and discontinued the study.

Kit dispensed and kit returned will be identified from "yes" responses to the questions "was this kit dispensed" and "was this kit returned", respectively.

4.8.2 Adverse Events

Refer to the BHV3000 Core SAP for AE start date imputation, AE counting rules, definition of treatment-emergent adverse events (TEAEs), and definition of AEs related to study drug.

Tables will present the number and percentage of subjects experiencing AEs by SOC and PT, unless specified otherwise.

A by-subject listing of all AEs will be provided for screened subjects that will flag on-treatment and treatment-emergent AEs. Additional by-subject listings of deaths, SAEs, AEs leading to study drug discontinuation, hepatic-related AEs, and AEs of special interest (i.e., potential drug abuse, CV, and suicidality) will be provided for screened subjects. Refer to the BHV3000 Core SAP for listing content and AEs of special interest.

AE Overview

An AE overview without SOC and PT will present the number and percentage of subjects with any the following AEs: any AE; severe AE; AE related to study drug (unlikely related, possibly related, or related); SAE; SAE related to study drug; AE leading to study drug discontinuation; AE leading to death; hepatic-related AE; severe hepatic-related AE; hepatic-related SAE; hepatic-related AE leading to study drug discontinuation; potential drug abuse AE; CV AE; suicidality AE. An AE overview will be produced for each the following analysis periods and populations:

- Pre-treatment AEs for screened subjects by enrollment group and overall
- Pre-treatment AEs for treated subjects by enrollment group and overall
- TEAEs for treated subjects by enrollment group and overall
- On-treatment AEs for treated subjects by enrollment group and overall
- On-treatment AEs for treated subjects by subgroup level and overall for all subgroups of interest specified in Section 4.2.6
- Follow-up AEs for follow-up subjects by enrollment group and overall.

Pre-Treatment AEs

Pre-treatment AEs will be summarized by SOC and PT by enrollment group and overall for screened subjects for the following endpoints:

- AEs
- SAEs.

Pre-treatment AEs will be summarized by SOC and PT for treated subjects by enrollment group and overall for the following endpoints:

- AEs by severity (total, mild, moderate, severe, moderate or severe, not reported)
- SAEs.

On-Treatment AEs

On-treatment AEs will be summarized by SOC and PT for treated subjects by enrollment group and overall for the following endpoints:

- AEs by severity*
- TEAEs by severity
- TEAEs occurring in ≥ 2% of subjects in any enrollment group after rounding. Percentages will be displayed rounded to integers, and AEs will be displayed in alphabetical order by SOC and PT.
- AEs occurring in ≥ 2% of subjects in any enrollment group or subgroup level^
- AEs occurring in ≥ 5% of subjects in any enrollment group by severity (primary safety endpoint, see Section 4.6.1)
- AEs occurring in ≥ 10% of subjects in any enrollment group
- Exposure-adjusted AEs
- AEs related to study drug by severity*
- AEs related to study drug occurring in ≥ 2% of subjects in any enrollment group or subgroup level^
- SAEs (primary safety endpoint, see Section 4.6.1)*
- Exposure-adjusted SAEs
- AEs leading to study drug discontinuation (primary safety endpoint, see Section 4.6.1)*
- Hepatic-related AEs by severity (secondary safety endpoint, see Section 4.6.2)#
- Hepatic-related SAEs#
- Hepatic-related AEs leading to study drug discontinuation (secondary safety endpoint, see Section 4.6.2)#
- Additional AEs of special interest: potential drug abuse^; CV; suicidality. Potential drug abuse AEs will be displayed in alphabetical order by severity and PT without SOC.

Endpoints marked with "*" will also be summarized by subgroup level and overall for all subgroups of interest specified in Section 4.2.6. Endpoints marked with "#" will also be summarized by subgroup level and overall only for extrinsic exposure factors (see Section 4.2.6). Endpoints marked with "^" will also be summarized by subgroup level and overall only for key extrinsic exposure factors (see Section 4.2.6).

