Biohaven Pharmaceuticals

Protocol BHV3000-305

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

Statistical Analysis Plan

Version 10.0

Date: 16-Nov-2021

SIGNATURE PAGE

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

Sponsor: Biohaven Pharmaceuticals, Inc.

Protocol Number: BHV3000-305

Document Version/Date: Version 10.0/16-Nov-2021

Author: PPD , PPD Biohaven Pharmaceuticals

Signature:_____

Date:_____

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 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:

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Date:_____

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ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ASE	Asymptotic standard error
AST	Aspartate aminotransferase
BMI	Body mass index
CGI-c	Clinical Global Impression - change
CGRP	Calcitonin gene-related peptide
CI	Confidence interval
COVID-19	Cornonavirus disease 2019
CRF	Case report form
CSR	Clinical study report
CV	Cardiovascular
DB	Double-blind
DBT	Double-blind treatment
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EOD	Every other day
EOFU	End of follow-up
EOT	End of treatment
HDL	High-density lipoprotein
IWRS	Interactive web response system
J2R	Jump to reference
LDL	Low-density lipoprotein
LFT	Liver function test
LLN	Lower limit of normal
LSM	Least-squares mean
MDRD	Modification of diet in renal disease
MIDAS	Migraine Disability Assessment
MR	Menstrually-related
MRM	Menstrually-related migraine
MSQoL	Migraine Specific Quality of Life
OL	Open-label
OLE	Open-label extension

Abbreviation	Definition
OP	Observational period
OR	Outcomes research
POM	Preference of medication
PT	Preferred term
S-STS	Sheehan-Suicidality Tracking Scale
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SI	Systeme Internationale
SOC	System organ class
SM	Satisfaction with medication
TEAE	Treatment-emergent adverse event
TBL	Total bilirubin
TLF	Table, listing, and figure
ULN	Upper limit of normal
US	United States

REVISION HISTORY

Version	Description of Change
1.0	Original Issue
2.0	- General: Changed "during" to "in" when referring to DBT and OLE phases throughout document. Changed "rimegepant" to "DB or OL rimegepant" when referring to the DB or OL rimegepant phase, population, and study drug dates. Changed "dimension" to "domain" for MSQoL. - Section 2.3.3: Removed ", Rimegepant Treated Subjects" from Table 3 OR endpoints. - Section 6.1: Specified exceptions for treatment group displays in tables. - Section 6.2.1: Added subsection titles and moved text for clarity. - Section 6.2.3: Removed tables for enrolled subjects not in the mITT population. Added tables of demographics and baseline characteristics and migraine history for randomized subjects not in the mITT population. Added tables of demographics and rimegepant baseline characteristics for DB or OL rimegepant treated subjects by subgroup level and overall for all safety subgroups of interest specified in Section 6.1.3. Added a table of prophylactic migraine medication use randomization strata for randomized subjects. - Section 6.2.3.1: Added prophylactic migraine medication use randomization stratum to baseline characteristics. - Section 6.2.3.2: Changed "rimegepant frequency" to "overall frequency". - Section 6.3.2.3: Specified that treatment group comparisons will be based on evaluable mITT subjects with MSQoL restrictive role function domain scores at both baseline and Week 12 of the on-DBT efficacy analysis period. - Section 6.2.4.1: Added tables of eDiary DB or OL rimegepant exposure for DB or OL rimegepant treated subjects by subgroup level and overall for all safety subgroups of interest. Added time in follow-up for follow-up subjects to the table of eDiary study drug exposure. - Section 6.2.4.2: Changed "study" to "study drug" in table of drug accountability compliance. - Section 6.2.4.4: Added subsection titles and moved text for clarity. - Section 6.3: Added 3 by-subject efficacy listings: subjects excluded from the efficacy analysis for randomized subjects not in the evaluable mITT population; primary and secondary efficacy endpoints for randomized subjects; exploratory endpoints for mITT subjects. - Section 6.3.1: Specified additional details about 2 efficacy listings. - Sections 6.3.1.1 and 6.3.2.1: Removed the phrase "(except prophylactic migraine medication use)". - Section 6.3.3.1: Specified additional details about the MRM day listing. - Section 6.5: Replaced "EOS" with "EOFU" throughout section. - Section 6.5.1.5: New section of "AEs Across All Study Phases Combined". Moved text from Section 6.5. Added 1 table of all hepatic-related AEs leading to study drug discontinuation. - Section 6.5.2.1: Moved text to Section 6.5.2.2. - Section 6.5.2.2: Added subsection titles and moved text for clarity. Specified that exposure-adjusted LFT elevations are multiple LFT elevation rates are assessed only for cumulative LFT elevations. Specified additional details about eDISH plots. Moved text from Section 6.5.2.1 about LFT ULN shifts from baseline. For by-subject longitudinal LFT plots, added subjects with ALP > 2 x ULN elevations and specified that treated migraine days will be displayed with symbols along the x-axis. - Section 6.5.4.2: Modified section title.

Version	Description of Change
	• Section 6.5.4.3: Specified that ECG abnormalities will be summarized together with vital sign and physical measurement abnormalities in the same tables.
	• Sections 6.6.3, 6.6.4, and 6.6.5: Removed baseline as a scheduled visit.
	• Section 7.6.2: Defined treated migraine days.
	• Section 7.3: Changed "last contact date/time" to "last contact date".
	• Section 7.4: Changed "last date/time" to "last date" for on-treatment and follow-up safety analysis periods.
3.0	• General: Changed "populations for analyses" to "population samples for analyses". Removed "survey" when referring to SM. Changed "95% normal CI" to "normal 95% CI". Changed "SE" to "ASE" for binary efficacy endpoints. Changed "screening epoch" to "OP epoch", "treatment epoch" to "DBT epoch", and "extension epoch" to "OLE epoch".
	• Abbreviations: Added asymptotic standard error (ASE).
	• Section 1.1: Changed protocol version from 4 to 7.
	• Section 1.2.2: Modified the first objective to be based on moderate or severe migraines, and added an objective about comparing the change from baseline in the MIDAS total score at Week 12 of the DBT phase between rimegepant and placebo, as per Protocol Version 7.
	• Section 1.2.3: Added 2 efficacy objectives, modified 5 existing efficacy objectives to be assessed by severity (total; moderate or severe), and updated language about MSQoL and MIDAS scores to align with Protocol Version 7.
	• Section 2.3: Defined estimands and intercurrent events in greater detail. Modified Tables 1 to 3 to (1) exclude "Population" rows and (2) display "Endpoint" instead of "Variables".
	• Section 2.3.2: Modified Table 2 to be consistent with changes to Section 1.2.2.
	• Section 2.3.3: Modified Table 3 to be consistent with changes to Section 1.2.3.
	• Section 6.1: Specified that exposure, efficacy, and safety results for the DBT phase will be presented only by treatment group without an overall column.
	• Section 6.1.2: Modified bulleted list to be consistent with changes to Section 1.2.2.
	• Section 6.1.3: Added a by-subject listing of efficacy and safety subgroups for treated subjects.
	• Section 6.2.1.3: Added another category to the subject disposition in the DBT phase table per CRF Version 3.
	• Section 6.2.4.1: Added parameters to the tables of DB or OL rimegepant exposure and study drug exposure.
	• Section 6.2.4.4: Defined migraine standard or care medications. Revised the bulleted lists of tables.
	• Section 6.3.1.1: Specified that the principal analysis of the primary endpoint will be repeated for moderate or severe migraine severity.
	• Section 6.3.2.1: Specified that analyses will be stratified by severity (total; moderate or severe). Specified that subgroup analyses will be stratified by prophylactic migraine medication use at randomization.
	• Section 6.3.2.3: Replaced text about calculating domain scores and imputing missing data with a reference to the BHV3000 Core SAP. Specified that 2-sided normal 95% CIs for mean change from baseline will also be presented in a descriptive analyses over time.
	• Section 6.3.2.4: New section "MIDAS in the DBT Phase" added to address the new secondary objective in Section 1.2.2. Moved description of MIDAS from Section 6.6.2 to here. Cross-referenced methodology in Section 6.3.2.3 and the BHV3000 Core SAP.

Version	Description of Change
	• Section 6.3.2.5: New section "Overall Summary of Primary and Secondary Endpoints" added to present the hierarchical testing of primary and secondary endpoints.
	• Section 6.3.3.2: Specified that analyses will be repeated for moderate or severe migraine severity.
	• Section 6.5.2: 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 6.5.2.2: Added mutually exclusive elevations for TBL and ALP in LFT elevation summary. Replaced "treated migraine days" with "DBT and OL rimegepant dosing days" in by-subject longitudinal LFT plots.
	• Section 6.5.5: Replaced the sentence "If the total score > 0, then responses to all questions will be presented; otherwise, only the ideation subscale, behavioral subscale, and total scores will be presented." with a reference to the BHV3000 Core SAP for listing content.
	• Section 6.6: Replaced the sentence about listing contents with a reference to the BHV3000 Core SAP for contents of these listings.
	• Section 6.6.1: Specified that 2-sided normal 95% CIs for mean change from baseline will also be presented in a descriptive analyses over time.
	• Section 6.6.2: Moved description of MIDAS to new Section 6.3.2.4. Added absenteeism and presenteeism scores to descriptive analyses. Specified that 2-sided normal 95% CIs for mean change will also be presented in descriptive analyses over time.
	• Section 6.6.3 through 6.6.5: Modified descriptions of rating scales to be consistent with the BHV3000 Core SAP. Specified that combined categories defined in the BHV3000 Core SAP will also be summarized in descriptive analyses over time.
	• Section 7.5: Modified Table 4 by removing column for OR endpoints and using same visit windows as on-treatment safety for OR.
	• Section 7.6.2.1: New section "eDiary Reference Time Point Date/Time and Epoch" added to define derivations for these 2 variables.
	• Section 7.6.2.2: Removed sentence about treated migraine days.
	• Section 7.6.3: New section "Non-Study Medications" added to define medication types.
4.0	• Abbreviations: Removed "ATC".
	• Section 3: Added a table of inclusion and exclusion from the evaluable mITT sample population for randomized subjects.
	• Section 6.2.4.1: Removed 3 references to epoch.
	• Section 6.2.4.4: Replaced "ATC" with "therapeutic class".
	• Section 6.3: Added a reference to Section 3. Replaced "eDiary date" with "eDiary reference time point date" throughout.
	• Section 6.5.2: Specified that LDL cholesterol and triglycerides will be assessed by fasting status rather than by 8-hour fasting status. Specified that the by-subject listing of LFT values and ratios to ULN will display all results over time for enrolled subjects with select LFT elevations (ALT or AST > 3 x ULN; ALP or TBL > 2 x ULN) at any time point.
	• Section 7.3: Added eDiary reference date/time. Added definitions of DBT and OL rimegepant study drug date/times to be based on the Week 12 kit assigned date/time rather than epoch. Modified definitions of DBT and OL rimegepant start/end date/times, and OP start/end dates. Removed eDiary date.
	• Section 7.4: Added new analysis periods for eDiary efficacy endpoints. Modified analysis periods for OR efficacy endpoints.

Version	Description of Change
	• Section 7.6.2.1: Modified the derivation of epoch to be based on the DBT and OL rimegepant start dates.
	• Section 7.6.2.2: Added 1 more criterion to determine whether a headache lasted $\geq$ 30 minutes. Added text to clarify the use of finding date/time for determining whether a headache lasted $\geq$ 30 minutes and on determining multiple migraine characteristics. Revised text about determining migraine date. Removed text about counting a migraine day as 2 days.
5.0	• Abbreviations: Added LSM.
	• Section 1.1: Changed Protocol Version from 7 to 8.0.
	• Section 1.2: Aligned objectives with Protocol Version 8.0.
	• Section 2.3.1 to 2.3.3: Aligned objectives and estimands in Tables 1, 2, and 3 with Protocol Version 8.0.
	• Section 3: Defined interim subjects.
	• Section 6.1: Specified that interim subjects will be assessed by as-treated treatment group.
	• Section 6.1.2: Aligned endpoints with Protocol Version 8.0.
	• Section 6.2.2: Changed "treated subjects" to "randomized subjects".
	• Section 6.2.4.1: Changed "4 weeks" to "month" throughout section.
	• Sections 6.3: Changed "4 weeks" and "interval" to "month" throughout section. Changed "mean" to "LSM" throughout section in treatment group comparisons. Combined the by-subject listing of primary and secondary efficacy endpoints.
	• Section 6.3.1.1:
	○ Descriptive Analyses: Changed y-axis of scatter plots to be on change instead of reduction, and consistent with primary objective.
	○ Principal Analysis: Clarified which GLMEM results supported primary, secondary, versus exploratory objectives. Removed mean values by visit from model estimates. Specified that the model will be repeated by prophylactic migraine medication use at randomization. Added 2 longitudinal plots of LSM changes from OP in the number of migraine days per month by severity (total; moderate or severe) versus month.
	○ Subgroup Analyses: Specified that subgroup analyses of the primary endpoint will not include prophylactic migraine medication use at randomization in the model. Removed mean values by visit from model estimates.
	• Section 6.3.1.2: Descriptive Analyses: Changed y-axis of scatter plots to be on change instead of reduction. Specified that results will support the exploratory objective about OLE phase efficacy. Added 2 longitudinal plots of mean changes from OP in the number of migraine days per month by migraine severity (total; moderate or severe) versus month.
	• Section 6.3.2.1:
	○ Replaced 2 paragraphs with text defining responders and failures.
	○ DBT Descriptive Analyses: Specified that analyses by month will be presented using 2 methods, Non-Evaluable = Failure and Non-Evaluable = Missing. Removed the "< 1" reduction category. Added 3 tables of percentage of subjects with reduction outcomes by migraine severity (total; moderate or severe) for each select percentage reduction ($\geq$ 50%, $\geq$ 75%, and $\geq$ 100%).

Version	Description of Change
	o DBT Phase Treatment Group Comparisons: Specified that response rates will be based on responder outcomes described previously. Specified that results will support the secondary and exploratory objectives about percent reductions. Specified that endpoints will also be compared between treatment groups using unstratified CMH tests for each subgroup level; removed "stratified" from 2 bullets. Added 6 longitudinal plots of percentage of subjects with reduction versus month by select percentage reduction ($\geq$ 50%, $\geq$ 75%, and $\geq$ 100%) and migraine severity (total; moderate or severe). o OLE Phase: Specified that analyses by month will be presented using 2 methods, Non-Evaluable = Failure and Non-Evaluable = Missing. Specified that results will support the exploratory objective about OLE phase efficacy. • Section 6.3.2.2: DBT Phase Treatment Group Comparisons: Clarified which GLMEM results supported secondary versus exploratory objectives. Specified that the model will be repeated by prophylactic migraine medication use at randomization. • Sections 6.3.2.3 and 6.3.2.4: DBT Phase Treatment Group Comparisons: Changed GLMEM to GLM and removed subject as a random effect from the model. Removed mean values by visit from model estimates. Specified that the model will be repeated by prophylactic migraine medication use at randomization. • Section 6.3.2.5: Aligned endpoints with Protocol Version 8.0. • Section 6.3.3.1: DBT Phase Treatment Group Comparisons: Specified that the model will be repeated by prophylactic migraine medication use at randomization. • Section 6.3.3.2: Treatment Group Comparisons: Changed GLMEM to GLM and removed subject as a random effect from the model. Specified that the model will be repeated by prophylactic migraine medication use at randomization. Removed mean values from model estimates. • Section 6.5: Added post-DBT pre-OL rimegepant to the list of safety analysis periods. Specified that measurements will be slotted into analysis periods based on "measurement dates", which are (1) imputed start dates for AEs, and (2) collection or assessment dates for all other safety parameters. • Section 6.5.1.1: Added an overall AE summary table during post-DBT pre-OL rimegepant for interim subjects. • Section 6.5.1.6: New section "Post-DBT Pre-OL Rimegepant AEs". Added 3 tables of AEs during post-DBT pre-OL rimegepant for interim subjects. • Section 6.5.2.1: Added a table of worst laboratory test abnormalities during post-DBT pre-OL rimegepant for interim subjects. • Section 6.5.2.2: Added a table of LFT elevations during post-DBT pre-OL rimegepant for interim subjects. Removed 2 tables of multiple cumulative LFT elevation rates assessed as continuous parameters. • Section 6.6: Specified that measurements will be slotted into analysis periods according to assessment dates. • Section 7.4: Changed "interim efficacy" to "post-DBT pre-OL rimegepant efficacy". Modified the definition of the on-DBT safety analysis period. Defined the post-DBT pre-OL rimegepant safety analysis period. • Section 7.6.1: Modified the definition of the on-DBT safety analysis period. • Section 7.6.3: Modified the definition of DBT concomitant non-study medications.

Version	Description of Change
6.0	• Section 6.2.4.1: Replaced "study medication" with "study drug" where applicable. Specified that imputed OL rimegepant to treat headache date/time will be derived for subjects who answer "yes" to the question about having already taken study medication to treat a headache on the eDiary scheduled dosing report, but do not have study drug data from any other eDiary source on the same day. Specified that subjects with non-missing imputed OL rimegepant to treat headache date/times will be credited with taking 1 tablet of OL rimegepant on each of those days to account for missed OL rimegepant exposure from eDiary non-compliance. • Section 6.3.2.1: Added another category to the outcomes table. • Section 7.3: Defined imputed OL rimegepant to treat headache date/time, and added it to the derivation of study drug date/time. Specified that the reference date from the medication reconciliation form is compared with the IWRS Week 12 kit assigned date. • Section 7.6.2.2: Added imputed OL rimegepant to treat headache date/time to the derivation of item 2a.
7.0	• Abbreviations: Added eGFR, LLN, and MDRD. • Section 3: Moved text about tables and listings to Section 6.2.1. • Section 6.1.3: Modified subgroup levels of historical number of moderate or severe migraine attacks per month. Removed the cumulative rimegepant exposure subgroup and the by-subject listing of efficacy and safety subgroups. Removed subsequent references to safety subgroups of interest throughout. • Section 6.2.1: New section "Population Samples for Analyses". Moved text from Section 3 here. • Section 6.2.2: New section "Enrollment". Added 3 tables: enrollment by country and site; enrollment by age group; accrual by randomization year and month. • Section 6.2.3.3: Replaced "mITT" with "evaluable mITT". • Section 6.2.5: Modified the derivation of age at rimegepant baseline. Removed birth date from the demographics listing. Replaced "mITT" with "evaluable mITT". Modified the listing of baseline characteristics. • Section 6.2.5.1: Removed the derivation of age at informed consent. Added country to demographics. • Section 6.2.5.3: Modified the contents of the migraine history table. • Section 6.2.6.1: Specified multiple sources of study drug in the eDiary. Modified the contents of eDiary exposure tables. Modified the formulas for total study drug exposure and time in follow-up. • Section 6.2.6.2: Added 1 table of eDiary versus drug accountability cumulative exposure. • Section 6.2.6.3: Modified the contents of eDiary compliance tables. • Section 6.3.1.1: Added "through Month 3" to the definition of the overall DBT mean. • Section 6.3.1.2: Added "through Month 13" to the definition of the overall OL rimegepant mean. • Sections 6.3.2.2 and 6.3.3.1: Added "through Month 3" to the definition of the overall DBT mean. Added "through Month 13" to the definition of the overall OL rimegepant mean. • Section 6.3.2.3: Removed EOT. • Section 6.5.2: Specified that eGFR will be calculated using the MDRD formula and an LLN of 60. Added a by-subject listing of local laboratory CK fractionation. • Section 7.1.2: New section "Duplicate Subjects". • Section 7.2: Replaced text with "Not applicable".

Version	Description of Change
	• Section 7.7: New section "Age at a Reference Date".
8.0	• Signature page: Replaced PPD with PPD , and PPD with PPD .
	• Abbreviations: Added COVID-19.
	• General: Changed "rimegepant baseline" to "DB or OL rimegepant baseline" throughout. Changed references to Section 6.1.3 to Section 6.1.3.1.
	• Section 3: Defined COVID-19 impacted subjects.
	• Section 6.1: Specified that all by-subject listings except administrative listings will identify subjects impacted by COVID-19.
	• Section 6.1.3: Moved text to new subsection 6.1.3.1 "Efficacy Subgroups for Evaluable mITT Subjects". Added subsections 6.1.3.2, 6.1.3.3, and 6.1.3.4.
	• Section 6.1.3.1: Modified subgroup levels for historical number of moderate or severe migraine attacks per month and historical chronic migraine.
	• Section 6.2.3: Specified that listings for the OLE and follow-up phases will identify subjects who terminated the phase prematurely due COVID-19.
	• Section 6.2.3.3: Modified definitions of completed DBT phase, did not complete DBT phase, and completed DBT phase but not continuing to OLE phase. Added tables of subject disposition in the DBT phase for treated subjects by safety subgroup level and overall for each treatment group.
	• Section 6.2.3.4: Modified definitions of completed OLE phase and did not complete OLE phase. Added reasons for premature OLE phase termination to the subject disposition table. Added tables of subject disposition in the OLE phase for OL rimegepant treated subjects by subgroup level and overall for all safety subgroups of interest.
	• Section 6.2.3.5: Added reasons for premature follow-up phase termination to the subject disposition table.
	• Section 6.2.5: Added the following tables: (1) demographics and baseline characteristics by safety subgroup level and overall for treated subjects; (2) migraine history for DB or OL rimegepant treated subjects by treatment group and overall; (3) demographics and baseline characteristics, migraine history, and cardiac and other risk factors by safety subgroup level and overall for DB or OL rimegepant treated subjects and OL rimegepant treated subjects. Defined age at OL rimegepant baseline and OL rimegepant baseline.
	• Section 6.2.6.1: Specified that the listing of eDiary exposure and drug accountability will display COVID-19 visit impact code for visits impacted by COVID-19. Added eDiary exposure tables by safety subgroup level and overall for treated subjects, DB or OL rimegepant treated subjects, and OL rimegepant treated subjects. Modified contents of exposure tables. Modified the definition of study discontinuation.
	• Section 6.2.6.2: Changed ">" to "≥" in eDiary versus drug accountability cumulative exposure table. Added methods for the drug accountability compliance table.
	• Section 6.2.6.4: Section 6.2.6.1: Specified that non-study medication listings will display COVID-19 visit impact code for visits impacted by COVID-19. Added the following tables: (1) non-study prophylactic migraine standard of care medications for mITT subjects with prophylactic migraine medication use at randomization; (2) non-study concomitant medications by safety subgroup level and overall for DB or OL rimegepant treated subjects and OL rimegepant treated subjects.
	• Section 6.3.1: Specified that the listing of eDiary evening report and follow-up headache logs will display COVID-19 visit impact code for visits impacted by COVID-19.

Version	Description of Change
	• Section 6.3.2.1: Added reduction categories to descriptive tables of reductions from the OP over time during DBT and OLE. Added a category "Not evaluable" to Not Evaluable = Failure analyses by month. Specified that analyses for the Non-Evaluable = Failure method during the OLE phase will only be shown in the Addendum Report.
	• Section 6.3.3.1: Specified that the menstrual periods listing will display COVID-19 visit impact code for visits impacted by COVID-19.
	• Section 6.3.3.3: New section "Triptan or Ergotamine Days per Month". Added 3 tables.
	• Section 6.3.3.4: New section "Medication Days per Month on Non-Scheduled Dosing Days in the OLE Phase". Added 1 table.
	• Section 6.5: Specified that safety listings will display COVID-19 visit impact code for visits impacted by COVID-19.
	• Section 6.5.1: Defined TEAEs on OL rimegepant.
	• Section 6.5.1.1: Added tables of AE overviews by safety subgroup level and overall for DB or OL rimegepant treated subjects and OL rimegepant treated subjects.
	• Section 6.5.1.3: Added AE tables by safety subgroup level and overall for treated subjects, DB or OL rimegepant treated subjects, and OL rimegepant treated subjects.
	• Section 6.5.1.2: Added laboratory test tables by safety subgroup level and overall for treated subjects, DB or OL rimegepant treated subjects, and OL rimegepant treated subjects.
	• Section 6.5.2: Specified which laboratory test listings will display COVID-19 visit impact code for visits impacted by COVID-19.
	• Section 6.5.2.2: Added LFT tables by safety subgroup level and overall for DB or OL rimegepant treated subjects and OL rimegepant treated subjects. Added eDISH plots by mutually-exclusive safety subgroup level for DB or OL rimegepant treated subjects and OL rimegepant treated subjects.
	• Sections 6.5.3.2, 6.5.4.2, and 6.5.4.3: Added tables by safety subgroup level and overall for DB or OL rimegepant treated subjects and OL rimegepant treated subjects.
	• Section 6.6: Specified that OR listings will display COVID-19 visit impact code for visits impacted by COVID-19.
	• Sections 6.6.1 and 6.6.2: Added 7 tables of treatment group comparisons of MSQOL and MIDAS score changes from baseline at Week 12 of DBT OR analysis period for treated subjects.
	• Section 6.7: New section "COVID-19 Impact". Added 3 tables and 2 listings.
	• Section 7.3: Replaced "Week 12 kit assigned" with "Week 12 kit assigned local". Modified the definitions of OL rimegepant last date/time, eDiary efficacy date/time, and last contact date. Defined the COVID-19 visit date.
	• Section 7.5: Defined randomization days. Modified the title and contents of Table 4.
	• Section 9: New section "Appendices".
	• Section 9.1: New section "COVID-19 Visit Impact".
9.0	• General: Changed "CGI-C" to "CGI-c".
	• Sections 2.3.3, 6.3.2.4, and 6.6.2: Removed the MIDAS lost productivity time score.
	• Sections 6.2.2, 6.2.5.1, 6.2.5.3, and 6.2.5.4: Replaced text with reference to the BHV3000 Core SAP.
	• Section 6.2.6.1: Added patient-years of exposure to tables of eDiary rimegepant or placebo exposure during double-blind treatment and eDiary OL rimegepant exposure.
	• Section 6.5: Specified that deaths are slotted into analysis periods according to the death date.

Version	Description of Change
	• Section 6.5.1: Moved text about deaths to new Section 6.5.1.1. Renumbered subsections.
	• Section 6.5.1.1: New section "Deaths". Added a table of deaths. Specified contents of the deaths listing.
	• Section 6.5.1.2: Removed AE leading to death from AE overview tables.
	• Section 6.5.1.4:
	○ DBT Phase: Changed "in ≥ X% of subjects" to "with ≥ X% frequency". Removed 2 tables of exposure-adjusted AEs. Added tables of exposure-adjusted multiple occurrences of unique AEs.
	○ DB or OL Rimegepant Phase: Removed all tables of exposure-adjusted AEs. Added tables of AEs occurring with ≥ 5% frequency by severity and exposure-adjusted multiple occurrences of unique AEs.
	○ OLE Phase: Added tables of AEs occurring with ≥ 5% frequency by severity and exposure-adjusted multiple occurrences of unique AEs.
	• Section 6.5.2: Replaced the eGFR MDRD formula with a reference to the BHV3000 Core SAP.
	• Sections 6.5.2.1, 6.5.2.2, 6.5.3.2, 6.5.4.3, and 6.5.5: Replaced text with references to the BHV3000 Core SAP.
	• Section 7.3: Modified the derivation of the last contact date. Added the death date.
	• Section 7.6.1: Changed "exposure-adjusted AEs" to "exposure-adjusted multiple occurrences of unique AEs".
10.0	Modified after the final database lock for the Addendum Report to correct errors and make analyses consistent.
	• General: Replaced "Interim Week 12 CSR" with "CSR" and "final CSR" with "Addendum Report".
	• Sections 1.1 and 7.1.1: Specified the Addendum Report.
	• Sections 3 and 6.3.3.1: Replaced "evaluable mITT menstruating female subjects" with "menstrual migraine evaluable mITT menstruating female subjects", and "evaluable OL rimegepant mITT menstruating female subjects" with "menstrual migraine evaluable OL rimegepant mITT menstruating female subjects". Defined these 2 new cohorts to align MRM days per month analyses with migraine days per month analyses.
	• Section 6.3.3.4: Changed section title to "Medication Days per Month on Non-Scheduled Days in the OLE Phase". Removed text about sources of rimegepant and the definition of non-scheduled dosing days. Added a reference to Section 7.6.2.3. Replaced "non-scheduled dosing day" with "non-scheduled day".
	• Section 7.3: Modified definition of efficacy date.
	• Section 7.6.2.2: Modified criterion 2a for no qualified migraine headache.
	• Section 7.6.2.3: New section "Scheduled and Non-Scheduled Days in the OLE Phase". Defined scheduled and non-scheduled days in the OLE phase, and provided an example.

1   INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1   Introduction

This document presents the statistical analysis plan (SAP) for Biohaven Pharmaceuticals, Protocol BHV3000-305: A Phase 2/3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Rimegepant in Migraine Prevention.

This SAP is based on BHV3000-305 Protocol Version 8.0, and describes the analysis of the double-blind treatment (DBT), open-label extension (OLE), and follow-up phases of the study. It contains 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 90-Day Safety Update, CSR, and Addendum Report. 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 compare the efficacy of rimegepant to placebo as a preventive treatment for migraine, as measured by the reduction from baseline in the mean number of migraine days per month in the last 4 weeks of the DBT phase (a month is defined as 4 weeks for the purpose of this protocol).

1.2.2   Secondary Objectives

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

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

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

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

- To evaluate the safety and tolerability of rimegepant.

- To evaluate the frequency of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3x upper limit of normal (ULN) with concurrent elevations in total bilirubin (TBL) > 2x ULN in subjects treated with rimegepant.

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

- To compare the change from baseline in the Migraine-Specific Quality-of-Life Questionnaire (MSQoL) v2.1 restrictive role function domain score at Week 12 of the DBT phase between rimegepant and placebo.

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

1.2.3   Exploratory Objectives

- To compare the efficacy of rimegepant to placebo on the reduction from baseline in the mean number of migraine days per month by severity (total; moderate or severe) in each month and the entire course of the DBT phase.

- To compare the efficacy of rimegepant to placebo on the proportion of subjects who have at least a 50% reduction from baseline in the mean number of migraine days per month by severity (total; moderate or severe) in each month and the entire course of the DBT phase.

- To evaluate the reduction in the number of migraine days per month by severity (total; moderate or severe) in each month and the entire course of the OLE phase.

- To compare the efficacy of rimegepant to placebo as a preventive treatment for menstrually-related migraine (MRM), as measured by the reduction from baseline in the mean number of MRM days per month in each month and the entire course of the DBT phase.

- To compare the efficacy of rimegepant to placebo on the proportion of subjects who have at least a 75% reduction from baseline in the mean number of migraine days per month by severity (total; moderate or severe) in each month and the entire course of the DBT phase.

- To compare the efficacy of rimegepant to placebo on the proportion of subjects who have a 100% reduction from baseline in the mean number of migraine days per month by severity (total; moderate or severe) in each month and the entire course of the DBT phase.

- To evaluate the frequency of elevated liver function tests (LFT: AST, ALT, or TBL) in subjects treated with rimegepant.

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

- To evaluate the effect of rimegepant treatment on the MSQoL v2.1 domain scores.

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

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

- To evaluate the effect of rimegepant treatment on the MIDAS scores.

- To evaluate the effect of rimegepant treatment on the Clinical Global Impression of Change (CGI-c) scale.

- To compare the efficacy of rimegepant to placebo on the reduction from baseline in the mean number of migraine days per week by severity (total; moderate or severe) in the first week of the DBT phase.

- To compare the frequency of use of rescue medications between rimegepant and placebo in each month and the entire course of the DBT phase.

2 STUDY DESIGN

2.1 Synopsis of Study Design

BHV3000-305 is a multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of rimegepant in migraine prevention with DBT, OLE, and follow-up phases.

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

After providing informed consent, patients will first participate in the screening phase to determine eligibility for the study. Upon completion of the screening visit, subjects will be provided an eDiary to document each day of the 28-day OP if a migraine occurred, the migraine intensity, and if the migraine was treated. Subjects will record the standard of care migraine treatment received on a paper diary and female subjects will record their menstrual period information on a paper log.

Subjects will have blood drawn for baseline lab profiles at the pre-randomization laboratory visit; this visit must occur within 96 hours (4 days) of the baseline visit. Subjects will then return for the baseline visit.

After completing the 28-day OP and the pre-randomization laboratory visit, patients will return to the study site for their baseline visit where eligibility for continued participation in the study will be assessed prior to randomization and dispensement of study medication. After the investigator reviews the results of the pre-randomization laboratory visit and determines continued eligibility, the site staff will inform the patient whether or not they are eligible to start dosing. If eligible, subjects will be instructed that they must take one tablet of blinded study medication (rimegepant or placebo) every other day (EOD). If subjects have a migraine during the DBT phase of the study, if needed, they may treat the migraine with their standard of care medication and continue to take blinded study medication on their regular EOD schedule (scheduled dosing days only). Refer to BHV3000-305 Protocol Table 1: Schedule of Assessments – Double-Blind Treatment.

At the completion of the 12-week DBT phase, subjects may be entered into the 52-week OLE phase following laboratory test results are within acceptable ranges per protocol. During the OLE phase, subjects will be instructed that they must take one tablet of open-label (OL) rimegepant EOD. If subjects have a migraine on a day that they are not scheduled to dose with study drug, then they may take one tablet of OL rimegepant on that calendar day to treat a migraine. Thus, during the OLE phase, subjects can take a maximum of one tablet of study drug per calendar day for this 52-week period. Refer to BHV3000-305 Protocol Table 2: Schedule of Assessments – Open-Label Extension Phase Including End of Treatment (EOT) and Follow-up Visits.

Study visits will occur at screening (enrollment), pre-randomization lab visit (which must occur within 96 hours of the baseline visit), baseline (randomization), Weeks 2, 4, 8, and 12. At the completion of the 12-week DBT phase, subjects may enter into the 12-week OLE phase if they continue to meet study entry criteria and laboratory test results are acceptable per protocol. During the OLE phase, visits occur at Weeks 14, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, and 64/EOT. Subjects will return to the study site at the end of Week 64 for the EOT visit. There is also a 2-Week and 8-Week follow-up visit 14 days and 8 weeks after the EOT visit, respectively, for assessment of LFTs. Subjects who do not complete the DBT phase and/or do not enter or complete the OLE phase should complete the EOT visit, the 2-Week or the 8-Week safety follow-up visit.

2.2   Randomization Methodology

After the completion of the 28-day OP, subjects will enter the DBT phase and up to approximately 800 eligible subjects will be randomized to receive rimegepant or placebo with an EOD dosing schedule. Subjects will be randomized in a 1:1 ratio to rimegepant or placebo treatment groups, stratified by current use of prophylactic migraine medication (yes or no). It is estimated that approximately 675 subjects will enter the OLE phase. Subject numbers, treatment group, and study medication will be assigned via the Interactive Web Response System (IWRS).

A by-subject administrative listing of randomization scheme and codes will be provided for all randomization numbers and block numbers, even those not assigned to a subject. This listing will be sorted by randomization number and block number.

Figure 1: **Study Schematic (Up to 12 Weeks of Double-blind Treatment with EOD Dosing, Followed by Up to 52 Weeks of Open-label Treatment with at Least EOD Dosing)**
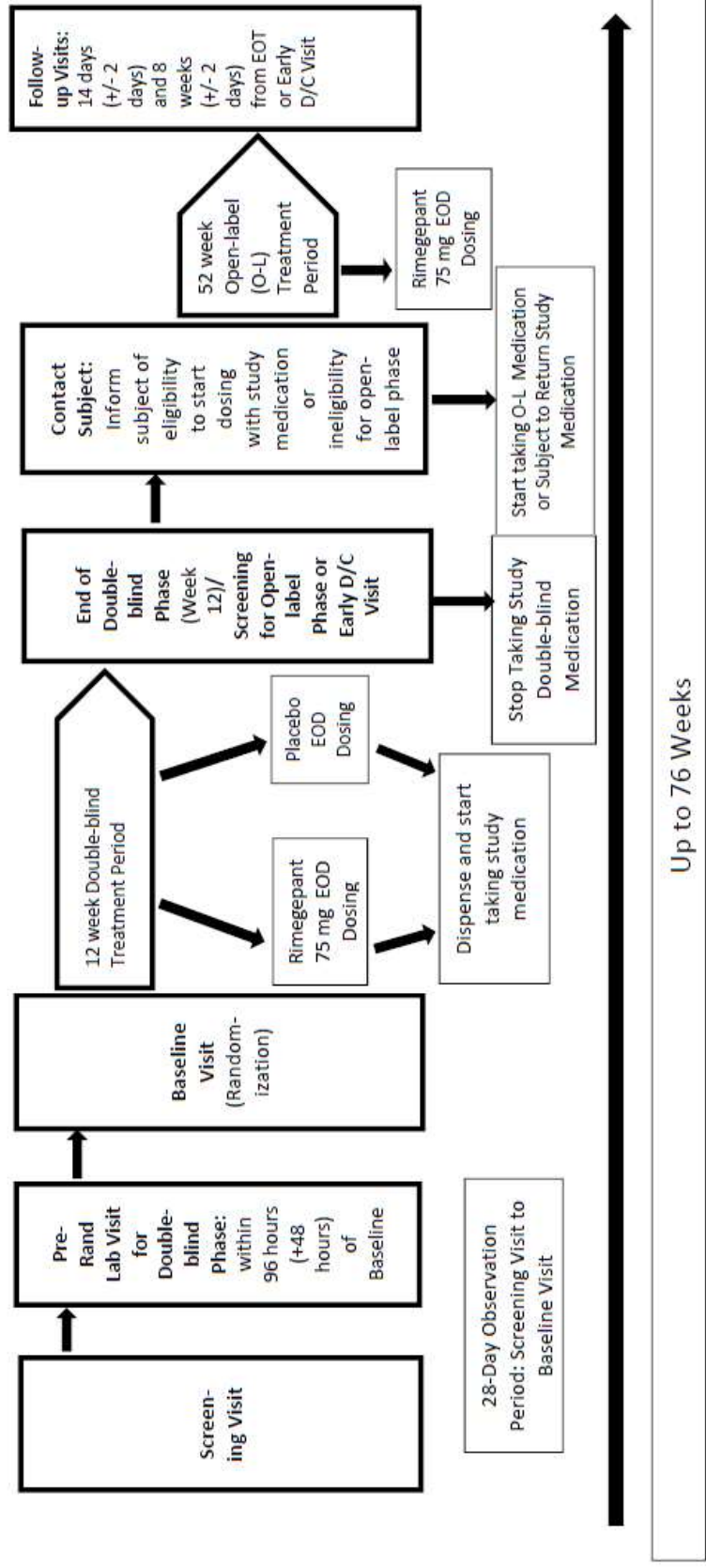
2.3   Study Estimands

An estimand is the target of estimation to address the scientific question of interest posed by a study objective. The four attributes of an estimand include the population of interest, endpoint of interest, specification of how intercurrent events are reflected in the scientific question of interest, and the population-level summary for the endpoint.

For all objectives, the population of interest is defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population for approval. Refer to the BHV3000-305 Protocol for inclusion/exclusion criteria.

Intercurrent events are those that occur after treatment initiation and either preclude observation of the endpoint or affect its interpretation. The following will be considered intercurrent events:

- Study drug discontinuation before the time point of interest defining the endpoint. For efficacy and safety objectives, study drug discontinuation will be handled with a while-on-treatment strategy, i.e., response to treatment prior to the occurrence of the intercurrent event of interest, such that all observed values of the endpoint of interest will be used prior to study drug discontinuation. For outcomes research objectives, study drug discontinuation will be handled with a treatment policy strategy, i.e., the occurrence of the intercurrent event will be considered irrelevant, such that all observed values of the endpoint of interest will be used regardless of study drug discontinuation.

- Use of non-study migraine standard of care medications on or before the time point of interest. For all objectives, this intercurrent event will be handled with a treatment policy strategy, such that all observed values of the endpoint of interest will be used.