Refer to the BHV3000 Core SAP for exposure-adjusted AEs. Calculations for on-treatment exposure-adjusted AEs will set reference start date to the study drug first dose date, reference end date to the study drug end dose date, and reference last date to the study drug last dose date + 7 days.

Follow-up AEs

Follow-up AEs will be summarized by SOC and PT for follow-up subjects by enrollment group and overall for the following endpoints:

- AEs by severity
- SAEs.

AEs in All Safety Analysis Periods Combined

AEs in all safety analysis periods combined (i.e., pre-treatment, on-treatment, and follow-up) will be summarized by SOC and PT for treated subjects by enrollment group and overall for the following endpoints:

- AEs leading to study drug discontinuation (primary safety endpoint, see Section 4.6.1)
- Hepatic-related AEs leading to study drug discontinuation (secondary safety endpoint, see Section 4.6.2).

4.8.3 Laboratory Tests

Clinical safety laboratory testing will be performed at early termination and the following visits: Screening; Baseline; Weeks 4, 24, and 52 for the 52-week PRN (2-8) and (9-14) dosing groups; Weeks 4 and 12 for the 12-week EOD+PRN and PRN (2-8) dosing groups. Urinalysis will be collected at early termination and the following visits: Baseline; Week 52 for the 52-week PRN (2-8) and (9-14) dosing groups; Week 12 for the 12-week EOD+PRN and PRN (2-8) dosing groups. Lipids (cholesterol, HDL cholesterol, LDL cholesterol, triglycerides) will be collected at early termination and the following visits: Baseline; Weeks 24 and 52 for the 52-week PRN (2-8) and (9-14) dosing groups; Week 12 for the 12-week EOD+PRN and PRN (2-8) dosing groups. LFTs (ALT, AST, ALP, TBL, direct bilirubin) will be collected routinely at Screening, Baseline, all visits during the treatment period, early termination, and Follow-up Week 2 for all enrollment groups.

Clinically significant laboratory abnormalities will be identified as grade 3 to 4 laboratory test results. Refer to the BHV3000 Core SAP for laboratory tests of clinical interest and toxicity grading. Laboratory test groups of clinical interest will include hematology, serum chemistry, and urinalysis.

LDL cholesterol and triglycerides will be analyzed as separate laboratory test parameters according to 8-hour fasting status: fasting ≥ 8 hours; not fasting ≥ 8 hours; overall. Refer to the the BHV3000 Core SAP for additional details.

Tables, listings, and figures (TLFs) will be provided to show data in both Systeme Internationale (SI) and United States (US) unit systems, if applicable.

Tables will present results by treatment group and overall, and laboratory tests alphabetically within laboratory test group, as applicable.In analyses of the worst abnormality or category in a safety analysis period, subjects must have a non-missing measurement in the safety analysis

period to be included for a given parameter. In shift from baseline analyses, subjects must have a non-missing measurement at baseline and in the safety analysis period to be included for a given parameter.

By-subject listings of the following select laboratory test groups will be provided for screened subjects: hematology; serum chemistry; urinalysis (US units only); pregnancy (US units only); endocrinology, serology, drug screen, and miscellaneous laboratory tests (US units only). In addition, a by-subject listing of LFT values and ratios to ULN (i.e., ALT, AST, TBL and ALP) will also be provided for screened subjects. Refer to the BHV3000 Core SAP for listing content.

Worst Laboratory Test Abnormalities

A primary safety endpoint is the frequency of clinically significant laboratory test abnormalities (see Section 4.6.1). The number and percentage of treated subjects with the worst (highest) on-treatment laboratory test abnormality will be presented in the following toxicity grade categories for each graded laboratory test: Grade 0; Grade 1 to 2; Grade 3 to 4; Grade 3; Grade 4. Grade 3 to 4 abnormalities are considered clinically significant. Bi-directional tests will be assessed separately for each component (i.e., calcium low, calcium high).

The worst on-treatment laboratory test abnormalities will also be summarized by subgroup level and overall for treated subjects for all subgroups of interest described in Section 4.2.6.

The worst follow-up laboratory test abnormalities will also be summarized by enrollment group and overall for follow-up subjects.

Laboratory Test Low/Normal/High Shifts From Baseline

Laboratory test low/normal/high shifts from baseline to any on-treatment abnormal value will be summarized by treatment group and overall as the number and percentage of treated subjects in each category (low, normal, high), which does not depend on US or SI units. Subjects with both low and high on-treatment values will be counted in both on-treatment low and high categories (thus, these categories are not mutually exclusive). Subjects must have only normal values on treatment to be counted in the on-treatment normal category.

LFT ULN Shifts From Baseline

LFT ULN shifts from baseline to the worst (highest) on-treatment value will be summarized by treatment group and overall as the number and percentage of treated subjects in the following categories: ≤ ULN, > ULN to ≤ 3 x ULN, > 3 x ULN to ≤ 5 x ULN, > 5 x ULN to ≤ 10 x ULN, > 10 x ULN to ≤ 20 x ULN, and > 20 x ULN (US and SI units are identical). LFTs will be limited to ALT and AST.

Laboratory Test Toxicity Grade Shifts From Baseline

Laboratory test toxicity grade shifts from baseline to the worst (highest) on-treatment toxicity grade will be summarized by treatment group and overall as the number and percentage of treated subjects in each toxicity grade category (Grade 0, Grade 1, Grade 2, Grade 3, Grade 4) for each graded laboratory test. Bidirectional tests will be assessed separately for each component (e.g., calcium, low; calcium, high).

Laboratory Test Changes From Baseline Over Time

Values and changes from baseline in hematology and serum chemistry laboratory tests will be summarized using descriptive statistics at baseline and each scheduled visit in the on-treatment and follow-up safety analysis periods.

4.8.4 Vital Signs and Physical Measurements

Vital signs, body weight, and height will be measured at Screening, Baseline, every visit during the treatment period, early termination, and Follow-up Week 2 for all enrollment groups.

A by-subject listing of vital signs and physical measurements will be provided for screened subjects.

Vital Sign and Physical Measurement Changes From Baseline Over Time

Values and changes from baseline in vital signs and physical measurements will be summarized using descriptive statistics at baseline and each scheduled visit in the on-treatment and follow-up safety analysis periods by enrollment group and overall.

Vital Sign and Physical Measurement Abnormalities

Vital sign and physical measurement abnormalities in safety analysis periods will be summarized by treatment group and overall as the number and percentage of subjects in the following categories:

- Systolic blood pressure (mmHg): < 90 , > 140, > 160
- Diastolic blood pressure (mmHg): < 50, > 90, > 100
- Heart rate (bpm): < 60, > 100
- Temperature (C): < 36, > 38
- Respiratory rate (breaths/min): < 12, > 20
- Weight change from baseline: $\leq -7\%$, $\geq 7\%$.

Abnormalities will be summarized on-treatment for treated subjects, and follow-up for follow-up subjects. Subjects have a non-missing measurement in the safety analysis period (plus baseline for weight change) to be included for a given parameter.

4.8.5 Electrocardiograms

ECGs will be measured at the following visits: Screening; Baseline; Weeks 4, 24, and 52 for the 52-week PRN (2-8) and (9-14) dosing groups; Weeks 4 and 12 for the 12-week EOD+PRN and PRN (2-8) dosing groups; early termination; Follow-up Week 2.

A by-subject listing of ECG results will be provided for screened subjects.

ECG Interpretation Shifts From Baseline

The shift from baseline to worst on-treatment ECG interpretation will be summarized as the number and percentage of treated subjects with normal, abnormal, and clinically significant abnormal interpretations by enrollment group and overall. Subjects must have a non-missing ECG interpretation at baseline and an on-treatment visit to be included.

ECG Changes From Baseline Over Time

Values and changes from baseline in ECG intervals (e.g., RR, QRS, PR, QT, QTcB, QTcF) and ventricular heart rate will also be summarized using descriptive statistics at baseline and each scheduled visit in the on-treatment and follow-up safety analysis periods by enrollment group and overall.