2.3.1   Primary Objective Estimands

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

Table 1:   Primary Objective Estimands

Objective	**Reduction in the mean number of migraine days per month in the last 4 weeks of the DBT phase – Efficacy**
Endpoint	Change from OP in the mean number of migraine days per month on treatment in the last month (Weeks 9 to 12) of the DBT phase
Pop. Summary	Change from OP by treatment group using descriptive statistics and model, and difference between treatment groups from model

2.3.2   Secondary Objective Estimands

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

Table 2: Secondary Objective Estimands

Objective	**Proportion of subjects who have ≥ 50% reduction in moderate or severe migraine days per month in the last 4 weeks of the DBT phase – Efficacy**
Endpoint	Number and percentage of subjects who have ≥ 50% reduction from OP in the mean number of moderate or severe migraine days per month on treatment in the last month of the DBT phase
Pop. Summary	Frequency by treatment group and difference in percentages between treatment groups
Objective	**Reduction from baseline in the mean number of migraine days per month over the entire course of the DBT phase – Efficacy**
Endpoint	Change from baseline in the mean number of migraine days per month over the entire double-blind treatment phase (Weeks 1 to 12)
Pop. Summary	Change from OP by treatment group using descriptive statistics and model, and difference between treatment groups from model
Objective	**Frequency of use of rescue medication days per month in the last 4 weeks of the DBT phase – Efficacy**
Endpoint	Mean number of rescue medication days per month on treatment in the last month of the DBT phase
Pop. Summary	Value by treatment group using descriptive statistics and model, and difference between treatment groups from model
Objective	**Reduction from baseline in the mean number of migraine days per month in the first 4 weeks of the DBT phase – Efficacy**
Endpoint	Change from OP in the mean number of migraine days per month on treatment in the first month (Weeks 1 to 4) of the DBT phase
Pop. Summary	Change from OP by treatment group using descriptive statistics and model, and difference between treatment groups from model
Objective	**Safety and Tolerability**
Endpoint	Percentage of subjects with AEs, serious AEs (SAE), AEs leading to study drug discontinuation, and clinically significant laboratory abnormalities on treatment in the DBT and OLE phases
Pop. Summary	Frequency by treatment group and overall
Objective	**Concurrent LFT elevations – Safety**
Endpoint	Number and percentage of subjects with ALT or AST > 3 x ULN concurrent with elevations in TBL > 2 x ULN on treatment in the DBT and OLE phases
Pop. Summary	Frequency by treatment group and overall
Objective	**Hepatic-related AEs – Safety**
Endpoint	Number and percentage of subjects with hepatic-related AEs and hepatic-related AEs leading to study drug discontinuation on treatment in the DBT and OLE phases
Pop. Summary	Frequency by treatment group and overall

Objective	**MSQoL restrictive role function domain score change from baseline at Week 12 – Efficacy**
Endpoint	Change from baseline in the MSQoL restrictive role function domain score at Week 12 in the DBT phase
Pop. Summary	Change from baseline by treatment group using descriptive statistics and model, and difference between treatment groups from model
Objective	**MIDAS total score change from baseline at Week 12 – Efficacy**
Endpoint	Change from baseline in the MIDAS total score at Week 12 in the DBT phase
Pop. Summary	Change from baseline by treatment group using descriptive statistics and model, and difference between treatment groups from model

2.3.3 Exploratory Objective Estimands

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

Table 3: Exploratory Objective Estimands

Objective	**Reduction in the mean number of migraine days per month by migraine severity (total; moderate or severe) in each month and the entire course of the DBT phase – Efficacy**
Endpoint	Change from OP in the mean number of migraine days per month on treatment by migraine severity in each month and overall in the DBT phase
Pop. Summary	Change from OP by treatment group using descriptive statistics and model, and difference between treatment groups from model
Objective	**Proportion of subjects who have ≥ 50% reduction in migraine days per month by migraine severity (total; moderate or severe) in each month and the entire course of the DBT phase – Efficacy**
Endpoint	Number and percentage of subjects who have ≥ 50% reduction from OP in the mean number of migraine days per month on treatment by migraine severity in each month and overall in the DBT phase
Pop. Summary	Frequency by treatment group and difference in percentages between treatment groups
Objective	**Reduction in the number of migraine days per month by migraine severity (total; moderate or severe) in each month and the entire course of the OLE phase – Efficacy**
Endpoint	(1) Change from OP in the mean number of migraine days per month and (2) number and percentage of subjects who have ≥ 50%, 75% and 100% reductions from OP in the mean number of migraine days per month, on treatment by migraine severity in each month and overall in the OLE phase
Pop. Summary	Change from OP and frequency by treatment group and migraine severity using descriptive statistics

Objective	**Reduction in the mean number of MRM days per month in each month and the entire course of the DBT phase – Efficacy**
Endpoint	Change from OP in the mean number of MRM days per month on treatment in each month and overall in the DBT phase
Pop. Summary	Change from OP by treatment group using descriptive statistics and model, and difference between treatment groups from model
Objective	**Proportion of subjects who have ≥ 75% reduction in migraine days per month by migraine severity (total; moderate or severe) in each month and the entire course of the DBT phase – Efficacy**
Endpoint	Number and percentage of subjects who have ≥ 75% reduction from OP in the mean number of migraine days per month on treatment by migraine severity in each month and overall in the DBT phase
Pop. Summary	Frequency by treatment group and difference in percentages between treatment groups by migraine severity
Objective	**Proportion of subjects who have ≥ 100% reduction in migraine days per month by migraine severity (total; moderate or severe) in each month and the entire course of the DBT phase – Efficacy**
Endpoint	Number and percentage of subjects who have ≥ 100% reduction from OP in the mean number of migraine days per month on treatment by migraine severity in each month and overall in the DBT phase
Pop. Summary	Frequency by treatment group and difference in percentages between treatment groups by migraine severity
Objective	**LFT elevations – Safety**
Endpoint	Number and percentage of subjects with LFT elevations (ALT, AST, or TBL) on treatment in DBT and OLE phases
Pop. Summary	Frequency by treatment group and overall
Objective	**LFT elevations > 3 x ULN in temporal association with AEs – Safety**
Endpoint	Number and percentage of subjects with ALT or AST elevations > 3 x ULN concurrent with nausea, vomiting, anorexia, abdominal pain, or fatigue on treatment in DBT and OLE phases
Pop. Summary	Frequency by treatment group and overall
Objective	**MSQoL – Outcomes Research**
Variable	Change from baseline in the MSQoL score over time for each domain in the DBT and OLE phases
Pop. Summary	Change in MSQoL score from baseline at each visit and last visit for each domain by treatment group and overall using descriptive statistics
Objective	**PoM – Outcomes Research**
Variable	Number and percentage of subjects in each of 5 preference categories of study medication relative to previous migraine medications over time
Pop. Summary	Frequency by treatment group and overall at each visit and last visit

Objective	**SM – Outcomes Research**
Variable	Number and percentage of subjects in each of the 7 satisfaction categories (completely satisfied to completely dissatisfied) of study medication over time
Pop. Summary	Frequency by treatment group and overall at each visit and last visit
Objective	**MIDAS – Outcomes Research**
Variable	Change from baseline in MIDAS scores over time
Pop. Summary	Change in total, absenteeism, presenteeism, and item scores from baseline at each visit and last visit by treatment group and overall using descriptive statistics
Objective	**CGI-c – Outcomes Research**
Variable	Number and percentage of subjects in each of the 7 improvement categories (very much improved to very much worse) relative to OP over time
Pop. Summary	Frequency of subjects at each visit and last visit by treatment group and overall
Objective	**Reduction in the mean number of migraine days per week by migraine severity (total; moderate or severe) in the first week of the DBT phase – Efficacy**
Endpoint	Change from OP in the mean number of migraine days per week on treatment by migraine severity in the first week of the DBT phase
Pop. Summary	Change from OP by treatment group using descriptive statistics and model, and difference between treatment groups from model by migraine severity
Objective	**Frequency of use of rescue medication days per month in each month and the entire course of the DBT phase – Efficacy**
Endpoint	Mean number of rescue medication days per month on treatment in each month and overall in the DBT phase
Pop. Summary	Value by treatment group using descriptive statistics and model, and difference between treatment groups from model

3   POPULATION SAMPLES FOR ANALYSES

The following population samples for analyses ("analysis sets") will be evaluated and used for presentation and analysis of data:

- **Enrolled subjects**: Subjects who sign an informed consent form and are assigned a subject identification number by IWRS, i.e., non-missing informed consent date.

- **Randomized subjects**: Enrolled subjects who are assigned a randomized treatment group and prophylactic medication use stratum by IWRS, i.e., non-missing IWRS randomization date.

- **Modified intent-to-treat (mITT) subjects**: Enrolled subjects who were randomized only once and received at least one dose of double-blind (DB) study medication (rimegepant or

placebo), i.e., non-missing DBT start date. This corresponds to the Full Analysis Set in the BHV3000-305 Protocol.

- o **Evaluable mITT subjects**: mITT subjects with ≥ 14 days of eDiary efficacy data (not necessarily consecutive) in both the OP and at least one month (i.e., 4-week interval) in the DBT phase. This corresponds to the Efficacy Analysis Set in the BHV3000-305 Protocol.

- o **Evaluable first week mITT subjects**: mITT subjects with at least one day of eDiary efficacy data in both the OP and the first week of the DBT phase.

- o **Menstrual migraine evaluable mITT menstruating female subjects**: mITT menstruating female subjects with ≥ 1 day of eDiary menstrually-related (MR) efficacy data and ≥ 14 days of eDiary efficacy data (not necessarily consecutive) in both the OP and at least one month (i.e., 4-week interval) in the DBT phase.

- o **OL rimegepant mITT subjects**: mITT subjects who received at least one dose of OL rimegepant, i.e., non-missing OL rimegepant start date.

  - ▪ **Evaluable OL rimegepant mITT subjects**: OL rimegepant mITT subjects with ≥ 14 days of eDiary efficacy data (not necessarily consecutive) in both the OP and at least one month (i.e., 4-week interval) in the OLE phase.

  - ▪ **Menstrual migraine evaluable OL rimegepant mITT menstruating female subjects**: OL rimegepant mITT menstruating female subjects with ≥ 1 day of eDiary MR efficacy data and ≥ 14 days of eDiary efficacy data (not necessarily consecutive)in both the OP and at least one month (i.e., 4-week interval) in the OLE phase.

- **Treated subjects**: Enrolled subjects who received at least one dose of study drug (DB or OL), i.e., non-missing study drug start date. This corresponds to the Safety Analysis Set in the BHV3000-305 Protocol.

- **OL rimegepant treated subjects**: Enrolled subjects who received at least one dose of OL rimegepant, i.e., non-missing OL rimegepant start date.

  - o **Interim subjects:** OL rimegepant treated subjects with OL rimegepant start date – DBT last date > 7 days.

- **DB or OL rimegepant treated subjects**: Enrolled subjects who received at least one dose of rimegepant (DB or OL) i.e., non-missing DB or OL rimegepant start date. This corresponds to the Rimegepant Safety Analysis Set in the BHV3000-305 Protocol.

- **Follow-up subjects**: Treated subjects whose last contact date is in the follow-up safety analysis period.

- Coronavirus Disease 2019 (COVID-19) impacted: Enrolled subjects who are impacted by COVID-19 (see Section 9.1.2).

See Sections 7.3 and 7.4 for derived dates and analysis periods, respectively.

4   SCHEDULE OF ANALYSES

The following planned analyses will be conducted:

- Blinded interim analysis for the 90-Day Safety Update with a scheduled database snapshot date of 13-June-2019. Analyses will focus on key safety endpoints (e.g., deaths, AEs by severity, SAEs, AEs leading to study drug discontinuation, worst laboratory test abnormalities, LFT elevations) and supportive endpoints (e.g., subject disposition, demographics and baseline characteristics, study drug exposure).

- Week 12 unblinded analysis for the CSR when the last treated subject completes the last visit in the DBT phase. All analyses described in this SAP will be performed.

- Final unblinded analysis for the Addendum Report when the last treated subject completes the last visit in the follow-up phase. Analyses will focus on efficacy during the OLE phase, and safety during the DB or OL rimegepant phase and follow-up phase.

Additional unplanned analyses may be performed based on regulatory agency requests.

5   SAMPLE SIZE AND POWER

With a sample size of roughly 800 subjects randomized, and 400 subjects per treatment group, we expect roughly 370 subjects per treatment group in the evaluable mITT population (i.e., Efficacy Analysis Set in the BHV3000-305 Protocol). Assuming rimegepant provides roughly a 1-day advantage over placebo on the primary endpoint and a common standard deviation (SD) of 3.75 days, then the study will have roughly 95% power on the primary endpoint. The estimates for the change in migraine days per month and the SD are consistent with publicly available information from another investigational oral calcitonin gene-related peptide (CGRP) antagonist for this indication.

6   STATISTICAL METHODS

6.1   General Methods

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

Tables will present results by treatment group (i.e., rimegepant and placebo) and overall with the following exceptions:

- Results for enrolled subjects will be presented only by overall without treatment group.

- Exposure, efficacy, and safety results for the DBT phase will be presented only by treatment group without overall.

- Results for follow-up subjects will be presented by 6 groups: rimegepant, placebo, placebo to open-label rimegepant, placebo no open-label rimegepant, double-blind or open-label rimegepant, and overall. "Placebo to open-label rimegepant" denotes as-treated placebo subjects who received open-label rimegepant, and "placebo no open-label

rimegepant" denotes as-treated placebo subjects who never received open-label rimegepant; note that these 2 groups add to the "placebo" group. Also note that the "rimegepant" and "placebo to open-label rimegepant" groups add to the "double-blind or open-label rimegepant" group.

The population samples of treated subjects, OL rimegepant treated subjects, DB or OL rimegepant treated subjects, interim subjects, and follow-up subjects will be assessed by as-treated treatment group, i.e., by the treatment actually received, unless specified otherwise. Otherwise, all other population samples will be assessed by as-randomized treatment group.

All listings except administrative listings will identify subjects who are impacted by COVID-19 (see Section 9.1.2).

Select listings of measurements over time will display COVID-19 visit impact code for visits that are impacted by COVID-19 (see Section 9.1.5.2).

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

6.1.1   Missing Data

All analyses will be based on observed data unless specified otherwise. A sensitivity analysis of the primary endpoint will impute missing data (see Section 6.3.1.1).

6.1.2   Type 1 Error Control

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

1. Proportion of subjects with $\geq 50\%$ reduction from OP in the mean number of moderate or severe migraine days per month in the last month of the DBT phase

2. Change from OP in the mean number of migraine days per month in the entire DBT phase

3. Mean number of rescue medications days per month in the last month of the DBT phase

4. Change from OP in the mean number of migraine days per month in the first month of the DBT phase

5. Change from baseline in MSQoL restrictive role function score at Week 12 of the DBT phase

6. Change from baseline in MIDAS total score at Week 12 of the DBT phase.

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

6.1.3   Subgroups

Efficacy subgroup tables will present results by subgroup level for subjects with non-missing subgroup level data, unless specified otherwise. Safety subgroup tables will present results by subgroup level and overall analogously.

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

6.1.3.1   Efficacy Subgroups for Evaluable mITT Subjects

For evaluable mITT subjects, the following efficacy subgroups are of interest:

- Age: $< 40, \geq 40, < 65, \geq 65$

- Sex: female, male

- Race: White, Black or African American, Other Including Asian, Asian

- Ethnicity: Hispanic or Latino, Not Hispanic or Latino

- Baseline body mass index (BMI; kg/m2): $< 25, \geq 25$ to $< 30, \geq 30$

- Historical number of moderate or severe migraine attacks per month: $< 6, \geq 6, < 8, \geq 8, < 12, \geq 12, < 15, \geq 15$

- Historical primary migraine type: migraine with aura, migraine without aura

- Historical chronic migraine: yes, no

- Prophylactic migraine medication use at randomization (i.e., IWRS randomization strata): yes, no

- Total migraine days per month in the OP: $< 14, \geq 14$.

6.1.3.2   Safety Subgroups for Treated Subjects

For treated subjects, the following safety subgroups are of interest:

- Age: $< 40, \geq 40, < 65, \geq 65$

- 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

- Baseline body mass index (BMI; kg/m2): $< 25, \geq 25$ to $< 30, \geq 30$

- Prophylactic migraine medication use at randomization: yes, no.

6.1.3.3   Safety Subgroups for DB or OL Rimegepant Treated Subjects

For DB or OL rimegepant treated subjects, the following safety subgroups are of interest:

- Time on DB or OL rimegepant: < 6 months, ≥ 6 months, ≥ 1 year (see Section 6.2.6.1).

These apply to the Addendum Report.

6.1.3.4   Safety Subgroups for OL Rimegepant Treated Subjects

For OL rimegepant treated subjects, the following safety subgroups are of interest:

- Average OL rimegepant exposure (tablets per month): ≤ 14, > 14 to ≤ 16, > 16 (see Section 6.2.6.1).

6.2   Study Population

6.2.1   Population Samples for Analyses

The number of subjects in each population sample listed in Section 3 will be presented by as-randomized or as-treated treatment group (see Section 6.1), not randomized, and overall.

Inclusion and exclusion from the evaluable mITT sample population will be summarized by as-randomized treatment group and overall for randomized subjects. Reasons for exclusion categories are mutually exclusive and will include the following: (1) not mITT: not treated with DBT; (2) not mITT: treated with DBT but randomized more than once; (3) mITT but not evaluable: < 14 days of efficacy data in OP only; (4) mITT but not evaluable: < 14 days of efficacy data in all 3 months of the DBT phase only; (5) mITT but not evaluable: < 14 days of efficacy data in both OP and in all 3 months of the DBT phase. See Section 6.3.1.1 for months.

A by-subject listing of population samples for analyses will be provided for enrolled subjects. The listing will flag subjects in populations, and include as-treated treatment group.

6.2.2   Enrollment

Enrollment by (1) country and site and (2) age group will be tabulated for enrolled subjects. The enrollment by country and site table also displays results for randomized subjects and treated subjects. Refer to the BHV3000 Core SAP for additional details.

A frequency table of accrual by randomization year and month will also be provided for randomized subjects.

6.2.3   Subject Disposition

By-subject listings of subject disposition in the DBT, OLE, and follow-up phases will be provided respectively for enrolled subjects, OL rimegepant treated subjects, and follow-up subjects. Listings for the OLE and follow-up phases will identify subjects who terminated the phase prematurely due to COVID-19 (see Section 9.1.4).

Another by-subject listing of eligibility with inclusion and exclusion criteria will be provided for enrolled subjects.

6.2.3.1   Subject Disposition From Enrollment to Randomization

Subject disposition from enrollment to randomization will be summarized for enrolled subjects overall as the number and percentage of subjects in the following categories:

- Randomized

- Not randomized

- Reasons for discontinuation, including not reported (based on the DB Subject Status Case Report Form [CRF]).

6.2.3.2   Subject Disposition From Randomization to Treatment

Subject disposition from randomization to treatment will be summarized for randomized subjects by as-randomized treatment group and overall as the number and percentage of subjects in the following categories:

- Treated

- Not treated

- Reasons for discontinuation, including not reported (based on the DB Subject Status CRF).

6.2.3.3   Subject Disposition in the DBT Phase

Subject disposition in the DBT phase will be summarized for treated subjects by as-treated treatment group and overall as the number and percentage of subjects in the following categories:

- Ongoing in DBT phase (identified as subjects with missing response to the question about completing all DB visits on the DB Subject Status CRF)

- Completed DBT phase (identified as subjects with primary completion/discontinuation reason of "Completed Double Blind Phase" on the DB Subject Status CRF)

- Did not complete DBT phase (identified as subjects with "no" response to the question about completing all DB visits or primary completion/discontinuation reason not missing but not equal to "Completed Double Blind Phase" on the DB Subject Status CRF)

  o Reasons for not completing, including not reported

- Continuing to OLE phase (identified as subjects with "yes" response to the question about continuing to OL on the DB Subject Status CRF)

- Continuing to follow-up phase (identified as subjects with "yes" response to the question about continuing to follow-up on the DB Subject Status CRF)

- Not continuing to follow-up phase (identified as subjects with "no" response to the question about continuing to follow-up on the DB Subject Status CRF)

  o Reasons for not continuing, including not reported

- Completed DBT phase but not continuing to OLE phase (identified as subjects with primary completion/discontinuation reason of "Completed Double Blind Phase" and "no" response to the question about not continuing to OL on the DB Subject Status CRF)

  o Reasons for not continuing, including not reported.

Subject disposition in the DBT phase will be summarized analogously for evaluable mITT subjects by as-randomized treatment group and overall only.

Subject disposition in the DBT phase will be summarized analogously for treated subjects by subgroup level and overall for all safety subgroups of interest described in Section 6.1.3.2 for each treatment group.

6.2.3.4 Subject Disposition in the OLE Phase

Subject disposition in the OLE phase will be summarized for OL rimegepant treated subjects by as-treated treatment group and overall as the number and percentage of subjects in the following categories:

- Ongoing in OLE phase (identified as subjects with missing response to the question about completing all OL visits on the OL Subject Status CRF)

- Completed OLE phase (identified as subjects with primary completion/discontinuation reason of "Completed Open Label Phase" on the OL Subject Status CRF)

- Did not complete OLE phase (identified as subjects with "no" response to the question about completing all OL visits or primary completion/discontinuation reason not missing but not equal to "Completed Open Label Phase" on the OL Subject Status CRF)

  o Reasons for not completing, including not reported

- Terminated OLE phase prematurely due to COVID-19 (see Section 9.1.4)

  o Reasons for termination, including not reported

- Continuing to follow-up phase (identified as subjects with "yes" response to the question about continuing to follow-up on the OL Subject Status CRF)

- Not continuing to follow-up phase (identified as subjects with "no" response to the question about continuing to follow-up on the OL Subject Status CRF)

  o Reasons for not continuing, including not reported.

Subject disposition in the OLE phase will be summarized analogously for OL rimegepant mITT subjects by as-randomized treatment group and overall.

Subject disposition in the OLE phase will also be summarized analogously for OL rimegepant treated subjects by subgroup level and overall for all safety subgroups of interest described in Section 6.1.3.4.

6.2.3.5   Subject Disposition in the Follow-up Phase

Subject disposition in follow-up phase will be summarized for follow-up subjects by as-treated treatment group and overall as the number and percentage of subjects in the following categories:

- Did not formally enter the follow-up phase (identified as subjects with missing response to the question about completing all follow-up visits on the Follow-up Subject Status CRF and without "yes" response to the question about continuing to follow-up on the DB or OL Subject Status CRF)

- Ongoing in follow-up phase (identified as subjects with missing response to the question about completing all follow-up visits on the Follow-up Subject Status CRF and with "yes" response to the question about continuing to follow-up on the DB or OL Subject Status CRF)

- Completed follow-up phase (identified as subjects with "yes" response to the question about completing all follow-up visits on the Follow-up Subject Status CRF)

- Did not complete follow-up phase (identified as subjects with "no" response to the question about completing all follow-up visits on the Follow-up Subject Status CRF)

  o Reasons for not completing, including not reported

- Terminated follow-up phase prematurely due to COVID-19 (see Section 9.1.4)

  o Reasons for termination, including not reported.

6.2.4   Protocol Deviations

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

- Informed Consent

- Inclusion/Exclusion Criteria (specify #)

- Concomitant Medication

- SAE Reporting

- Regulatory

- Drug Storage/Preparation

- Drug Administration

- Visit Schedule

- EPro Diary Non-compliance

- Non-compliance (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 randomized subjects with significant protocol deviations will be summarized by deviation type and by as-randomized treatment 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 enrolled subjects.

6.2.5 Pre-Treatment Characteristics

Pre-treatment characteristics will include the following: demographics and baseline characteristics; medical history; migraine history; and cardiac and other risk factors.

Pre-treatment characteristics will be summarized descriptively by as-randomized treatment group and overall for evaluable mITT subjects to support efficacy.
Pre-treatment characteristics will also be summarized by as-treated treatment group and overall for treated subjects to support safety.

Demographics and baseline characteristics, as well as migraine history, will also be summarized by as-randomized treatment group and overall for randomized subjects not in the evaluable mITT population.

Demographics and baseline characteristics will also be summarized analogously for treated subjects by subgroup level and overall for all safety subgroups of interest described in Section 6.1.3.2 for each treatment group.

Demographics and DB or OL rimegepant baseline characteristics (including both age at informed consent and age at DB or OL rimegepant baseline), as well as migraine history and cardiac and other risk factors, will be summarized by as-treated treatment group and overall for DB or OL rimegepant treated subjects to support DB or OL rimegepant safety. Age at DB or OL rimegepant baseline is defined using DB or OL rimegepant start date as the reference date (see Section 7.7). These will also be summarized

analogously by subgroup level and overall for all safety subgroups of interest described in Section 6.1.3.3.

Demographics and OL rimegepant baseline characteristics (including both age at informed consent and age at OL rimegepant baseline), as well as migraine history and cardiac and other risk factors, will be summarized by subgroup level and overall for all safety subgroups of interest described in Section 6.1.3.4 for OL rimegepant treated subjects to support OL rimegepant safety. Age at OL rimegepant baseline is defined using OL rimegepant start date as the reference date (see Section 7.7).

Prophylactic migraine medication use at randomization (i.e., IWRS randomization strata) will be summarized as categorical parameters for randomized subjects.

Baseline will be defined according to population as follows:

- Enrolled subjects not randomized: Last non-missing value

- Randomized subjects not treated: Last non-missing value on or before the IWRS randomization date/time

- mITT subjects and treated subjects: Last non-missing value on or before the study drug start date/time (i.e., in the pre-treatment analysis period; see Sections 7.3 and 7.4)

- DB or OL rimegepant treated subjects: Last non-missing value on or before the DB or OL rimegepant start date (i.e., DB or OL rimegepant baseline)

- OL rimegepant treated subjects: Last non-missing value on or before the OL rimegepant start date (i.e., OL rimegepant baseline).

The following listings will be provided for enrolled subjects:

- Demographics, including informed consent date. All reported races will be displayed for subjects who reported multiple races.

- Baseline characteristics, including previous BHV3000-305 subject identifier from the Rescreen CRF

- Medical history, displaying results by SOC and PT

- Migraine history split into general migraine history, migraine symptom history, and migraine aura history

- Cardiac and other risk factors for subjects with any risk factor present. Only records with "yes" responses to questions about having risk factors will be displayed.

6.2.5.1   *Demographics and Baseline Characteristics*

Refer to the BHV3000 Core SAP for the table of demographics and baseline characteristics. This table will also summarize the following parameters:

- Experiences menstrual periods (yes, no; if female)

- Screened for previous BHV3000 study (any previous study, BHV3000-111, BHV3000-201, BHV3000-301, BHV3000-302, BHV3000-303)

- Prophylactic migraine medication use at randomization (yes, no).

6.2.5.2   Medical History

Medical history will be summarized by system organ class (SOC) and preferred term (PT), and displayed in descending order of overall frequency within SOC and PT.

6.2.5.3   Migraine History

Refer to the BHV3000 Core SAP for the migraine history table.

6.2.5.4   Cardiac and Other Risk Factors

Refer to the BHV3000 Core SAP for the table of cardiac and other risk factors.

6.2.6   Exposure

Analyses will be based on as-treated treatment group to support safety, unless specified otherwise.

6.2.6.1   Study Medication

The eDiary has multiple sources of study drug exposure. Subjects are required to report study drug date/times and doses in the following 4 eDiary sources as appropriate: (1) study medication from the scheduled dosing report; (2) study medication to treat headache or aura from the evening report headache log; (3) additional study medication to treat headache or aura from the evening report headache log; or (4) study medication to treat headache or aura from the follow-up headache log. In addition, sites may report study drug dates and doses in the eDiary medication reconciliation form from missed scheduled dosing reports or evening report headache logs.

Imputed OL rimegepant to treat headache date/time will be derived for subjects who answer "yes" to the question about having already taken study medication to treat a headache on the eDiary scheduled dosing report, but do not have study drug data from any other eDiary source on the same day. Subjects with non-missing imputed OL rimegepant to treat headache date/times will be credited with taking 1 tablet of OL rimegepant on each of those days to account for missed OL rimegepant exposure from eDiary non-compliance. Otherwise, if no study drug data were reported in the eDiary on a given day (i.e., missing study drug date/time), then it is assumed that the subject did not take study drug that day. See Section 7.3 for derived dates.

A by-subject listing will present eDiary exposure (i.e., number of tablets taken) and drug accountability for randomized subjects. This listing will include all drug accountability data including treatment (DB rimegepant; DB placebo; OL rimegepant) corresponding to the kit ID, but only eDiary records with non-missing study drug start date/time and number of tablets > 0. The eDiary subcategory of question (scheduled dosing report; evening report headache log [study medication; additional study medication]; follow-up headache log; and medication reconciliation form) will also be displayed. COVID-19 visit impact code for visits impacted by COVID-19 will also be displayed (see Section 9.1.5.2).

Another by-subject listing will present eDiary exposure (i.e., total number of tablets taken) in each month (i.e., 4-week interval) in the DBT and OLE phases for treated subjects. This will also display cumulative DBT, OL rimegepant, and DB or OL rimegepant exposures from both sources (i.e., eDiary and drug accountability), and flag subjects with ≥ 10 cumulative tablet difference between the 2 sources.

A by-subject administrative listing of batch numbers sorted by batch number and site-subject ID will be provided for treated subjects.

eDiary Rimegepant or Placebo Exposure During Double-Blind Treatment

eDiary rimegepant or placebo exposure during the DBT phase will be summarized descriptively by treatment group for treated subjects, and will include the following parameters:

- Time on DBT (weeks), derived as (DBT end date – DBT start date + 1)/7

- Cumulative DB exposure (tablets), derived by summing number of tablets across DB study drug records

- Average DB exposure (tablets per month), derived as 4 × cumulative DB exposure/time on DBT

- Total DB exposure (tablets) summed across all subjects, derived by summing cumulative DB exposure across all subjects

- Total DB exposure (patient-years), derived by summing (DBT end date – DBT start date + 1)/365.25 across all subjects.

- Number and percentage of subjects in the following average DB exposure (tablets per month) categories:
  - \> 16.8 (\> 20% above EOD dosing)
  - \> 15.4 (\> 10% above EOD dosing)
  - $\geq$ 12.6 to $\leq$ 15.4 ($\pm$ 10% of EOD dosing)
  - $\geq$ 11.2 to $\leq$ 16.8 ($\pm$ 20% of EOD dosing)
  - $\geq$ 12.6 ($\geq$ 90% compliant with EOD dosing)
  - $\geq$ 11.2 ($\geq$ 80% compliant with EOD dosing)

- Number and percentage of subjects who took \> 1 DB tablet on any 1 day. This could be from the same bottle or different bottles due to an unscheduled visit or erroneous eDiary usage.
  - Single study drug record (i.e., $\geq$ 2 tablets taken from a single source)
  - Multiple study drug records (i.e., $\geq$ 2 tablets taken based on multiple sources with the same study drug date)

- Subject-reported duplicate data (i.e., duplicate study drug times from ≥ 2 eDiary subject-reported sources)

- Subject-reported non-duplicate data (i.e., non-duplicate study drug times from ≥ 2 eDiary subject-reported sources)

- Both site-reported data on medication reconciliation form and subject-reported data (i.e., duplicate study drug dates from the medication reconciliation form and an eDiary subject-reported source)

- Site-reported data on medication reconciliation form only (i.e., duplicate study drug dates only from the medication reconciliation form)

- Number and percentage of subjects who took:

  ○ ≥ 12 DB tablets per month for 3 consecutive months, i.e., 3 consecutive 4-week intervals (see first paragraph below)

  ○ ≥ 13 , ≥ 14, ≥ 15, and ≥ 16 DB tablets per month for 3 consecutive months

- Number and percentage of subjects who took the incorrect DB study drug:

  ○ All the time (i.e., as-treated treatment group not equal to as-randomized treatment group)

  ○ At least once (i.e., subject randomized to rimegepant who took placebo; subject randomized to placebo who took rimegepant).

eDiary rimegepant or placebo exposure during DBT will also be summarized descriptively by subgroup level and overall for all safety subgroups of interest described in Section 6.1.3.2 for each treatment group.

eDiary tablets per month will assess the number of 4-week (28-day) intervals in which a subject exceeded select tablet counts from the DBT start date to the DBT end date, where the number of 4-week intervals are consecutive (see Section 6.3.1.1 for months). For example, suppose a subject takes 20 tablets through 4 weeks, 10 tablets after 4 weeks to 8 weeks, and 25 tablets after 8 weeks to 12 weeks. Thus, this subject is not considered to have taken ≥ 14 tablets (more than EOD frequency) per month for 3 consecutive months.

See Section 7.5 for the definition of study days used to define analysis visit windows.

In order to determine subjects who took incorrect DB study drug, eDiary DB study drug dates will be compared to sorted kit dispense dates recorded on the Drug Accountability CRF. Study drug will be considered to be taken from a kit if the kit dispense date $\leq$ study drug date $<$ next kit dispense date; if > 1 kit ID has the same dispense date, then study drug will be considered to be taken from the kit with the smallest kit ID. Kit IDs from drug accountability will then be compared to kit IDs in the unblinded container file to determine whether the kit contained DB rimegepant, DB placebo, or OL rimegepant.

A Kaplan-Meier mortality table will summarize time to DBT discontinuation in 4-week intervals (i.e., ≤ 4, > 4 to ≤ 8, > 8 to ≤ 12, > 12) by treatment group and overall for treated subjects. A

Kaplan-Meier mortality plot by treatment group will display the percentage of treated subjects on DBT (y-axis) versus weeks (x-axis). Time to DBT discontinuation (weeks) is defined as (DBT end date – DBT start date + 1)/7. Subjects will be considered to have discontinued DBT if they have non-missing DBT last date. Otherwise, in an interim analysis or snapshot before the Week 12 interim analysis database lock, subjects will be censored at the DBT end date.

eDiary DB or OL Rimegepant Exposure During the Entire Study

eDiary DB or OL rimegepant exposure during the entire study (i.e., both DBT and OLE phases combined) will be summarized descriptively by treatment group and overall for DB or OL rimegepant treated subjects, and will include the following parameters:

- Time on DB or OL rimegepant (weeks), derived as (DB or OL rimegepant end date – DB or OL rimegepant start date + 1)/7

- Number and percentage of subjects in the following time on DB or OL rimegepant (weeks) categories: ≥ 11, < 23, ≥ 23, ≥ 51, ≥ 63. These correspond to using a 1-week lower bound on 3, 6, 12, and 15 months, respectively.

- Cumulative DB or OL rimegepant exposure (tablets), derived by summing number of DB or OL rimegepant tablets across records with non-missing DB or OL rimegepant date/times.

- Average DB or OL rimegepant exposure (tablets per month), derived as $4 \times$ cumulative DB or OL rimegepant exposure/time on DB or OL rimegepant

- Total DB or OL rimegepant exposure (tablets) summed across all subjects, derived by summing cumulative DB or OL rimegepant exposure across all subjects

- Number and percentage of subjects who took > 1 DB or OL rimegepant tablet on any 1 day
  - Single study drug record
  - Multiple study drug records
    - Subject-reported duplicate data
    - Subject-reported non-duplicate data
    - Both site-reported data on medication reconciliation form and subject-reported data
    - Site-reported data on medication reconciliation form only

  Note that imputed OL rimegepant to treat headache date/time by definition will not contribute to taking more than 1 OL rimegepant tablet per day.

- Total DB or OL rimegepant exposure (patient-years), derived by summing (DB or OL rimegepant end date – DB or OL rimegepant start date + 1)/365.25 across all subjects.

eDiary DB or OL rimegepant exposure during the entire study will also be summarized descriptively by subgroup level and overall for all safety subgroups of interest described in Section 6.1.3.3.

A Kaplan-Meier mortality table will summarize time to rimegepant discontinuation in 4-week intervals (i.e., ≤ 4, > 4 to ≤ 8, etc.) by treatment group and overall for DB or OL rimegepant treated subjects. A Kaplan-Meier mortality plot (overall, not by treatment group) will display the percentage of DB or OL rimegepant treated subjects on rimegepant (y-axis) versus weeks (x-axis). Time to DB or OL rimegepant discontinuation (weeks) is defined as (DB or OL rimegepant end date – DB or OL rimegepant start date + 1)/7. Subjects will be considered to have discontinued DB or OL rimegepant if they have non-missing DB or OL rimegepant last date. Otherwise, in an interim analysis, subjects will be censored at the DB or OL rimegepant end date.

eDiary Study Drug Exposure

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

- Time in the OP (weeks)

- Time from randomization to last contact (weeks), where study drug start date will be used if IWRS randomization date is missing

- Time on DBT (weeks)

- Cumulative DB exposure (tablets)

- Average DB exposure (tablets per month)

- Total DB exposure (tablets) summed across all subjects

- Time on OL rimegepant (weeks)

- Cumulative OL rimegepant exposure (tablets)

- Average OL rimegepant exposure (tablets per month)

- Total OL rimegepant exposure (tablets) summed across all subjects

- Time on study drug (weeks), derived as (study drug end date – study drug start date + 1)/7

- Number and percentage of subjects in the following time on study drug (weeks) categories: ≥ 11, ≥ 23, ≥ 51, ≥ 63. These correspond to using a 1-week lower bound on 3, 6, 12, and 15 months, respectively.

- Cumulative study drug exposure (tablets), derived by summing number of tablets across study drug records (DBT + OLE)

- Average study drug exposure (tablets per month), derived as $4 \times$ cumulative study drug exposure/time on study drug

- Total study drug exposure (tablets) summed across all subjects, derived by summing cumulative study drug exposure across all subjects

- Total study drug exposure (patient-years), derived by summing (study drug end date – study drug start date + 1)/365.25 across all subjects

- Time in follow-up (weeks), derived as derived as (last contact date – study drug last date)/7, for follow-up subjects

- Time on study (weeks), derived as (last contact date – study drug start date + 1)/7

- Number and percentage of subjects in the following time on study (weeks) categories: ≥ 11, ≥ 23, ≥ 51, ≥ 63. These correspond to using a 1-week lower bound on 3, 6, 12, and 15 months, respectively.

Kaplan-Meier mortality tables will summarize time to study drug discontinuation and time to study discontinuation in 4-week intervals (i.e., ≤ 4, > 4 to ≤ 8, etc.) by treatment group and overall for treated subjects. A Kaplan-Meier mortality plot by treatment group will display the percentage of treated subjects on study drug (y-axis) versus weeks (x-axis).

- Time to study drug discontinuation (weeks) is defined as (study drug end date – study drug start date + 1)/7. Subjects will be considered to have discontinued study drug if they have non-missing study drug last date/time. Otherwise, in an interim analysis or snapshot before the final database lock, subjects will be censored at the study drug end date.

- Time to study discontinuation (weeks) is defined as (last contact date – IWRS randomization date + 1)/7. If a subject is not randomized, then the study drug start date will be used instead of IWRS randomization date. In an interim analysis or snapshot before the final database lock, subjects will be considered to have discontinued the study if any of the following criteria 1 through 4 are met:

  1) All of the following criteria from the DB Subject Status CRF are met (see Section 6.2.3.3):

     a) Completed or did not complete the DB phase

     b) Not continuing to OLE phase

     c) Not continuing to follow-up phase

  2) All of the following criteria from the OL Subject Status CRF are met (see Section 6.2.3.4)

     a) Completed or did not complete the OLE phase

     b) Not continuing to follow-up phase

  3) Did not formally enter the follow-up phase (see Section 6.2.3.5)

  4) Completed or did not complete the follow-up phase (see Section 6.2.3.5)

  Otherwise, subjects will be censored at the last contact date. At the final database lock, all subjects will be considered to have discontinued the study. (This definition of study discontinuation was applied to the CSR.)

eDiary OL Rimegepant Exposure

eDiary OL rimegepant exposure will be summarized descriptively by subgroup level and overall for all safety subgroups of interest described in Section 6.1.3.4, and will include the following parameters:

- Time on OL rimegepant (weeks)

- Number and percentage of subjects in the following time on OL rimegepant (weeks) categories: ≥ 11, ≥ 23, ≥ 51. These correspond to using a 1-week lower bound on 3, 6, and 12 months, respectively.

- Cumulative OL rimegepant exposure (tablets)

- Average OL rimegepant exposure (tablets per month)

- Number and percentage of subjects in the subgroup categories defined in Section 6.1.3.4

- Number and percentage of subjects who took > 1 OL rimegepant tablet on any 1 day
  - Single study drug record
  - Multiple study drug records
    - Subject-reported duplicate data
    - Subject-reported non-duplicate data
    - Both site-reported data on medication reconciliation form and subject-reported data
    - Site-reported data on medication reconciliation form only

- Total OL rimegepant exposure (tablets) summed across all subjects

- Total OL rimegepant exposure (patient-years), derived by summing (OL rimegepant end date – OL rimegepant start date + 1)/365.25 across all subjects.

6.2.6.2   *Drug Accountability*

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

Drug Accountability Exposure

Drug accountability exposure will be summarized with descriptive statistics by treatment group and overall for treated subjects:

- Time from first DB kit dispensed to last DB kit returned (weeks), derived as (latest DB kit return date – earliest DB kit dispense date + 1)/7. Subjects who were dispensed ≥ 1 DB kit but never returned any DB kit will be credited with 1 day.

- Cumulative DB exposure (tablets) based on DB kits dispensed and returned, derived as summing (30 – number of tablets remaining) across records with non-missing DB kit dispense and return dates.

- Average DB exposure (tablets per month) based on DB kits dispensed and returned, derived

as 4 × cumulative DB exposure based on DB kits dispensed and returned/time from first DB kit dispensed to last DB kit returned.

- Time from first OL kit dispensed to last OL kit returned (weeks), derived as (latest OL kit return date – earliest OL kit dispense date + 1)/7. Subjects who were dispensed ≥ 1 OL kit but never returned any OL kit will be credited with 1 day.

- Cumulative OL exposure (tablets) based on OL kits dispensed and returned, derived as summing (30 – number of tablets remaining) across records with non-missing OL kit dispense and return dates.

- Average OL exposure (tablets per month) based on OL kits dispensed and returned, derived as 4 × cumulative OL exposure based on OL kits dispensed and returned/time from first OL kit dispensed to last OL kit returned.

- Time from first DB or OL rimegepant kit dispensed to last DB or OL rimegepant kit returned (weeks). This is time from first DB kit dispensed to last DB kit returned for subjects whose as-treated treatment group is rimegepant. This is time from first OL kit dispensed to last OL kit returned for subjects whose as-treated treatment group is placebo.

- Cumulative DB or OL rimegepant exposure (tablets) based on DB or OL rimegepant kits dispensed and returned. This is cumulative DB and OL combined exposure for subjects whose as-treated treatment group is rimegepant, and cumulative OL exposure for subjects whose as-treated treatment group is placebo.

- Average DB or OL rimegepant exposure (tablets per month) based on DB or OL rimegepant kits dispensed and returned, derived as 4 × cumulative DB or OL rimegepant exposure based on DB or OL rimegepant kits dispensed and returned/time from first DB or OL rimegepant kit dispensed to last DB or OL rimegepant kit returned.

eDiary versus drug accountability cumulative exposure will be summarized by treatment group and overall with the number and percentage of subjects in the following categories:

- ≥ 10, ≥ 20, ≥ 30 absolute tablet difference in cumulative DB exposure for treated subjects

- ≥ 10, ≥ 20, ≥ 30, ≥ 40, ≥ 50 absolute tablet difference in OL rimegepant exposure for OL rimegepant treated subjects.

Absolute tablet difference is defined as the absolute value of {eDiary cumulative exposure (tablets) – drug accountability cumulative exposure (tablets)}.

Drug Accountability Compliance

Drug accountability compliance will be summarized by as-randomized treatment group and overall with the number and percentage of randomized subjects in the following categories:

- Any kit dispensed

- Did not return ≥ 1 kit dispensed and discontinued study drug, defined as any of the following:

  o Randomized subjects who were not treated and did not return ≥ 1 DB kit dispensed

    o   Treated subjects who did not return ≥ 1 DB kit dispensed and discontinued DBT (i.e., non-missing DBT last date)

    o   OL rimegepant treated subjects who did not return ≥ 1 OL rimegepant kit dispensed and discontinued OL rimegepant (i.e., non-missing OL rimegepant last date).

- Did not return any kit dispensed and discontinued study drug.

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

6.2.6.3   *eDiary Compliance*

eDiary Compliance During Pre-Randomization and in the DBT Phase

eDiary compliance in the OP and DBT phase will be summarized descriptively by treatment group and overall for treated subjects for each source (subject; subject or site). Subject sources are the scheduled dosing report, evening report headache log, follow-up headache log, PoM, and SM survey. Site source is the medication reconciliation form.

Finding days are those with complete finding dates from any subcategory of question. Compliance will be derived for the following periods:

- Last 28 days before randomization: $100 \times$ (total number of finding days in the last 28 days before the IWRS randomization date)/28

- Randomization to last DBT visit: $100 \times$ (total number of finding days from the IWRS randomization date to the last DBT visit date)/(total number of days from the IWRS randomization date to the last DBT visit date).

DBT start date will be used if IWRS randomization date is missing.

For each source and period, eDiary compliance will be summarized as a continuous parameter and as the number and percentage of subjects with ≥ 80% and ≥ 90% compliance.

eDiary Compliance in the DB or OL Rimegepant Phase

eDiary compliance in the DB or OL rimegepant phase will be summarized analogously to eDiary compliance by treatment group and overall for DB or OL rimegepant treated subjects. Compliance will be derived for the following period:

- DB or OL rimegepant start to last DB or OL rimegepant visit: $100 \times$ (total number of finding days from the DB or OL rimegepant start date to the last DB or OL rimegepant visit date)/total number of days from the DB or OL rimegepant start date to the last DB or OL rimegepant visit date).