ECG Abnormalities

ECG abnormalities in safety analysis periods will be summarized by treatment group and overall as the number and percentage of subjects in the following categories:

- QTcB (msec): > 450, > 480, > 500
- QTcF (msec): > 450, > 480, > 500.

Abnormalities will be summarized on-treatment for treated subjects, and follow-up for follow-up subjects. Subjects have a non-missing measurement in the safety analysis period to be included for a given parameter.

ECG abnormalities will be presented together with vital sign and physical measurement abnormalities in the same tables (see Section 4.8.4).

4.9 Non-Study Medications

The following non-study medications will be summarized by anatomical therapeutic class (ATC) and preferred name by enrollment group and overall for treated subjects:

- Prior medications, defined as those with an imputed start or stop date < IWRS enrollment date – 14 days.
- Concomitant medications, defined as those with an imputed start or stop date ≥ IWRS enrollment date – 14 days.

- Prophylactic migraine medications taken on or after informed consent and before the start of study drug, defined as those with (1) informed consent date ≤ imputed start or stop date < study drug first dose date, or (2) imputed start date ≤ informed consent date < study drug first dose date – 1 day ≤ imputed stop date.
- Prophylactic migraine medications taken on or after the start of study drug, defined as those with an imputed start or stop date on or after the study drug first dose date.*
- Standard of care migraine medications taken on or after informed consent and before the start of study drug.
- Standard of care migraine medications taken on or after the start of study drug.*

Endpoints marked with "*" will also be summarized by subgroup level and overall for key extrinsic exposure factors (see Section 4.2.6).

For each subject, multiple records of the same medication will be counted only once within each ATC and preferred name.

Medications will be presented in descending order of overall frequency within ATC and preferred name.

By-subject listings of non-study medications, non-study prophylactic migraine medications, and non-study standard of care migraine medications will be provided for screened subjects.

Refer to the BHV3000 Core SAP for non-study medication start and stop date imputation, and listing content.

5 CONVENTIONS

5.1 General

5.1.1 Output Layout

A list of TLFs and corresponding templates will be presented separately in the Mock TLF document.

Refer to the BHV3000 Core SAP for TLF layout conventions.

5.1.2 Duplicate Subjects

If the same subject participates in the study more than once and is assigned more than one subject identifier, then the following conventions will apply to analyses:

- The subject identifier corresponding to the first treatment will be populated across all records in analysis datasets if the subject was treated. Otherwise, the subject identifier corresponding to the first enrollment will be populated if the subject was enrolled but never treated. Otherwise, the subject identifier corresponding to the first screening will be populated if the subject was never enrolled. This will ensure that the output shows unique subjects.
- Pre-treatment parameters (e.g., IWRS screening date, IWRS enrollment date, OP start/end dates, LTT start date, study drug first dose date, enrollment group, demographics, baseline characteristics, medical history, migraine history, cardiac and other risk factors, prior triptan response, current triptan response) will be derived using data only from the subject identifier identified in the previous bullet.
- On-treatment and follow-up parameters (e.g., LTT end date, study drug last/end dates, EOT visit date, last contact date) will be derived using data from all duplicate subject identifiers to ensure that protocol deviations, safety, exposure, migraine, and outcomes research endpoints will be assessed comprehensively.
- Subject disposition will be derived from study exit status data from the last duplicate subject identifier.

5.2 Subgroups

5.2.1 Triptan Non-Responders

Triptan non-responders are identified using the "Prior Triptan Response" Case Report Form (CRF) pages, which capture reasons for discontinuing triptans taken historically. The definition of triptan non-responder is based on the number of triptans that a subject failed for efficacy reasons. For each triptan and route of administration, the subject is asked the questions shown in Table 4. A subject is considered to have failed a drug for efficacy reasons if they indicated "most or all of the time" for any of the reasons in the table.

A triptan non-responder is defined as any subject that fails two or more molecular entities for efficacy reasons. To be considered a failure for a molecular entity, the subject must have failed on all routes of administration that the subject tried for the molecular entity.