6.2.6.4   Non-Study Medications

Non-study medications will be summarized by therapeutic class and preferred name. For each subject, multiple records of the same medication will be counted only once within each therapeutic class and preferred name. Medications will be displayed in descending order of overall frequency within therapeutic class and preferred name, unless specified otherwise.

Non-study medications will be identified from the Concomitant Medication and Migraine Standard of Care Medications CRFs.

Migraine standard of care medications are defined as those reported on either the (1) Migraine Standard of Care Medications CRF, or (2) Concomitant Medication CRF with medical history, AE, additional AE, or other indication indicative of migraine.

Prophylactic migraine standard of care medications are defined as migraine standard of care medications with a "yes" response to the question about prophylactic migraine medication on the Migraine Standard of Care Medications CRF. Otherwise, all other migraine standard of care medications will be considered to be non-prophylactic.

See Section 7.6.3 for the definitions of non-study medication types, e.g., prior, current, DBT concomitant, DB or OL rimegepant concomitant, follow-up.

By-subject listings of non-study medications and standard of care migraine medications will be provided by therapeutic class and preferred name for enrolled subjects, and will display COVID-19 visit impact code for visits impacted by COVID-19 (see Section 9.1.5.2). Prophylactic and non-prophylactic migraine standard of care medications will be identified, as well as medication type.

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

Non-Study Medications for Treated Subjects

Non-study medications will be summarized by therapeutic class and preferred name by treatment group and overall for treated subjects and the following medication types and subsets:

- Prior medications: all; migraine standard of care; prophylactic migraine standard of care

- Current medications: all; migraine standard of care; prophylactic migraine standard of care

- DBT concomitant medications (excluding overall treatment group): all; migraine standard of care; prophylactic migraine standard of care.

Medications will be displayed in descending order of rimegepant frequency within therapeutic class and preferred name.

Non-study prophylactic migraine standard of care medications will also be summarized analogously by treatment group for mITT subjects with prophylactic migraine medication use at

randomization. Medications will be displayed in descending order of overall frequency within therapeutic class and preferred name. (This was an adhoc analysis for the CSR.)

Non-Study Medications for DB or OL Rimegepant Treated Subjects

Non-study DB or OL rimegepant concomitant medications will be summarized analogously by treatment group and overall for DB or OL rimegepant treated subjects and the following subsets: all; migraine standard of care; prophylactic migraine standard of care.

Non-study DB or OL rimegepant concomitant medications will also be summarized analogously by subgroup level and overall for all safety subgroups of interest described in Section 6.1.3.3.

Non-Study Medications for OL Rimegepant Treated Subjects

Non-study OL rimegepant concomitant medications will be summarized analogously by subgroup level and overall for all safety subgroups of interest described in Section 6.1.3.4. Medication subsets include the following: all; migraine standard of care; prophylactic migraine standard of care.

Non-Study Medications for Follow-up Subjects

Non-study follow-up medications will be summarized analogously by treatment group and overall for follow-up subjects and the following subsets: all; migraine standard of care; prophylactic migraine standard of care.

6.3   Efficacy

Efficacy endpoints will be assessed by as-randomized treatment group.

Randomization is stratified by prophylactic migraine medication use at randomization (i.e., IWRS randomization stratum; yes or no). Hence, treatment group comparisons of continuous efficacy endpoints will be *adjusted* by prophylactic migraine medication use at randomization, whereas treatment group comparisons of binary efficacy endpoints will be *stratified* by prophylactic migraine medication use at randomization (except in subgroup analyses). If there are sparse data within a stratum, then results may be presented unstratified.

In treatment comparisons of binary efficacy endpoints, CIs will be based on a normal approximation to the binomial distribution using asymptotic standard error (ASE). Otherwise, CIs for continuous efficacy endpoints will be based on the normal distribution. All CIs will be 2-sided.

Select efficacy listings will display efficacy analysis period (i.e., OP, on-DBT, on-OL rimegepant, and follow-up). See Sections 7.4 and 7.5 for the definition of efficacy analysis periods and study days.

The following general by-subject efficacy listings will be provided:

- Subjects excluded from the efficacy analysis for randomized subjects not in the evaluable mITT population sample, including the reason for exclusion (see Section 3).

- Primary and secondary efficacy endpoints for randomized subjects, including the reason for exclusion from the evaluable mITT population sample (see Sections 6.3.1.1 and 6.3.2)

- Exploratory endpoints for mITT subjects (see Section 6.3.3).

6.3.1   Reduction in Migraine Days per Month

Subjects are instructed to report headache status (yes, no), severity (mild, moderate, severe, none), and characteristics (e.g., aura, nausea, vomiting), as well as medication taken to treat headache or during aura, in the eDiary evening report headache log or follow-up headache log recorded every day in the OP, DBT, and OLE phases.

Migraine days per month will be assessed as "migraine days per 4 weeks" to correspond with the 4-week visit schedule. Migraine days per month are based on data from the previous visit to the current visit (i.e., 4-week interval), and are prorated to account for missing migraine reports.

A by-subject listing will present efficacy analysis period and the following from the eDiary evening report headache log and follow-up headache log for enrolled subjects who had a "yes" response to having a headache or an aura-only event: headache status; aura-only event status, headache lasting ≥ 30 minutes status; headache start and end dates; headache severity; headache pain features present* (i.e., unilateral, pulsating, worsen or avoid activity), headache pain characteristics present (i.e., aura, nausea, vomiting, photophobia, phonophobia); medication used to treat headache or during aura* (i.e., study medication, additional study medication, triptan, ergotamine, other medication). Migraine days, rescue medication days, and MRM days will also be identified in the listing. Parameters marked with "*" will be displayed only for subjects with a "yes" response to these questions. COVID-19 visit impact code for visits impacted by COVID-19 will be displayed (see Section 9.1.5.2).

Another by-subject listing for treated subjects will present the following: number of migraine days per month by severity (total; moderate or severe) in the OP efficacy analysis period, overall DBT mean, overall OL rimegepant mean, and in each month (i.e., 4-week interval) in the on-DBT and on-OL rimegepant efficacy analysis periods; number of days of efficacy data in the aforementioned intervals, overall DBT mean, and overall OL rimegepant mean; and migraine day values, changes and percent changes from OP in the aforementioned intervals, overall DBT mean, and overall OL rimegepant mean.

See Section 7.6.2.2 for the definitions of efficacy data days and migraine days.

6.3.1.1   Reduction in Migraine Days per Month in the DBT Phase: Primary Efficacy Endpoint

The number of migraine days per month in the DBT phase will be examined relative to the number of migraine days per month in the OP for evaluable mITT subjects, i.e., subjects with ≥

14 days of eDiary efficacy data (not necessarily consecutive) in both the OP analysis period and ≥ 1 month (i.e., 4-week interval) in the on-DBT analysis period.

Months in the DBT phase are defined as follows:

- Month 1 (≤ 4 weeks; study days 1 to 28)

- Month 2 (> 4 to ≤ 8 weeks; study days 29 to 56)

- Month 3 (> 8 to ≤ 12 weeks; study days 57 to 84)

Analyses will be based on eDiary efficacy dates in the OP and on-DBT efficacy analysis periods.

The number of migraine days per month 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 efficacy data days in the OP analysis period).

- Month (i.e., 4-week interval) in the on-DBT efficacy analysis period: 28 × (total number of migraine days in the month)/(total number of efficacy data days in the month). Subjects must have ≥ 14 days of efficacy data (not necessarily consecutive) in the specified month to be evaluable.

- Overall DBT mean: 28 × (total number of migraine days through Month 3 in the on-DBT efficacy analysis period)/(total number of efficacy data days through Month 3 in the on-DBT efficacy analysis period).

Missing Efficacy Data

Missing efficacy data in the OP and DBT phases will be assessed using the number and percentage of mITT subjects in the following categories:

- Evaluable

- Not evaluable, i.e., < 14 days of efficacy data in the OP and < 14 days of efficacy data in all 3 months (i.e., 4-week intervals) of the DBT phase

  o < 14 days of efficacy data in the OP

  o < 14 days of efficacy data in any of the following months (i.e., 4-week intervals) of the DBT phase:

    ▪ Month 1: ≤ 4 weeks

    ▪ Month 2: > 4 to ≤ 8 weeks

    ▪ Month 3: > 8 to ≤ 12 weeks

Descriptive Analyses

Analyses will be based on evaluable mITT subjects.

Values and changes (both absolute and percent) from the OP in the number of migraine days per month in the DBT phase will be summarized descriptively as continuous parameters (including 2-sided normal 95% CIs for mean change) by treatment group and migraine severity in each month of the DBT phase and overall DBT mean. Migraine severity categories are (1) total (mild, moderate, severe, none, or not reported) and (2) moderate or severe.

Values and changes will also be summarized by subgroup level for all efficacy subgroups of interest described in Section 6.1.3.1.

The following scatter plots will be produced by treatment group:

- Change from OP in the number of total migraine days per month in the last month of the DBT phase (y-axis) versus number of migraine days per month in the OP (x-axis)

- Percent change from OP in the number of total migraine days per month in the last month of the DBT phase (y-axis) versus number of migraine days per month in the OP (x-axis)

- Change from OP in the number of total migraine days per month in the overall DBT mean (y-axis) versus number of migraine days per month in the OP (x-axis)

- Percent change from OP in the number of total migraine days per month in the overall DBT mean (y-axis) versus number of migraine days per month in the OP (x-axis).

Plots will include a horizontal reference line at 0. The last 2 plots were included as adhoc analyses in the CSR.

In the percent change analyses, subjects must also have ≥ 1 migraine day (i.e., absolute not prorated to 28 days) of appropriate migraine severity in the OP analysis period to be included.

Treatment Group Comparisons

Analyses will be based on evaluable mITT subjects and total migraine severity, unless specified otherwise.

Principal Analysis

The principal analysis of the primary endpoint will use a generalized linear mixed effect model with the following variables: change from the OP in number of total migraine days per month as the dependent variable; subject as a random effect; number of total migraine days per month in the OP as a covariate; treatment group, prophylactic migraine medication use at randomization, month (i.e., months 1 to 3 of the DBT phase), and the month-by-treatment group interaction as fixed effects. The model will be repeated by prophylactic migraine medication use at randomization (yes, no).The following model estimates will be reported:

- Least-squares mean (LSM) change from OP, SE, and 95% CI by month and randomization stratum (yes, no, overall) for each treatment group

- Difference in LSM changes from OP between treatment groups (rimegepant – placebo), SE, 95% CI, and p-value by randomization stratum (yes, no) for each month

- Difference in LSM changes from OP between treatment groups (rimegepant – placebo), SE, 95% CI, and p-value for each month. <u>Results in the last month will support the primary objective, results in the first month will support the fourth secondary objective, and results in the second month will support the first exploratory objective.</u>

- Overall LSM change from OP, SE, and 95% CI by randomization stratum (yes, no, overall) for each treatment group

- Difference in overall LSM changes from OP between treatment groups (rimegepant – placebo), SE, 95% CI, and p-value by randomization stratum (yes, no)

- Difference in overall LSM changes from OP between treatment groups (rimegepant – placebo), SE, 95% CI, and p-value. <u>Results will support the second secondary objective.</u>

These analyses will be repeated for moderate or severe migraine severity to support the first exploratory objective. All variables in the model will be the same, except (1) change from the OP in number of moderate or severe migraine days per month will be the dependent variable, and (2) number of moderate or severe migraine days per month in the OP will be the covariate.

A longitudinal plot will display the LSM change in the number of total migraine days from OP per month (y-axis) versus month of the DBT phase (x-axis). Another longitudinal plot will display the LSM change in the number of moderate or severe migraine days from OP per month (y-axis) versus month of the DBT phase (x-axis). Error bars will denote 95% CIs.

Sensitivity Analysis

A sensitivity analysis of the primary endpoint will use the same generalized linear mixed effect model as the principal analysis, but with jump to reference (J2R) to impute missing data in months 1 to 3 using N = 1000 datasets. The imputation model will use the following variables: age, sex, race, prophylactic migraine medication use at randomization, and the number of migraine days per month in the OP. Race may be reduced to fewer levels (e.g., white versus non-white) based on the availability of data.

Subgroup Analyses

Subgroup analyses of the primary endpoint will use the same generalized linear mixed effect model specified for the principal analysis of the primary endpoint, except without prophylactic migraine medication use at randomization. The following model estimates will be reported for each subgroup level of all efficacy subgroups of interest specified in Section 6.1.3.1, except prophylactic migraine medication use at randomization:

- LSM change from OP, SE, and 95% CI by month for each treatment group

- Difference in LSM changes from OP between treatment groups (rimegepant – placebo), SE, 95% CI , and p-value by month

- Overall LSM change from OP, SE, and 95% CI for each treatment group

- Difference in overall LSM changes from OP between treatment groups (rimegepant – placebo), SE, 95% CI, and p-value.

6.3.1.2 Reduction in Migraine Days per Month in the OLE Phase

The number of migraine days per month in the OLE phase will be examined relative to the number of migraine days per month in the OP for evaluable OL rimegepant mITT subjects, i.e., mITT subjects with ≥ 14 days of eDiary efficacy data (not necessarily consecutive) in both the OP analysis period and ≥ 1 month (i.e., 4-week interval) in the on-OL rimegepant efficacy analysis period. Results will support an exploratory objective.

Months in the OLE phase will be defined as:

- Month 1 (> 12 to ≤ 16 weeks; study days 85 to 112)

- Month 2 (> 16 to ≤ 20 weeks; study days 113 to 140)

- Month 3 (> 20 to ≤ 24 weeks; study days 141 to 168)

- Month 4 (> 24 to ≤ 28 weeks; study days 169 to 196)

- Month 5 (> 28 to ≤ 32 weeks; study days 197 to 224)

- Month 6 (> 32 to ≤ 36 weeks; study days 225 to 252)

- Month 7 (> 36 to ≤ 40 weeks; study days 253 to 280)

- Month 8 (> 40 to ≤ 44 weeks; study days 281 to 308)

- Month 9 (> 44 to ≤ 48 weeks; study days 309 to 336)

- Month 10 (> 48 to ≤ 52 weeks; study days 337 to 364)

- Month 11 (> 52 to ≤ 56 weeks; study days 365 to 392)

- Month 12 (> 56 to ≤ 60 weeks; study days 393 to 420)

- Month 13 (> 60 to ≤ 64 weeks; study days 421 to 448).

Analyses will be based on eDiary efficacy dates in the OP analysis period and on-OL rimegepant efficacy analysis period.

The number of migraine days per month will be prorated to 28 days, and derived as follows:

- OP: See Section 6.3.1.1.

- Month (i.e., 4-week interval) in the on-OL rimegepant efficacy analysis period: $28 \times$ (total number of migraine days in the month)/(total number of efficacy data days in the month). <u>Subjects must have ≥ 14 days of efficacy data (not necessarily consecutive) in the specified month to be evaluable.</u>

- Overall OL rimegepant mean: 28 × (total number of migraine days through Month 13 in the on-OL rimegepant efficacy analysis period)/(total number of efficacy data days through Month 13 in the on-OL rimegepant efficacy analysis period).

Missing Efficacy Data

Missing efficacy data in the OP and OLE phases will be assessed using the number and percentage of OL rimegepant mITT subjects by treatment group and overall in the following categories:

- Evaluable

- Not evaluable, i.e., < 14 days of efficacy data in the OP and all 13 months (i.e., all 13 4-week intervals) in the OLE phase

  ○ < 14 days of efficacy data in the OP

  ○ < 14 days of efficacy data in any of the following months in the OLE phase:

    ▪ Months 1 to 3: > 12 to ≤ 24 weeks

    ▪ Months 4 to 6: > 24 to ≤ 36 weeks

    ▪ Months 7 to 9: > 36 to ≤ 48 weeks

    ▪ Months 10 to 13: > 48 to ≤ 64 weeks

Descriptive Analyses

Analyses are based on evaluable OL rimegepant mITT subjects.

Values and changes (both absolute and percent) from the OP in the number of migraine days per month in the OLE phase will be summarized descriptively as continuous parameters (including 2-sided normal 95% CIs for mean change) by treatment group (including overall) and severity (total; moderate or severe) in each month of the OLE phase and overall OL mean. Results will support the exploratory objective about OLE phase efficacy.

A scatter plot by treatment group will display the change in the number of total migraine days per month in the OL overall mean (y-axis) versus number of migraine days per month in the OP (x-axis). Another scatter plot by treatment group will display the percent change in the number of total migraine days per month in the OL overall mean (y-axis) versus number of migraine days per month in the OP (x-axis). Plots will include a horizontal reference line at 0.

A longitudinal plot will display the mean change from OP in the number of total migraine days per month (y-axis) versus month of the OLE phase (x-axis). Another longitudinal plot will display the mean change from OP in the number of moderate or severe migraine days per month (y-axis) versus month of the OLE phase (x-axis). Error bars will denote 95% CIs.

In the percent change analyses, subjects must also have ≥ 1 migraine day (i.e., absolute not prorated to 28 days) of appropriate severity in the OP analysis period to be included.

6.3.2 Secondary Efficacy Endpoints

6.3.2.1 Percentages of Subjects with Reduction in Migraine Days per Month

Analyses will be based on evaluable mITT subjects and evaluable OL rimegepant mITT subjects.

In analyses by months, subjects must (1) achieve the reduction criterion from OP in the number of migraine days in the specified month, (2) be evaluable (i.e., have ≥ 14 days of efficacy data [not necessarily consecutive]) in the specified month, and (3) have ≥ 1 migraine day (absolute not prorated to 28 days) of appropriate migraine severity in the OP analysis period to be classified as responders in the specified month. Otherwise, subjects will be classified as failures in the specified month.

In analyses of the overall DBT or OLE mean, subjects must (1) achieve the reduction criterion from OP in the number of migraine days in the overall mean, and (2) have ≥ 1 migraine day (absolute not prorated to 28 days) of appropriate migraine severity in the OP analysis period to be classified as responders. Otherwise, subjects will be classified as failures.

Percentages of Subjects With Reduction in Migraine Days per Month in the DBT Phase

Analyses will be based on evaluable mITT subjects with eDiary efficacy dates in the OP and on-DBT efficacy analysis periods (see Section 6.3.1.1).

Descriptive Analyses

The number and percentage of evaluable mITT subjects with reductions from the OP in the number of migraine days per month in the DBT phase will be presented by treatment group and severity (total; moderate or severe) in each month of the DBT phase and overall DBT mean (see Section 6.3.1.1 for months). Reduction from OP categories will be: ≥ 1, ≥ 2, ≥ 3, ≥ 4, ≥ 5, ≤ 0; > 0 to ≤ 2; > 2 to ≤ 4; > 4 to ≤ 6; > 6 to ≤ 8; > 8 to ≤ 10; > 10 to ≤ 12; > 12 to ≤ 14; > 14; ≥ 20%, ≥ 25%, ≥ 30%, ≥ 35%, ≥ 40%, ≥ 45%, ≥ 50%, ≥ 75%, and ≥ 100%. Analyses by month will be presented using the following 2 methods:

- Non-Evaluable = Failure: Analyses will be based on all evaluable mITT subjects in all months. An additional reduction category "Not evaluable" will be included.

- Non-Evaluable = Missing: Evaluable mITT subjects with ≥ 1 migraine day of appropriate migraine severity in the OP analysis period and < 14 days of efficacy data in the specified month will be excluded from analyses of the specified month.

The number and percentages of evaluable mITT subjects with reduction outcomes will be presented by treatment group in each month of the DBT phase and overall DBT mean for each migraine severity (total; moderate or severe) and select percentage reduction (≥ 50%, ≥ 75%, and ≥ 100%). Outcomes categories at each month will be defined as follows:

- Responder, i.e., subjects with ≥ 14 days of efficacy data in the specified month, ≥ X% reduction in the specified month, and ≥ 1 migraine day of appropriate migraine severity in the OP analysis period.

- Failure

  o No migraine days of appropriate migraine severity in the OP.

  o Evaluable but $< X\%$ reduction in the month, i.e., subjects with ≥ 14 days of efficacy data and $< X\%$ reduction in the specified month.

  o $\geq X\%$ reduction but not evaluable in the month, i.e., subjects with $\geq X\%$ reduction and ≥ 1 to < 14 days of efficacy data in the specified month.

  o $< X\%$ reduction but not evaluable in the month, i.e., subjects with $< X\%$ reduction and ≥ 1 to < 14 days of efficacy data in the specified month.

  o No days of efficacy data in the month.

Outcomes categories for the overall DBT mean will be defined as follows:

- Responder, i.e., subjects with $\geq X\%$ reduction in the overall DBT mean and ≥ 1 migraine day of appropriate migraine severity in the OP analysis period.

- Failure

  o No migraine days of appropriate migraine severity in the OP.

  o $< X\%$ reduction, i.e., subjects with $< X\%$ reduction in the overall DBT mean.

In the above description, $X = 50$, 75, and 100. Failure subcategories are mutually exclusive, because subjects who meet more than 1 failure criterion will be classified according to the first failure criterion met in the hierarchy above.

The following histograms will be produced by treatment group for evaluable mITT subjects:

- Percentage of subjects in categories of reduction from OP in the number of total migraine days per month in the last month of the DBT phase (y-axis) versus reduction category (x-axis). This is based on evaluable mITT subjects in Month 3.

- Percentage of subjects in categories of reduction from OP in the number of total migraine days per month in the overall DBT mean (y-axis) versus reduction category (x-axis).

Reduction categories are displayed in descending order: > 14; > 12 to ≤ 14; > 10 to ≤ 12; > 8 to ≤ 10; > 6 to ≤ 8; > 4 to ≤ 6; > 2 to ≤ 4; > 0 to ≤ 2; increase or no reduction in migraine days/month (ie., ≤ 0). Histograms will include a vertical reference line between the last 2 categories. Histograms were included as adhoc analyses in the CSR.

Treatment Group Comparisons

For each migraine severity (total; moderate or severe) and select percentage reductions ($\geq 50\%$, $\geq 75\%$, and $\geq 100\%$), the percentages of evaluable mITT subjects with reductions will be compared between treatment groups using Cochran-Mantel-Haenszel (CMH) tests stratified by prophylactic migraine medication use at randomization (yes, no). Response rates will be based on responder outcomes described previously. The following statistics will be presented for each month of the DBT phase and overall DBT mean by migraine severity:

- Response rate ("n/N"), risk (i.e., percentage), ASE, and 95% normal CI by randomization stratum for each treatment group

- Overall response rate ("n/N"), stratified risk, ASE, and 95% normal CI for each treatment group

- Difference in risks between treatment groups (rimegepant – placebo), ASE, 95% CI, and p-value by randomization stratum

- Difference in overall stratified risks between treatment groups (rimegepant – placebo), ASE, 95% CI, and p-value.

Results for ≥ 50% reduction of moderate or severe migraine severity in the last month (i.e., month 3) will support the first secondary objective. All other results will support exploratory objectives about percentage reductions.

These endpoints will also be compared between treatment groups using unstratified CMH tests by migraine severity (total; moderate or severe) for each subgroup level of all efficacy subgroups of interest specified in Section 6.1.3.1 except prophylactic migraine medication use. For each migraine severity and subgroup level, the following statistics will be presented for each month in the DBT phase and overall DBT mean:

- Response rate ("n/N"), risk (i.e., percentage), ASE, and 95% normal CI by treatment group

- Difference in risks between treatment groups (rimegepant – placebo), ASE, 95% CI, and p-value.

Longitudinal plots will display the percentage of subjects with reduction (i.e., overall stratified risks on y-axis) versus month of the DBT phase (x-axis) for each select percentage reduction (≥ 50%, ≥ 75%, and ≥ 100%) and migraine severity (total; moderate or severe). Error bars will denote 95% CIs.

Percentages of Subjects With Reduction in Migraine Days per Month in the OLE Phase

Analyses will be based on evaluable OL rimegepant mITT subjects with eDiary efficacy dates in the OP and on-OL rimegepant efficacy analysis periods.

The number and percentage of evaluable OL rimegepant mITT subjects with reductions from the OP in the number of migraine days per month in the OLE phase will be presented by treatment group and overall, and severity (total; moderate or severe) in each month of the OLE phase and overall OL mean (see Section 6.3.1.2 for months). Reduction from OP categories will be same as those defined previously for the DBT phase. Analyses by month will be presented using the analogous Non-Evaluable = Failure and Non-Evaluable = Missing methods described previously for the DBT phase. Analyses for the Non-Evaluable = Failure method will only be shown in the Addendum Report. Results will support the exploratory objective about OLE phase efficacy.

6.3.2.2 Rescue Medication Days per Month

During the DBT and OLE phases, subjects may record taking triptan, ergotamine, and other medications to treat headache or during aura in the eDiary evening report headache log or follow-up headache log.

Rescue medication days per month will be assessed as "rescue medication days per 4 weeks" to correspond with the 4-week visit schedule. Rescue medication days per month are based on data from the previous visit to the current visit (i.e., 4-week interval) where a rescue medication day is defined as a day of efficacy data with complete reference time point date and a "yes" response to at least one of the following questions: taking triptan to treat headache or during aura; taking ergotamine to treat headache or during aura; taking other medication to treat headache.

Rescue Medication Days per Month in the DBT Phase

Analyses are based on evaluable mITT subjects with eDiary reference time point dates in the on-DBT efficacy analysis period.

The number of rescue medication days per month in the DBT phase will be prorated to 28 days and derived as follows:

- Month (i.e., 4-week interval) in the on-DBT efficacy analysis period: 28 × (total number of rescue medication days in the month)/(total number of efficacy data days in the month). Subjects must have ≥ 14 days of efficacy data (not necessarily consecutive) in the specified month to be evaluable.

- Overall DBT mean: 28 × (total number of rescue medication days through Month 3 in the on-DBT efficacy analysis period)/(total number of efficacy data days through Month 3 in the on-DBT efficacy analysis period).

Descriptive Analyses

The number of rescue medication days per month in the DBT analysis period will be summarized descriptively as a continuous parameter (including 2-sided normal 95% CIs for mean) by treatment group in each month of the DBT phase and overall DBT mean.

Treatment Group Comparisons

A generalized linear mixed effect model will have the following variables: number of rescue medication days per month as the dependent variable; subject as a random effect; treatment group, prophylactic migraine medication use at randomization, month (i.e., months 1 to 3 of the DBT phase), and the month-by-treatment group interaction as fixed effects. The model will be repeated by prophylactic migraine medication use at randomization (yes, no). The following model estimates will be reported:

- LSM, SE, and 95% CI by month and randomization stratum (yes, no, overall) for each treatment group

- Difference in LSMs between treatment groups (rimegepant – placebo), SE, 95% CI, and p-value by randomization stratum (yes, no) for each month

- Difference in LSMs between treatment groups (rimegepant – placebo), SE, 95% CI, and p-value for each month. Results in the last month will support the third secondary objective, whereas results in the other months will support an exploratory objective.

- Overall LSM, SE, and 95% CI by randomization stratum (yes, no, overall) for each treatment group

- Difference in overall LSMs between treatment groups (rimegepant – placebo), SE, 95% CI, and p-value by randomization stratum (yes, no)

- Difference in overall LSMs between treatment groups (rimegepant – placebo), SE, 95% CI, and p-value. Results will support an exploratory objective.

Rescue Medication Days per Month in the OLE Phase

Analyses are based on evaluable OL rimegepant mITT subjects with eDiary reference time point dates in the on-OL rimegepant efficacy analysis period.

The number of rescue medication days per month in the OLE phase will be prorated to 28 days and derived as follows:

- Month (i.e., 4-week interval) in the on-OL rimegepant efficacy analysis period: 28 × (total number of rescue medication days in the month)/(total number of efficacy data days in the month). Subjects must have ≥ 14 days of efficacy data (not necessarily consecutive) in the specified month to be evaluable.

- Overall OL rimegepant mean: 28 × (total number of rescue medication days through Month 13 in the on-OL rimegepant efficacy analysis period)/(total number of efficacy data days through Month 13 in the on-OL rimegepant efficacy analysis period).

The number of rescue medication days per month in the OLE phase will be summarized descriptively as a continuous parameter (including 2-sided normal 95% CIs for mean) by treatment group and overall in each month of the OLE phase and overall OLE mean.

6.3.2.3   MSQoL in the DBT Phase

The MSQoL will be assessed at early termination and the following visits: baseline; Week 12 of the DBT phase; and Weeks 24 and 64 of the OLE phase.

The MSQoL consists of 14 items across the following 3 domains: (1) restrictive role function, (2) preventative role function and (3) emotional function. Refer to the BHV3000 Core SAP for calculating transformed domain scores and imputing missing data.

Measurements will be first selected from the on-DBT efficacy period, and then slotted into the Week 12 analysis visit window (see Week 12 of the analysis visit window for outcome research

[OR] endpoints column in Table 4). If a subject has multiple values in the 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 6.2.5, 7.4, and 7.5 for definitions of baseline, analysis periods, and analysis visit windows, respectively.

Descriptive Analyses

Values and changes from baseline in transformed scores for each domain will be summarized descriptively (included 2-sided normal 95% CIs for mean change) as continuous parameters by treatment group at baseline and Week 12.

As-randomized analyses will be based on evaluable mITT subjects with MSQoL domain scores at both baseline and Week 12 of the on-DBT efficacy analysis period. See Section 6.6.1for as-treated analyses of MSQoL in the DBT and OLE phases for treated subjects.

Treatment Group Comparisons

Analyses will be based on evaluable mITT subjects with MSQoL restrictive role function domain scores at both baseline and Week 12 of the on-DBT efficacy analysis period.

A generalized linear model will have the following variables: Week 12 change from baseline in the restrictive role function transformed score as the dependent variable; baseline restrictive role function transformed score as a covariate; treatment group and the prophylactic migraine medication use at randomization as fixed effects. The model will be repeated by prophylactic migraine medication use at randomization (yes, no). The following model estimates will be reported:

- LSM change from baseline at Week 12, SE, and 95% CI by randomization stratum (yes, no, overall) for each treatment group

- Difference in LSM changes from baseline between treatment groups (rimegepant − placebo) at Week 12, SE, 95% CI, and p-value by randomization stratum (yes, no)

- Difference in LSM changes from baseline between treatment groups (rimegepant − placebo) at Week 12, SE, 95% CI, and p-value. Results will support the fifth secondary objective.

6.3.2.4 MIDAS in the DBT Phase

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 assessed at early termination and the following visits: baseline; Week 12 of the DBT phase; and Weeks 24 and 64 of the OLE phase.

Refer to the BHV3000 Core SAP for calculating MIDAS scores (i.e., total, absenteeism, presenteeism, item) and imputing missing data.

Measurements will be first selected from the on-DBT efficacy period, and then slotted into the Week 12 analysis visit window; see Section 6.3.2.3.

Descriptive Analyses

Values and changes from baseline in total, absenteeism, presenteeism, and item scores will be summarized as described in Section 6.3.2.3.

As-randomized analyses will be based on evaluable mITT subjects with MIDAS scores at both baseline and Week 12 of the on-DBT efficacy analysis period. See Section 6.6.2 for as-treated analyses of MIDAS in the DBT and OLE phases for treated subjects.

Treatment Group Comparisons

Analyses will be based on evaluable mITT subjects with MIDAS total scores at both baseline and Week 12 of the on-DBT efficacy analysis period.

A generalized linear model will have the following variables: Week 12 change from baseline in the total score as the dependent variable; baseline total score as a covariate; treatment group and prophylactic migraine medication use at randomization as fixed effects. The model will be repeated by prophylactic migraine medication use at randomization (yes, no). The same model estimates as those described in Section 6.3.2.3 will be reported. Results will support the last secondary objective.

6.3.2.5　Overall Summary of Primary and Secondary Endpoints

An overall summary of treatment comparisons of all primary and secondary endpoints tested hierarchically will present the following statistics:

- Continuous endpoints involving change from OP or baseline

  ○ Overall LSM change and 95% CI for each treatment group

  ○ Difference in overall LSM changes between treatment groups (rimegepant – placebo), 95% CI, and p-value.

  This applies to the following endpoints: primary endpoint; secondary endpoint of change in mean number of migraine days per month in the overall DBT phase; secondary endpoint of change in mean number of migraine days per month in the first month of the DBT phase; MSQoL restrictive role domain score change from baseline at Week 12; and MIDAS total score change from baseline at Week 12.

- Continuous endpoints not involving change from OP or baseline

  ○ Overall LSM and 95% CI for each treatment group

  ○ Difference in overall LSMs between treatment groups (rimegepant – placebo), 95% CI, and p-value.

  This applies to the secondary endpoint of the mean number of rescue medication days per month in the last month of the DBT phase.

- Binary endpoints

  ○ Overall response rate ("n/N"), stratified risk, and 95% CI for each treatment group

    ○ Overall stratified risk difference between treatment groups (rimegepant – placebo), 95% CI, and p-value.

This applies to the secondary endpoint of percentage of subjects with ≥ 50% reduction in mean number of moderate or severe migraine days per month in the last month of the DBT phase.

Analyses will be based on principal methods described in Sections 6.3.1.1 and 6.3.2. Endpoints will be displayed in the order presented in Sections 1.2.1 and 1.2.2. P-values that are determined to be significant based on the testing hierarchy will be flagged.

6.3.3   Exploratory Efficacy Endpoints

6.3.3.1   Reduction in MRM Days per Month

Female subjects will record their menstrual period start and stop dates in a menstrual period log. Menstruating females will be identified as females with either (1) a "yes" response to the question about experiencing menstrual periods on the Demographics CRF (see Section 6.2.5), or (2) at least one complete menstrual period start date from the Menstrual Period Log CRF.

An eDiary reference time point date is considered to be exclusively in a menstrual interval if the complete menstrual period start date − 2 days ≤ eDiary reference time point date ≤ complete menstrual period start date + 2 days.

A day of MR efficacy data is defined as a non-missing eDiary efficacy date inclusively in a menstrual interval.

An MRM day is defined as a non-missing eDiary migraine date inclusively in a menstrual interval.

MRM days per month will be assessed as "MRM days per 4 weeks" to correspond with the 4-week visit schedule. MRM days per month are based on data from the previous visit to the current visit (i.e., 4-week interval), and are prorated to account for missing migraine reports.

A by-subject listing of menstrual periods that includes efficacy analysis period will be provided for enrolled female subjects, and will display COVID-19 visit impact code for visits impacted by COVID-19 (see Section 9.1.5.2).

A by-subject listing of MRM days will be provided for menstruating female treated subjects, and will present the following: number of MRM days per month by migraine severity (total; moderate or severe) in the OP efficacy analysis period, overall DBT mean, overall OL rimegepant mean, and in each month of the on-DBT and on-OL rimegepant efficacy analysis periods, number of days of MR efficacy data in these aforementioned periods, overall DBT mean, and overall OL rimegepant mean; MRM day values, changes and percent changes from OP in the aforementioned months, overall DBT mean, and overall OL rimegepant mean.

Reduction in MRM Days per Month in the DBT Phase

The number of MRM days per month in the DBT phase will be examined relative to the number of MRM days per month in the OP for menstrual migraine evaluable mITT menstruating female subjects, i.e., mITT menstruating females with ≥ 1 day of eDiary MR efficacy data and ≥ 14 days of eDiary efficacy data (not necessarily consecutive) in both the OP analysis period and at least one month (i.e., 4-week interval) in the on-DBT efficacy analysis period (see Section 7.6.2).

Months in the DBT phase are defined in Section 6.3.1.2.

Analyses will be based on eDiary efficacy dates in the OP analysis period and on-DBT efficacy analysis period.

The number of MRM days per month will be prorated to 28 days, and derived as follows:

- OP: 28 × (total number of MRM days in the OP analysis period)/(total number of efficacy data days in the OP analysis period).

- Month (i.e., 4-week interval) in the on-DBT efficacy analysis period: 28 × (total number of MRM days in the month)/(total number of efficacy data days in the month). Subjects must have at least one day of MR efficacy data in the specified month to be evaluable.

- Overall DBT mean: 28 × (total number of MRM days through Month 3 in the on-DBT efficacy analysis period)/(total number of efficacy data days through Month 3 in the on-DBT efficacy analysis period).

Missing MR Efficacy Data

Missing MR efficacy data in the OP and DBT phases will be assessed using the number and percentage of mITT menstruating female subjects in the following categories:

- Evaluable

- Not evaluable, i.e., no days of MR efficacy data in the OP and no days of MR efficacy data in all 3 months (i.e., all 3 4-week intervals) of the DBT phase

  ○ No days of MR efficacy data in the OP

  ○ No days of MR efficacy data in any of the following months (i.e., 4-week intervals) of the DBT phase:

    ▪ Month 1: ≤ 4 weeks

    ▪ Month 2: > 4 to ≤ 8 weeks

    ▪ Month 3: > 8 to ≤ 12 weeks

Descriptive Analyses

Values and changes (both absolute and percent) from the OP in the number of MRM days per month in the DBT phase will be summarized descriptively as continuous parameters (including 2-sided normal 95% CIs for mean change) by treatment group and migraine severity (total; moderate or severe) in each month of the DBT phase and overall DBT mean.

Analyses are based on evaluable mITT menstruating female subjects. In the percent change analyses, subjects must also have ≥ 1 MRM day of appropriate migraine severity in the OP analysis period to be included.

Treatment Group Comparisons

A generalized linear mixed effect model similar to the one described for the primary endpoint in Section 6.3.1.1 will be used with the following variables: change from the OP in number of total MRM days per month as the dependent variable; subject as a random effect; number of total MRM days per month in the OP as a covariate; treatment group, prophylactic migraine medication use at randomization, month (i.e., months 1 to 3 of the DBT phase), and the month-by-treatment group interaction as fixed effects. The model will be repeated by prophylactic migraine medication use at randomization (yes, no). The same model estimates will be reported as for the primary endpoint (see Section 6.3.1.1).

Reduction in MRM Days per Month in the OLE Phase

The number of MRM days per month in the OLE phase will be examined relative to the number of MRM days per month in the OP for menstrual migraine evaluable OL rimegepant mITT menstruating female subjects, i.e., defined as OL rimegepant mITT menstruating female subjects with ≥ 1 day of MR efficacy data and ≥ 14 days of eDiary efficacy data (not necessarily consecutive) in both the OP analysis period and at least one month (i.e., 4-week interval) in the on-OL rimegepant efficacy analysis period.

Months in the OLE phase are defined in Section 6.3.1.2.

Analyses will be based on eDiary efficacy dates in the OP and on-OL rimegepant efficacy analysis periods.

The number of MRM days per month will be prorated to 28 days and derived as follows:

- OP: See Section 6.3.1.1.

- Month (i.e., 4-week interval) in the on-OL rimegepant efficacy analysis period: 28 × (total number of MRM days in the month)/(total number of efficacy data days in the month). Subjects must have ≥ 1 day of MR efficacy data in the specified month to be evaluable.

- Overall OL rimegepant mean: 28 × (total number of MRM days through Month 13 in the on-OL rimegepant efficacy analysis period)/(total number of efficacy data days through Month 13 in the on-OL rimegepant efficacy analysis period).

Missing MR Efficacy Data

Missing MR efficacy data in the OP and OLE phases will be assessed using the number and percentage of OL rimegepant mITT menstruating female subjects in the following categories:

- Evaluable

- Not evaluable, i.e., no days of MR efficacy data in the OP and no days of MR efficacy data in all 13 months (i.e., all 13 4-week intervals) of the OLE phase

  ○ No days of MR efficacy data in the OP

  ○ No days of MR efficacy data in any of the following months (i.e., 4-week intervals) of the OLE phase:

    ▪ Months 1 to 3: > 12 to ≤ 24 weeks

    ▪ Months 4 to 6: > 24 to ≤ 36 weeks

    ▪ Months 7 to 9: > 36 to ≤ 48 weeks

    ▪ Months 10 to 13: > 36 to ≤ 64 weeks

Descriptive Analyses

Values and changes (both absolute and percent) from the OP in the number of MRM days per month in the OLE phase will be summarized descriptively as continuous parameters (including 2-sided normal 95% CIs for mean change) by as-randomized treatment group and overall and migraine severity (total; moderate or severe) in each month of the OLE phase and overall OL rimegepant mean.

Analyses are based on evaluable OL rimegepant mITT menstruating female subjects. In the percent change analyses, subjects must also have ≥ 1 MRM day of appropriate migraine severity in the OP analysis period to be included.

6.3.3.2   Reduction in Migraine Days in the First Week of the DBT Phase

The number of migraine days in the first week of the DBT phase will be examined relative to the number of migraine days per week in the OP for evaluable first week mITT subjects, i.e., mITT subjects with at least one day of eDiary efficacy data in both the OP analysis period and the first week of the on-DBT analysis period.

The first week of the DBT phase is defined as study days 1 to 7. See Sections 7.4 and 7.5 for the definition of analysis periods and study days used to define analysis visit windows.

Analyses will be based on evaluable first week mITT subjects with eDiary efficacy dates in the OP analysis period and the on-DBT efficacy analysis period.

The number of migraine days per week will be prorated to 7 days, and derived as follows:

- OP: 7 × (total number of migraine days in the OP analysis period)/(total number of efficacy data days in the OP analysis period).

- First week of the on-DBT efficacy analysis period: 7 × (total number of migraine days in the first week)/(total number of efficacy data days in the first week). <u>Subjects must have at least one day of efficacy data in the first week to be evaluable.</u>

Descriptive Analyses

Values and changes (both absolute and percent) from the OP in the number of migraine days per first week of the DBT phase will be summarized descriptively as continuous parameters (including 2-sided normal 95% CIs for mean change) by treatment group and migraine severity (total; moderate or severe).

In the percent change analyses, subjects must also have ≥ 1 migraine day of appropriate severity in the OP analysis period to be included.

Treatment Group Comparisons

Analyses will be based on total severity, unless specified otherwise.

A generalized linear model will use the following variables: change from the OP in number of total migraine days per week in the first week as the dependent variable; number of total migraine days per week in the OP as a covariate; treatment group and prophylactic migraine medication use at randomization as fixed effects. The model will be repeated by prophylactic migraine medication use at randomization (yes, no). The following model estimates will be reported:

- LSM change from OP, SE, and 95% CI by randomization stratum (yes, no, overall) for each treatment group

- Difference in mean changes from OP between treatment groups (rimegepant – placebo), SE, 95% CI, and p-value by randomization stratum (yes, no)

- Difference in mean changes from OP between treatment groups (rimegepant – placebo), SE, 95% CI, and p-value. Results will support the exploratory objective.

These analyses will be repeated for moderate or severe migraine severity. All variables in the model will be the same, except (1) change from the OP in number of moderate or severe migraine days per week will be the dependent variable, and (2) number of moderate or severe migraine days per week in the OP will be the covariate.