Table 4: Questions Used to Determine Triptan Non-response

	Most or All of the Time	Some of the Time	Rarely	Never
The treatment took too long to relieve my headache pain.				
The pain returned after it was relieved within 24 hours				
The treatment did not relieve my other symptoms (nausea, sensitivity to light or sound, for example).				
I could not count on this treatment to relieve my pain and symptoms every time				

5.2.2 CV Risk Contradindicating Triptans

Subjects with CV risk that contraindicates triptans are identified using the "Cardiac and Other Risk Factors" CRF pages. The pages are used to identify subjects with CV conditions cited in triptan labels as contraindications. A subject is identified as someone with cardiovascular risk factors contraindicating triptans if any of the following questions are answered as "yes":

- Does the subject have ischemic coronary artery disease?
- Does the subject have coronary artery vasospasm including Prinzmetal's angina?
- Does the subject have Wolff-Parkinson-White Syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders?
- Does the subject have history of stroke or transient ischemic attack (TIA)?
- Does the subject have peripheral vascular disease (PVD)?
- Does the subject have ischemic bowel disease?
- Does the subject have uncontrolled hypertension?

5.2.3 Rimegepant Exposure

Rimegepant exposure subgroups are derived from parameters defined in Section 4.8.1 as follows:

- Time on rimegepant subgroups are based on quintiles of total weeks on treatment (< P20, ≥ P20 to < P40, ≥ P40 to < P60, ≥ P60 to < P80, ≥ P80) based on eDiary for treated subjects pooled across enrollment group. Percentiles will be rounded to 1 decimal place.

- Cumulative rimegepant exposure subgroups are based on quintiles of the total number of study drug tablets taken (< P20, ≥ P20 to < P40, ≥ P40 to < P60, ≥ P60 to < P80, ≥ P80) based on eDiary for treated subjects pooled across enrollment group. Percentiles will be rounded to integers.

- Average rimegepant exposure subgroups are based on average rimegepant exposure (tablets per 4 weeks), which is calculated as 4*cumulative rimegepant exposure/time in the LTT period for treated subjects pooled across enrollment group.

5.3 Derived Dates

Derived dates for defining analysis periods are defined as follows:

- OP start date/time: Earliest complete date during the screening epoch in the eDiary.

- OP end date/time: Latest complete date during the screening epoch in the eDiary.

- LTT start date/time: Earliest complete date during the treatment epoch in the eDiary.

- LTT end date/time: Latest complete date during the treatment epoch in the eDiary.

- Study drug first dose date/time: Earliest complete date where subjects indicated that they took medication during the treatment epoch in the eDiary.

- Study drug end dose date/time: Latest complete date where subjects indicated that they took medication during the treatment epoch in the eDiary.

- Study drug last dose date/time: Study drug end dose date derived only for subjects who have non-missing completion status on the Study Exit Status CRF. Thus, in an interim analysis, all post-treatment data will be included for a subject who is still on study. At the last database lock, the last dose date will be equal to the end dose date for treated subjects.

- EOT visit date: Maximum of the following: (1) LTT end date/time; (2) latest complete visit date excluding folder name “follow-up safety visit” on the Visit Date CRF. This is derived only for subjects who have non-missing completion status on the Study Exit Status CRF.

- Last contact date: (1) Complete death date, if it exists; (2) otherwise, the maximum complete date of the following: AE start/stop; ECG; eDiary; enrollment; informed consent; laboratory collection; non-study medication start/stop; physical measurement; procedure; rating scale; questionnaire; screening; study completion/discontinuation; vital sign; visit.

No imputations are performed on these derived dates. Complete dates are those with valid, non-missing day, month, and year.

5.4 Analysis Periods

Analysis periods are defined as follows:

- Observational Period (OP): measurement date/time on or after the OP start date/time through the OP end date/time. This period is used to assess the number of migraine days per 4 weeks during the OP.

- Pre-treatment: measurement date/time on or before the study drug first dose date/time. This period is used to derive baseline values, and to assess safety and outcomes research endpoints.