6.3.3.3 Triptan or Ergotamine Days per Month

This adhoc analysis was added to the CSR.

Triptan or ergotamine days are a subset of rescue medication days (see Section 6.3.2.2). Triptan or ergotamine days per month will be assessed as "Triptan or ergotamine days per 4 weeks" to correspond with the 4-week visit schedule. Triptan or ergotamine days per month are based on data from the previous visit to the current visit (i.e., 4-week interval) where a triptan or ergotamine day is defined as a day of efficacy data with complete reference time point date and a "yes" response to at least one of the following questions: taking triptan to treat headache or during aura; taking ergotamine to treat headache or during aura.

Triptan or Ergotamine Days per Month in the DBT Phase

Analyses are based on evaluable mITT subjects with eDiary reference time point dates in the on-DBT efficacy analysis period.

The number of triptan or ergotamine days per month in the DBT phase will be prorated to 28 days and derived as follows:

- Month (i.e., 4-week interval) in the on-DBT efficacy analysis period: 28 × (total number of triptan or ergotamine days in the month)/(total number of efficacy data days in the month). Subjects must have ≥ 14 days of efficacy data (not necessarily consecutive) in the specified month to be evaluable.

- Overall DBT mean: 28 × (total number of triptan or ergotamine days through Month 3 in the on-DBT efficacy analysis period)/(total number of efficacy data days through Month 3 in the on-DBT efficacy analysis period).

Descriptive Analyses

The number of triptan or ergotamine days per month in the DBT analysis period will be summarized descriptively as a continuous parameter (including 2-sided normal 95% CIs for mean) by treatment group in each month of the DBT phase and overall DBT mean.

Treatment Group Comparisons

A generalized linear mixed effect model will have the following variables: number of triptan or ergotamine days per month as the dependent variable; subject as a random effect; treatment group, prophylactic migraine medication use at randomization, month (i.e., months 1 to 3 of the DBT phase), and the month-by-treatment group interaction as fixed effects. The model will be repeated by prophylactic migraine medication use at randomization (yes, no). The following model estimates will be reported:

- LSM, SE, and 95% CI by month and randomization stratum (yes, no, overall) for each treatment group

- Difference in LSMs between treatment groups (rimegepant – placebo), SE, 95% CI, and p-value by randomization stratum (yes, no) for each month

- Difference in LSMs between treatment groups (rimegepant – placebo), SE, 95% CI, and p-value for each month.

- Overall LSM, SE, and 95% CI by randomization stratum (yes, no, overall) for each treatment group

- Difference in overall LSMs between treatment groups (rimegepant – placebo), SE, 95% CI, and p-value by randomization stratum (yes, no)

- Difference in overall LSMs between treatment groups (rimegepant – placebo), SE, 95% CI, and p-value.

Triptan or Ergotamine Days per Month in the OLE Phase

Analyses are based on evaluable OL rimegepant mITT subjects with eDiary reference time point dates in the on-OL rimegepant efficacy analysis period.

The number of triptan or ergotamine days per month in the OLE phase will be prorated to 28 days and derived as follows:

- Month (i.e., 4-week interval) in the on-OL rimegepant efficacy analysis period: 28 × (total number of triptan or ergotamine days in the month)/(total number of efficacy data days in the month). Subjects must have ≥ 14 days of efficacy data (not necessarily consecutive) in the specified month to be evaluable.

- Overall OL rimegepant mean: 28 × (total number of triptan or ergotamine days through Month 13 in the on-OL rimegepant efficacy analysis period)/(total number of efficacy data days through Month 13 in the on-OL rimegepant efficacy analysis period).

The number of triptan or ergotamine days per month in the OLE phase will be summarized descriptively as a continuous parameter (including 2-sided normal 95% CIs for mean) by treatment group and overall in each month of the OLE phase and overall OLE mean.

6.3.3.4   Medication Days per Month on Non-Scheduled Days in the OLE Phase

This adhoc analysis was added to the CSR and further modified for the Addendum Report.

See Section 7.6.2.3 for the definition of non-scheduled days in the OLE phase.

Rescue medication is defined as triptan, ergotamine, or other medication (see Section 6.3.2.2). On non-scheduled days, either OL rimegepant or rescue medication can be taken.

For a given medication, the number of medication days per month on non-scheduled days for the overall OL rimegepant mean is defined as: 28 × (total number of medication days on the same days as non-scheduled days through Month 13 in the on-OL rimegepant efficacy analysis period)/(total number of non-scheduled days through Month 13 in the on-OL rimegepant efficacy analysis period).

The number of medication days per month on non-scheduled days for the overall OL mean will be summarized descriptively as a continuous parameter for evaluable OL rimegepant mITT subjects by treatment group and overall for the following medications:

- Any medication: rimegepant or rescue medication

- Acute migraine medication, defined as rimegepant, triptan, or ergotamine

- Rimegepant only

- Rescue medication only

- Rimegepant and rescue medication

- Triptan or ergotamine only.

6.4 Pharmacokinetic Evaluations

No pharmacokinetic data were collected in this study.

6.5 Safety

Safety analyses will be tabulated by as-treated treatment group and overall, unless specified otherwise. Results for treated subjects on DBT will be tabulated by as-treated treatment group without overall treatment group.

Safety outcome measures will include deaths, AEs, laboratory tests, vital signs, physical measurements, electrocardiograms (ECGs), and S-STS.

Safety analysis periods are pre-treatment, pre-rimegepant treatment, on-DBT, on-OL rimegepant, on-treatment (on-DBT and on-OL rimegepant combined), on-rimegepant (DB or OL), post-DBT pre-OL rimegepant, and follow-up (see Section 7.4).

- For the blinded interim analysis in the 90-Day Safety Update, safety analysis periods of primary interest will be on-DBT, on-OL rimegepant, on-treatment, and follow-up.

- For unblinded analyses in CSRs, safety analysis periods of primary interest will be on-DBT, on-rimegepant, and follow-up.

Measurements will be slotted into analysis periods based on "measurement date", which is (1) imputed start date for AEs, (2) death date for deaths (see Section 7.3), and (3) collection or assessment date for all other safety parameters.

Select safety parameters will be summarized as continuous parameters at baseline and each scheduled visit over time in the various safety analysis periods. Measurements will be slotted into safety analysis periods and analysis windows as follows:

- For treated subjects, measurements will be first slotted into the on-DBT, on-OL rimegepant, and follow-up safety analysis periods. Next, measurements will be slotted into analysis visit windows in these analysis periods.

- For rimegepant treated subjects, measurements will be first slotted into the on-rimegepant and follow-up safety analysis periods (see Section 7.4). Next, measurements will be slotted into analysis visit windows in these analysis periods.

If a subject has multiple values in an analysis visit window in a safety analysis period, then the non-missing value in the analysis period 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. Results will also be shown at EOT for each phase, i.e., last non-missing measurement in the on-DBT, on-OL rimegepant, and on-DB or OL rimegepant safety analysis periods. Results will also be shown at end of follow-up (EOFU), i.e., last non-missing measurement in the follow-up safety analysis period.

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.

See Sections 6.2.5, 7.4, and 7.5 for the definitions of baseline, safety analysis periods, and analysis visit windows, respectively.

By-subject listings of safety data will include safety analysis period (i.e., pre-treatment, on-DBT, on-OL rimegepant, and follow-up), study day, rimegepant study day, COVID-19 visit impact code for visits impacted by COVID-19 (see Section 9.1.5.2), and are described in subsections. In addition, a by-subject listing of procedures will be provided for enrolled subjects.

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

6.5.1 Adverse Events

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

AEs will be displayed in tables and listings by SOC and PT, unless specified otherwise. AEs by SOC and PT on DBT will be displayed in descending order of rimegepant frequency within SOC and PT, unless specified otherwise. AEs by SOC and PT on OL rimegepant, on rimegepant, on treatment, and during follow-up will be displayed in descending order of overall frequency within SOC and PT, unless specified otherwise. TEAEs on DBT are those that developed, worsened, or became serious on DBT relative to pre-treatment. TEAEs on DB or OL rimegepant are those that developed, worsened, or became serious on DB or OL rimegepant relative to pre-rimegepant. TEAEs on OL rimegepant are those that developed, worsened, or became serious on OL rimegepant relative to pre-OL rimegepant.

A by-subject listing of all AEs will be provided for enrolled subjects that will flag on-DBT TEAEs and on-OL rimegepant TEAEs. Additional by-subject AE listings will be provided for SAEs, AEs leading to study drug discontinuation for treated subjects, hepatic-related AEs, and AEs of special interest (i.e., potential drug abuse AEs, CV, suicidality).

6.5.1.1 Deaths

Deaths will be identified from any of the following sources:

- AE CRF: PT or reported term containing "death", outcome of fatal, "yes" response to the question "Did the AE result in death?", or non-missing death date.

- DB Subject Status CRF: death as primary reason for phase completion/discontinuation; or death as reason for completing the DB phase through Week 12 and not entering the OL phase.

- OL Subject Status CRF: death as primary reason for phase completion/discontinuation.

- Follow-up Subject Status CRF: death as primary reason for phase completion/discontinuation.

Deaths will be tabulated by safety analysis period for enrolled subjects as follows: by treatment group for treated subjects; not treated; and overall. Counts will be displayed without percentages.

A by-subject listing of deaths will be provided for enrolled subjects, and will display all CRF sources of death, safety analysis period, death date (see Section 7.3), study day derived from the death date, rimegepant study day derived from the death date, and the following AE parameters: non-imputed start date; end date; SOC; PT; verbatim term; outcome; and response to the question "Did the AE result in death?".

6.5.1.2 AE Overviews

An AE overview without SOC and PT will present the number and percentage of subjects with any of the following AEs: any AE; mild AE; moderate AE; severe AE; AE related to study drug; SAE; SAE related to study drug; AE leading to study drug discontinuation; hepatic-related AE; severe hepatic-related AE; hepatic-related SAE; hepatic-related AE leading to study drug discontinuation; potential drug abuse AE; CV AE; and suicidality AE.

An AE overview will be produced by treatment group and overall for each the following safety analysis periods and populations:

- Pre-treatment for enrolled subjects (overall, not by treatment group)

- Pre-treatment for treated subjects

- Pre-rimegepant for DB or OL rimegepant treated subjects

- On-DBT for treated subjects (excluding overall)

- On-DBT for treated subjects limited to on-DBT TEAEs (excluding overall)

- On-DB or OL rimegepant for DB or OL rimegepant treated subjects

- On-DB or OL rimegepant for DB or OL rimegepant treated subjects limited to on-DB or OL rimegepant TEAEs

- Post-DBT pre-OL rimegepant for interim subjects

- Follow-up for follow-up subjects.

In addition, an AE overview will be produced by subgroup level and overall for all safety subgroups of interest described in Sections 6.1.3.3 and 6.1.3.4 for each the following safety analysis periods and populations:

- On-DB or OL rimegepant for DB or OL rimegepant treated subjects

- On-DB or OL rimegepant for DB or OL rimegepant treated subjects limited to on-DB or OL rimegepant TEAEs

- On-OL rimegepant for OL rimegepant treated subjects

- On-OL rimegepant for OL rimegepant treated subjects limited to on-OL rimegepant TEAEs.

6.5.1.3 Pre-Treatment AEs

Pre-treatment AEs will be summarized by SOC and PT for enrolled subjects (overall, not by treatment group) and the following endpoints:

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

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

- AEs by severity
- SAEs.

Pre-rimegepant AEs will be summarized for DB or OL rimegepant treated subjects analogously.

6.5.1.4 On-Treatment AEs

DBT Phase

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

- AEs by severity
- TEAEs by severity
- TEAEs occurring with ≥ 2% frequency on rimegepant and greater than placebo after rounding. Percentages will be displayed rounded to integers, and AEs will be displayed in alphabetical order by SOC and PT.
- AEs related to study drug by severity
- AEs related to study drug occurring with ≥ 2% frequency in any treatment group
- SAEs
- AEs leading to study drug discontinuation
- Hepatic-related AEs
- Hepatic-related AEs leading to study drug discontinuation
- Additional AEs of special interest: potential drug abuse, CV, and suicidality. Potential drug abuse AEs will be displayed in alphabetical order by severity and PT without SOC
- Exposure-adjusted multiple occurrences of unique AEs (see Section 7.6.1)
- Exposure-adjusted multiple occurrences of unique SAEs (see Section 7.6.1)

- Exposure-adjusted multiple occurrences of unique SAEs related to study drug (see Section 7.6.1)

- Exposure-adjusted multiple occurrences of unique non-SAEs occurring with ≥ 5% frequency in any treatment group (see Section 7.6.1).

AEs by severity will also be summarized analogously by subgroup level and overall for all safety subgroups of interest described in Section 6.1.3.2 for each treatment group.

DB or OL Rimegepant Phase

On-DB or OL rimegepant AEs will be summarized by SOC and PT for DB or OL rimegepant treated subjects by treatment group and overall for the same endpoints described above for the DBT phase. Data cuts (e.g., ≥ 2%) will be applied to overall, not each treatment group. Exposure-adjusted multiple occurrences of unique AEs will be presented only by overall.

In addition, on-DB or OL rimegepant AEs will be tabulated by SOC and PT for DB or OL rimegepant treated subjects by subgroup level and overall for all safety subgroups of interest described in Section 6.1.3.3 for the following endpoints:

- AEs by severity

- AEs occurring with ≥ 5% frequency by severity. The 5% cut applies only to total severity in overall (not in each subgroup level).

- TEAEs by severity

- TEAEs occurring with ≥ 2% frequency overall after rounding. Percentages will be displayed rounded to integers, and AEs will be displayed in alphabetical order by SOC and PT.

- AEs related to study drug by severity

- SAEs

- AEs leading to study drug discontinuation

- Additional AEs of special interest: hepatic-related AEs; potential drug abuse AEs, cardiovascular AEs, and suicidality AEs. Potential drug abuse AEs will be displayed in alphabetical order by severity and PT without SOC.

OLE Phase and On-Treatment Phase (90-Day Safety Update Only)

On-OL rimegepant AEs will be summarized by SOC and PT for OL rimegepant treated subjects by overall for the following endpoints:

- AEs by severity

- SAEs

- AEs leading to study drug discontinuation.

On-treatment AEs will be summarized analogously for treated subjects.

OLE Phase

On-OL rimegepant AEs will be summarized by SOC and PT for OL rimegepant treated subjects by subgroup level and overall for all safety subgroups of interest described in Section 6.1.3.4 for the following endpoints:

- AEs by severity

- AEs occurring with $\geq$ 5% frequency by severity. The 5% cut applies only to total severity in overall (not in each subgroup level).

- SAEs

- AEs leading to study drug discontinuation.

On-OL rimegepant AEs will be summarized by SOC and PT for OL rimegepant treated subjects by overall for the following endpoints (see Section 7.6.1):

- Exposure-adjusted multiple occurrences of unique AEs

- Exposure-adjusted multiple occurrences of unique SAEs

- Exposure-adjusted multiple occurrences of unique SAEs related to study drug

- Exposure-adjusted multiple occurrences of unique non-SAEs occurring with $\geq$ 5% frequency.

6.5.1.5   Follow-up AEs

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

- AEs by severity

- SAEs.

6.5.1.6   AEs Across All Study Phases Combined

AEs will be summarized by SOC and PT for treated subjects by treatment group and overall across all safety analysis periods combined for the following endpoints:

- AEs leading to study drug discontinuation

- Hepatic-related AEs leading to study drug discontinuation.

6.5.1.7   Post-DBT Pre-OL Rimegepant AEs

Post-DBT pre-OL rimegepant AEs will be summarized by SOC and PT for interim subjects by treatment group and overall for the following endpoints:

- AEs by severity

- SAEs

- AEs leading to study drug discontinuation.

6.5.2 *Laboratory Tests*

Clinical safety laboratory testing will be performed at early termination and the following visits: screening; baseline; Weeks 4, 8, and 12 of the DBT phase; and Weeks 16, 24, 48 and 64 of the OLE phase. Urinalysis will be collected at early termination and the following visits: baseline; and Weeks 24 and 64 of the OLE phase. Lipids (i.e., cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides) will be collected at early termination and the following visits: baseline; and Weeks 24 and 64 of the OLE phase. LFTs (ALT, AST, alkaline phosphatase [ALP], TBL, and direct bilirubin) will be collected routinely at early termination and the following visits: screening; pre-randomization lab visit; baseline; Weeks 2, 4, 8, and 12 of the DBT phase; Weeks 14, 16, and every 4 weeks through Week 64 of the OLE phase; and follow-up Weeks 2 and 8.

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 fasting status: fasting (i.e., fasting status of yes), not fasting (i.e., fasting status not equal to yes, including no, unknown, not reported, missing, etc.), and overall.

Estimated glomerular filtration rate (eGFR) will be derived using the modification of diet in renal disease (MDRD) formula; refer to 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 if applicable), and laboratory tests alphabetically within laboratory test group, as applicable.

By-subject listings of the following select laboratory test will be provided for enrolled subjects: hematology; serum chemistry (including eGFR derived using MDRD); urinalysis (US units only); pregnancy (US units only); endocrinology, serology, drug screen, and miscellaneous laboratory tests (US units only); and local laboratory CK fractionation. 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 enrolled subjects, which will include all results over time for those with select elevations (ALT or AST > 3 x ULN; ALP or TBL > 2 x ULN) at any time point. COVID-19 visit impact code for visits impacted by COVID-19 will be displayed for each laboratory test of clinical interest in the following listings: hematology; serum chemistry; urinalysis; pregnancy (urine tests only); and LFT values and ratios to ULN. Refer to the BHV3000 Core SAP for listing content.

6.5.2.1 *Laboratory Test Abnormalities*

Refer to the BHV3000 Core SAP for toxicity grade categories and additional details.

Worst Laboratory Test Abnormalities

The number and percentage of subjects with the worst (highest) laboratory test abnormality in a safety analysis period will be presented by treatment group (and overall if applicable) in toxicity grade categories separately for each graded laboratory test.

Worst laboratory test abnormalities will be summarized for the following safety analysis periods and populations: on-DBT for treated subjects; on-DB or OL rimegepant for DB or OL rimegepant treated subjects; post-DBT pre-OL rimegepant for interim subjects; on-OL rimegepant for OL rimegepant treated subjects by overall for the 90-Day Safety Update only; on-treatment for treated subjects by overall for the 90-Day Safety Update only; follow-up for follow-up subjects.

Worst laboratory test abnormalities will also be summarized for the following safety analysis periods and populations by subgroup level and overall for all safety subgroups of interest described in Sections 6.1.3.2, 6.1.3.3 and 6.1.3.4: on-DBT for treated subjects for each treatment group; on-DB or OL rimegepant for DB or OL rimegepant treated subjects; on-OL rimegepant for OL rimegepant treated subjects.

Laboratory Test Toxicity Grade Shifts From Baseline to Worst Abnormality

Laboratory test toxicity grade shifts from baseline to the worst (highest) toxicity grade in the safety analysis period will be summarized by treatment group (and overall if applicable) as the number and percentage of subjects in each toxicity grade category.

Shifts will be summarized for the following safety analysis periods and populations: (1) on-DBT for treated subjects, and (2) on-DB or OL rimegepant for DB or OL rimegepant treated subjects, using DB or OL rimegepant baseline instead of baseline.

Shifts will also be summarized for the following safety analysis periods and populations by subgroup level and overall for all safety subgroups of interest described in Sections 6.1.3.3 and 6.1.3.4: on-DB or OL rimegepant for DB or OL rimegepant treated subjects, using DB or OL rimegepant baseline instead of baseline; on-OL rimegepant for OL rimegepant treated subjects, using OL rimegepant baseline instead of baseline.

Laboratory Test Low/Normal/High Shifts From Baseline to any Abnormal Value

Laboratory test low/normal/high shifts from baseline to any abnormal value in the safety analysis period will be summarized by treatment group (and overall if applicable) as the number and percentage of subjects in each category for laboratory tests with normal ranges.

Shifts will be summarized for the following safety analysis periods and populations: (1) on-DBT for treated subjects, and (2) on-DB or OL rimegepant for DB or OL rimegepant treated subjects, using DB or OL rimegepant baseline instead of baseline.

Shifts will also be summarized for the following safety analysis periods and populations by subgroup level and overall for all safety subgroups of interest described in Sections 6.1.3.3 and

6.1.3.4: on-DB or OL rimegepant for DB or OL rimegepant treated subjects, using DB or OL rimegepant baseline instead of baseline; on-OL rimegepant for OL rimegepant treated subjects, using OL rimegepant baseline instead of baseline.

6.5.2.2   LFT Elevations

Subjects must have non-missing LFT data (i.e., ALT, AST, TBL, or ALP) in the safety analysis period to be included.

Refer to the BHV3000 Core SAP for additional details.

LFT Elevations

The number and percentage of subjects with pre-specified cumulative, mutually exclusive, and composite LFT elevations will be summarized by treatment group (and overall if applicable) separately for the following safety analysis periods and populations:

- Pre-treatment for treated subjects

- Pre-rimegepant treatment for DB or OL rimegepant treated subjects

- On-DBT for treated subjects (excluding overall)

- On-DB or OL rimegepant for DB or OL rimegepant treated subjects

- On-DB or OL rimegepant for DB or OL rimegepant treated subjects by subgroup level and overall for all safety subgroups of interest described in Sections 6.1.3.3

- Post-DBT pre-OL rimegepant for interim subjects

- On-OL rimegepant for OL rimegepant treated subjects by overall for the 90-Day Safety Update only

- On-OL rimegepant for OL rimegepant treated subjects by subgroup level and overall for all safety subgroups of interest described in Sections 6.1.3.4

- On-treatment for treated subjects by overall for the 90-Day Safety Update only

- Follow-up for follow-up subjects.