- Post-enrollment: measurement date/time after the IWRS enrollment date/time through the EOT visit date + 7 days. This period is used to derive analysis visit windows for slotting observations.

- Follow-up: measurement date after the EOT visit date + 7 days. This period is used to slot observations.

- Long-term treatment (LTT): measurement date/time on or after the LTT start date/time through the LTT end date/time. This period is used to assess the number of migraine days per 4 weeks and number of tablets taken during LTT.

- On-treatment safety: measurement date/time after the study drug first dose date/time through the study drug last dose date + 7 days. Note that AEs with imputed start date equal to the study drug first dose date are part of this period (refer to the BHV3000 Core SAP for AE start date imputation). This period is used to assess safety endpoints on treatment.

- Follow-up safety: measurement date after the study drug last dose date + 7 days. This period is used to assess safety endpoints during follow-up.

See Section 5.3 for derived dates for determining analysis periods. If measurement time is missing or not collected, then the measurement date will be compared to the derived date.

5.5 Analysis Visit Windows

Refer to Protocol Section 4.3 for the schedule of assessments.

Study days are calculated from enrollment as follows:

- Measurement date – IWRS enrollment date + 1, if measurement date ≥ IWRS enrollment date
- Measurement date – IWRS enrollment date, if measurement date < IWRS enrollment date

Follow-up days are calculated from the EOT visit as follows:

- Measurement date – EOT visit date + 1, if measurement date ≥ EOT visit date
- Measurement date – EOT visit date, if measurement date < EOT visit date

Evaluation intervals are based on study days derived in the post-enrollment analysis and follow-up analysis periods (see Section 5.4). Table 5 and Table 6 have analysis visit windows for the PRN and EOD+PRN dosing groups, respectively.

Table 5: Analysis Visit Windows: 52-Week PRN (2-8) and (9-14) Dosing Groups

Visit	Analysis-Specified Interval for PoM, SM, MSQoL, MIDAS, and CGI-C	Analysis-Specified Interval for Other Endpoints	Target Day
Screening Period			
Screening	≤ -1	≤ -1	
Baseline	1	1	1
Post-Enrollment Period			
Week 2		2 to 21	14
Week 4		22 to 42	28
Week 8		43 to 70	56
Week 12	43 to 126	71 to 98	84
Week 16		99 to 126	112
Week 20		127 to 154	140
Week 24	127 to 210	155 to 182	168
Week 28		183 to 210	196
Week 32		211 to 238	224
Week 36	211 to 308	239 to 266	252
Week 40		267 to 294	280
Week 44		295 to 322	308
Week 48		323 to 350	336
Week 52	≥ 309	351 to 378	364
Week 56		≥ 379	392
Follow-up			
Follow-up Week 2		8 to 21	14
Follow-up Week 4		≥ 22	28

Study days are used for screening and post-enrollment; follow-up days are used for follow-up.

Table 6: Analysis Visit Windows: 12-Week EOD+PRN and PRN (2-8) Dosing Groups

Visit	Analysis-Specified Interval for PoM, SM, MSQoL, MIDAS, and CGI-C	Analysis-Specified Interval for Other Endpoints	Target Day
Screening Period			
Screening	≤ -1	≤ -1	
Baseline	1	1	1
Post-Enrollment Period			
Week 2		2 to 21	14
Week 4		22 to 42	28
Week 8		43 to 70	56
Week 12	≥ 43	71 to 98	84
Week 16		99 to 126	112
Follow-up			
Follow-up Week 2		8 to 21	14
Follow-up Week 4		≥ 22	28

Study days are used for screening and post-enrollment; follow-up days are used for follow-up.

LTT study days are used in analyses of migraine days and exposure, and are calculated from LTT start as follows:

- Measurement date – LTT start date + 1, if measurement date ≥ LTT start date
- Measurement date – LTT start date, if measurement date < LTT start date.

6 CHANGES TO PLANNED ANALYSES IN THE PROTOCOL

There are no changes to planned analyses in the protocol at this time.