The following LFT elevations will be summarized for: (1) on-DBT for treated subjects, and (2) on-DB or OL rimegepant for DB or OL rimegepant treated subjects:

- Exposure-adjusted cumulative LFT elevations 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 7.6.1).

- Time to first LFT elevation with number and percentage of subjects with LFT elevations by time categories (weeks): ≤ 2, > 2 to ≤ 4, > 4 to ≤ 8, and additional 4-week intervals. LFT elevations are ALT > 3 x ULN, AST > 3 x ULN, and ALT or AST > 3 x ULN. Subjects must have an LFT elevation in the safety analysis period to be included.

LFT ULN Shifts From Baseline to Worst Elevation

LFT ULN shifts from baseline to the worst (highest) elevation in the safety analysis period will be summarized by treatment group and overall as the number and percentage of subjects in pre-specified LFT elevation categories.

Shifts will be summarized for the following safety analysis periods and populations: (1) on-DBT for treated subjects; and (2) on-DB or OL rimegepant for DB or OL rimegepant treated subjects, using rimegepant baseline instead of baseline.

Shifts will also be summarized for the following safety analysis periods and populations by subgroup level and overall for all safety subgroups of interest described in Sections 6.1.3.3 and 6.1.3.4: on-DB or OL rimegepant for DB or OL rimegepant treated subjects, using DB or OL rimegepant baseline instead of baseline; on-OL rimegepant for OL rimegepant treated subjects, using OL rimegepant baseline instead of baseline.

eDISH Scatter Plots

An evaluation of drug-induced serious hepatotoxicity (eDISH) scatter plot will display the maximum TBL ratio of value to ULN (y-axis) versus the maximum ALT ratio of value to ULN (x-axis), where both maxima will be in the same safety analysis period but not necessarily concurrent. eDISH scatter plots will be produced by treatment group for the following safety analysis periods and populations: (1) on-DBT for treated subjects; (2) on-DB or OL rimegepant for DB or OL rimegepant treated subjects.

eDISH scatter plots will also be produced for the following safety analysis periods and populations by mutually-exclusive subgroup level for all safety subgroups of interest described in Sections 6.1.3.3 and 6.1.3.4: on-DB or OL rimegepant for DB or OL rimegepant treated subjects; on-OL rimegepant for OL rimegepant treated subjects.

By-Subject Longitudinal LFT Plots

By-subject longitudinal plots will display ratios of values to ULN for AST, ALT, ALP, and TBL (y-axis) versus study week of the laboratory test result (x-axis) for treated subjects with any of the following LFT elevations in a safety analysis period (pre-treatment, on-treatment, follow-up): ALT > 3 x ULN, AST > 3 x ULN, TBL > 2 x ULN, or ALP > 2 x ULN. Study weeks are defined as study day/7, where study day is derived from the laboratory test collection date (see Section 7.5). Each figure will also display DBT and OL rimegepant dosing days using symbols along the x-axis (see Section 7.6.2), start of DBT, start of OL rimegepant, and start of the follow-up safety analysis period using vertical lines.

6.5.2.3 Laboratory Test Changes From Baseline Over Time

Values and changes from baseline in all hematology and serum chemistry laboratory tests will be summarized using descriptive statistics by treatment group and overall for treated subjects at the following time points: baseline; each scheduled visit through Week 12 and EOT of the on-DBT safety analysis period; each scheduled visit from Week 12 through EOT of the on-OL rimegepant safety analysis period; each scheduled visit and EOFU of the follow-up safety analysis period.

Values and changes from rimegepant baseline in all hematology and serum chemistry laboratory tests will be summarized analogously for DB or OL rimegepant treated subjects at the following time points: rimegepant baseline; each scheduled visit and EOT of the on-DB or OL rimegepant safety analysis period; each scheduled visit and EOFU of the follow-up safety analysis period. Note that scheduled visits vary according to laboratory test (see Section 6.5.2).

6.5.3   Vital Signs and Physical Measurements

Vital signs and physical measurements will be measured at early termination and the following visits: screening; baseline; Weeks 4, 8, and 12 of the DBT phase; Week 16 and every 4 weeks through Week 64 of the OLE phase; and follow-up Week 2.

Vital signs will include systolic blood pressure, diastolic blood pressure, heart rate, temperature, and respiratory rate. In summaries, only vital signs measured in the sitting position will be included. Physical measurements will include weight and BMI.

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

6.5.3.1   Vital Sign and Physical Measurement Changes From Baseline Over Time

Values and changes from baseline in vital sign and physical measurement parameters will be summarized as continuous parameters by treatment group and overall for treated subjects at the following time points: baseline; Weeks 4, 8, 12, and EOT of the on-DBT safety analysis period; Week 16, every 4 weeks through Week 64, and EOT of the on-OL rimegepant safety analysis period; follow-up Week 2 and EOFU of the follow-up safety analysis period.

Values and changes from rimegepant baseline in vital sign and physical measurement parameters will be summarized analogously for DB or OL rimegepant treated subjects at the following time points: rimegepant baseline; Week 4, every 4 weeks through Week 64, and EOT of the on-DB or OL rimegepant safety analysis period; follow-up Week 2 and EOFU of the follow-up safety analysis period.

6.5.3.2   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 prespecified categories defined in the BHV3000 Core SAP.

Abnormalities will be summarized for the following safety analysis periods and populations: (1) on-DBT for treated subjects; (2) on-DB or OL rimegepant for DB or OL rimegepant treated subjects, using DB or OL rimegepant baseline instead of baseline for weight change; and (3) follow-up for follow-up subjects.

Abnormalities will also be summarized for the following safety analysis periods and populations by subgroup level and overall for all safety subgroups of interest described in Sections 6.1.3.3 and 6.1.3.4: on-DB or OL rimegepant for DB or OL rimegepant treated subjects, using DB or OL

rimegepant baseline instead of baseline for weight change; on-OL rimegepant for OL rimegepant treated subjects, using OL rimegepant baseline instead of baseline for weight change.

6.5.4 Electrocardiograms

ECGs will be measured at early termination and the following visits: screening; baseline; Week 4 of the DBT phase; and Weeks 16, 24, 48, and 64 of the OLE phase; and follow-up Week 2. ECG parameters will include RR, QRS, PR, QT, QTcF, QTcB, and ventricular heart rate.

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

6.5.4.1 ECG Changes From Baseline Over Time

Values and changes from baseline in ECG parameters will be summarized as continuous parameters by treatment group and overall for treated subjects at the following time points: baseline; Week 4 and EOT of the on-DBT safety analysis period; Weeks 16, 24, 48, 64 and EOT of the on-OL rimegepant safety analysis period; follow-up Week 2 and EOFU of the follow-up safety analysis period.

Values and changes from rimegepant baseline in ECG parameters will be summarized analogously for DB or OL rimegepant treated subjects at the following time points: rimegepant baseline; Weeks 4, 16, 24, 48, 64, and EOT of the on-DB or OL rimegepant safety analysis period; follow-up Week 2 and EOFU of the follow-up safety analysis period.

6.5.4.2 ECG Interpretation Shifts From Baseline to Worst Category

The shift from baseline to worst ECG interpretation in safety analysis periods will be summarized by treatment group and overall as the number and percentage of subjects with normal, abnormal, and clinically significant abnormal interpretations.

Shifts will be summarized for the following safety analysis periods and populations: (1) on-DBT for treated subjects; and (2) on-DB or OL rimegepant for DB or OL rimegepant treated subjects, using DB or OL rimegepant baseline instead of baseline.

Shifts will also be summarized for the following safety analysis periods and populations by subgroup level and overall for all safety subgroups of interest described in Sections 6.1.3.3 and 6.1.3.4: on-DB or OL rimegepant for DB or OL rimegepant treated subjects, using DB or OL rimegepant baseline instead of baseline; on-OL rimegepant for OL rimegepant treated subjects, using OL rimegepant baseline instead of baseline.

6.5.4.3 ECG Abnormalities

ECG abnormalities in safety analysis periods will be summarized by treatment group and overall as the number and percentage of subjects in prespecified categories defined in the BHV3000 Core SAP.

Abnormalities will be summarized for the following safety analysis periods and populations: (1) on-DBT for treated subjects, (2) on-DB or OL rimegepant for DB or OL rimegepant treated subjects, and (3) follow-up for follow-up subjects.

Abnormalities will also be summarized for the following safety analysis periods and populations by subgroup level and overall for all safety subgroups of interest described in Sections 6.1.3.3 and 6.1.3.4: on-DB or OL rimegepant for DB or OL rimegepant treated subjects, using DB or OL rimegepant baseline instead of baseline; on-OL rimegepant for OL rimegepant treated subjects, using OL rimegepant baseline instead of baseline.

ECG abnormalities will be summarized together with vital sign and physical measurement abnormalities in the same tables (see Section 6.5.3.2).

6.5.5 Sheehan-Suicidality Tracking Scale

The S-STS is a prospective rating scale that contains 16 patient-reported questions and 6 clinician-reported questions to track both treatment-emergent suicidal ideation and behaviors. The S-STS will be assessed at early termination and the following visits: screening; baseline; Weeks 2, 4, 8, and 12 of the DBT phase; Weeks 14, 16, and every 4 weeks through Week 64 of the OLE phase; and follow-up Weeks 2 and 8.

S-STS scores are calculated as described in the BHV3000 Core SAP.

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.

In addition, 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 will also be presented by treatment group and overall for the ideation subscale, behavior subscale, and total score.

S-STS scores, worst score changes from baseline, and worst score change categories from baseline will be summarized for the following safety analysis periods and populations: (1) on-DBT for treated subjects; (2) on-DB or OL rimegepant for DB or OL rimegepant treated subjects, using DB or OL rimegepant baseline instead of baseline; and (3) follow-up for follow-up subjects.

A by-subject listing of the S-STS will be provided for enrolled subjects. Refer to the BHV3000 Core SAP for the listing content.

6.6 Outcomes Research

Analyses will be based on as-treated treatment group.

OR (non-safety) questionnaires and rating scales are MSQoL, MIDAS, CGI-c, PoM, and SM (see Section 2.3.3). These will be assessed at early termination and the following visits: baseline

(MSQoL and MIDAS only), Week 12 of the DBT phase, and Weeks 24 and 64 of the OLE phase.

Measurements will be slotted into analysis periods according to assessment dates.

OR endpoints will be summarized descriptively over time. For treated subjects, measurements will be first slotted into the DBT OR and OL rimegepant OR analysis periods. Next, measurements will be slotted into analysis visit windows in these analysis periods. If a subject has multiple values in an analysis visit window in an analysis period, then the non-missing value in the analysis period closest to the target date for the visit will be used; in the case of a tie, the latest value collected will be used. Results will also be shown at the "last visit" in each phase, i.e., last non-missing measurement in the DBT OR and OL rimegepant OR analysis periods, regardless of the analysis visit window.

See Sections 6.2.5, 7.4, and 7.5 for definitions of baseline, OR analysis periods, and analysis visit windows, respectively.

By-subject listings of OR questionnaires and rating scales (i.e., MSQoL, MIDAS, CGI-c, PoM, and SM) will be provided for enrolled subjects, and will include analysis period (pre-treatment, DBT OR, OL rimegepant OR), individual components, and COVID-19 visit impact code for visits impacted by COVID-19 (see Section 9.1.5.2). Refer to the BHV3000 Core SAP for the contents of the MSQoL and MIDAS listings.

6.6.1 MSQoL

See Section 6.3.2.3 for the description of the MSQoL.

Descriptive Analyses

Values and changes from baseline in transformed scores for each domain will be summarized as continuous parameters (including 2-sided normal 95% CIs for mean change) by treatment group and overall for treated subjects at the following time points: baseline; Weeks 4, 12 and last visit of the DBT OR analysis period; and Weeks 24, 64, and last visit of the OL rimegepant OR analysis period.

Treatment Group Comparisons

This adhoc analysis was added to the CSR.

Analyses are based on treated subjects with MSQoL domain scores at both baseline and Week 12 of the DBT OR analysis period. For each MSQoL domain, the score change from baseline at Week 12 between treatment groups is compared using the same methodology as described in Section 6.3.2.3.

6.6.2 MIDAS

See Section 6.3.2.4 for the description of the MIDAS.

Descriptive Analyses

Values and changes from baseline in the total, absenteeism, presenteeism, and item scores will be summarized as continuous parameters (including 2-sided normal 95% CIs for mean change) by treatment group and overall for treated subjects at the following time points: baseline; Week 12 and last visit of the DBT OR analysis period; and Weeks 24, 64, and last visit of the OL rimegepant OR analysis period.

Treatment Group Comparisons

This adhoc analysis was added to the CSR.

Analyses are based on treated subjects with MIDAS scores at both baseline and Week 12 of the DBT OR analysis period. For each MIDAS score (total, absenteeism, presenteeism), the score change from baseline at Week 12 between treatment groups is compared using the same methodology as described Section 6.3.2.4.

6.6.3 CGI-c Scale

The 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, and very much worse.

The number and percentage of treated subjects in each category (including combined categories) will be presented by treatment group and overall at the following time points: Week 12 and last visit of the DBT OR analysis period; and Weeks 24, 64, and last visit of the OL rimegepant OR analysis period. Percentages for categories will be based on subjects with non-missing data at each visit along with 2-sided Agresti-Coull 95% CIs for each percentage. Refer to the BHV3000 Core SAP for combined categories.

6.6.4 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 using the eDiary. 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; and much worse, I prefer my previous medication.

The number and percentage of treated subjects with PoM data and in each category (including combined categories) will be presented by treatment group and overall at the following time points: Week 12 and last visit of the DBT OR analysis period; and Weeks 24, 64 and last visit of the OL rimegepant OR analysis period. Percentages for categories will be based on subjects with non-missing data at each visit, along with 2-sided Agresti-Coull 95% CIs for each percentage. Refer to the BHV3000 Core SAP for combined categories.

6.6.5 SM

The SM is a 7-point rating scale that measures the patient's satisfaction with study medication to treat migraines using the eDiary. The 7 satisfaction categories are: completely satisfied, could not be better; very satisfied; somewhat satisfied; neither satisfied nor dissatisfied; somewhat dissatisfied; very dissatisfied; and completely dissatisfied, could not be worse.

The number and percentage of treated subjects with survey data in each category (including combined categories) will be presented by treatment group and overall at the following time points: Week 12 and last visit of the DBT OR analysis period; and Weeks 24, 64, and last visit of the OL rimegepant OR analysis period. Percentages for categories will be based on subjects with non-missing data at each visit along with 2-sided Agresti-Coull 95% CIs for each percentage. Refer to the BHV3000 Core SAP for combined categories.

6.7 COVID-19 Impact

COVID-19 impact will be assessed by treatment group and overall only for the combined population sample of OL rimegepant treated or follow-up subjects. Analyses are based on COVID-19 visit impact data with non-missing COVID-19 visit dates (see Section 7.3).

Measurements will be slotted into safety analysis periods according to COVID-19 visit dates.

When COVID-19 visit impact is summarized descriptively over time, measurements will be first slotted into safety analysis periods. Next, measurements will be slotted into analysis visits in these analysis periods (see Section 7.5).

6.7.1 COVID-19 Overall Impact

COVID-19 overall impact will be tabulated as the number and percentage of subjects in the categories defined by COVID-19 visit impact type, visit impact characteristics, and visit impact relationship (see Section 9.1.1). In addition, for each of the 3 COVID-19 visit impact type categories (i.e., missed visit; in-person visit at site; remote visit), the number and percentage of subjects in the following subcategories defined by the number of visits impacted by COVID-19 will be tabulated: ≥ 2 visits, ≥ 3 visits, ≥ 4 visits, etc. Visit counts are based on unique COVID-19 visit dates. Percentages are based on subjects with ≥ 1 visit with non-missing COVID-19 visit impact in the on-OL rimegepant or follow-up safety analysis period (see Section 9.1.3).

6.7.2 COVID-19 Impact Over Time

COVID-19 visit impact will be tabulated over time at each analysis visit. The number and percentage of subjects in the categories defined by COVID-19 visit impact type, visit impact characteristics, and visit impact relationship will be presented at each analysis visit in the on-OL rimegepant and follow-up safety analysis periods. If a subject has multiple values (e.g., scheduled missed visit and unscheduled remote visit) in an analysis visit window, then all results will be presented. Percentages are based on subjects with ≥ 1 non-missing COVID-19 visit impact in the analysis visit window (see Section 9.1.3).

Missing LFT data impacted by COVID-19 will be tabulated over time at each analysis visit in the on-OL rimegepant and follow-up safety analysis periods as the number and percentage of subjects in the following categories:

1. Missing LFT data, defined as missing values for all of the 4 following LFTs in the analysis visit window: ALT, AST, ALP, and TBL.

2. Missing LFT data at visits impacted by COVID-19, i.e., meeting criteria (1) and having ≥ 1 visit impacted by COVID-19 in the analysis visit window (see Section 9.1.3)

3. Missing LFT data at missed visits due to COVID-19, i.e., meeting criteria (1), (2), and having ≥ 1 missed visit in the analysis visit window (see Section 9.1.1).

Percentages are based on evaluable subjects at each analysis visit. At an analysis visit in the on-OL rimegepant safety analysis period, evaluable subjects are OL rimegepant treated subjects with (OL rimegepant end date – study drug start date + 1) $\geq$ lower bound of the analysis visit window. At an analysis visit in the follow-up safety analysis period, evaluable subjects are follow-up subjects with (last contact date – study drug last date + 1) $\geq$ lower bound of the analysis visit window.

6.7.3   COVID-19 Impact Listings

A by-subject listing of COVID-19 impact codes by visit will display visits with abbreviated labels (e.g., W36 = OL rimegepant Week 36; FU2 = Follow-up Week 2) in separate columns. Spanning headers above the visits display the safety analysis period (OL rimegepant or follow-up). Each column denotes an analysis visit and displays the COVID-19 visit impact code (see Section 9.1.5.1). If a subject has multiple COVID-19 visit impact codes in an analysis visit window, then results are displayed sorted by COVID-19 visit date and comma-concatenated across all COVID-19 visit dates in the analysis visit window (e.g., "#U,&M1" if "#U" has a visit date of 01MAY2020 and "&M1" has a visit date of 10MAY2020). Footnotes will describe the abbreviations in the COVID-19 visit impact code (see Section 9.1.5.2).

A by-subject listing of COVID-19 visit impact will display analysis period, analysis visit, COVID-19 visit date, study day derived from COVID-19 visit date, rimegepant study day derived from COVID-19 visit date, visit impact status, visit type, visit impact type, visit impact characteristics, visit impact relationship with specify text, and premature study termination (see Section 9.1.1).

7   CONVENTIONS

7.1   General

7.1.1   Output Layout

Refer to the BHV3000 Core SAP for TLF layout conventions.

For the CSR and Addendum Report, a list of TLFs and unique TLF templates will be provided in the corresponding Mock TLF documents.

For the 90-Day Safety Update, a list of TLFs will be provided in the 90-Day Safety Update List of Deliverables, which will cross-reference (but not display) TLF templates in the Mock TLF CSR document. Output will be by overall, not treatment group.

7.1.2   Duplicate Subjects

Duplicate subjects are those who enrolled in a previous BHV3000 study or rescreened more than once in study BHV3000-305 (either as per protocol or due to non-compliance), and are assigned more than 1 subject identifier in the BHV3000 project. These subjects will be identified from the (1) Demographics CRF which captures the previous BHV3000 subject identifier, and (2) Rescreen CRF which captures the previous BHV3000-305 subject identifier. The following conventions will apply:

- The unique subject identifier will be derived from the protocol number, site number, and subject number corresponding to the first randomization or treatment across all BHV3000 studies in which the subject enrolled. Otherwise, the unique subject identifier will be derived from the subject identifier.
- The raw datasets will contain data from all BHV3000-305 subject identifiers, with the unique subject identifier populated across records.
- The analysis datasets will contain data as follows:
  - If the subject was randomized or treated more than once in study BHV3000-305, then data from all subject identifiers corresponding to randomization or treatment in study BHV3000-305 will be included.
  - If the subject was randomized or treated only once in study BHV3000-305, then only data from the subject identifier corresponding to randomization or treatment in study BHV3000-305 will be included.
  - If the subject was not randomized or treated in study BHV3000-305, then only data from the subject identifier corresponding to the last enrollment in study BHV3000-305 will be included.
  - The unique subject identifier and previous BHV3000-305 subject identifier will be populated across records.
- By-subject listings will display subject identifier, but not unique subject identifier.

7.2   Subgroups

Not applicable.

7.3   Derived Dates

Derived dates for defining analysis periods are defined as follows:

- eDiary reference time/point date/time: See Section 7.6.2.1.

- eDiary dosing dates:

  ○ Study drug to treat headache or during aura date/time: Complete reference time point date/time from any of the following date/time questions: study medication to treat headache or during aura from the evening report headache log or follow-up headache log; additional study medication to treat headache or during aura from the evening report headache log.

  ○ Imputed OL rimegepant to treat headache date/time: Complete reference time point date/time from "yes" response to question about having already taken study medication to treat headache from the scheduled dosing report. Derived only if both of the following criteria are met:

    ▪ Reference time point date/time on or after the IWRS Week 12 kit assigned local date/time

    ▪ There are no complete reference time point dates on the same day as the "yes" response from any of the following questions: study medication to treat headache or during aura date/time from the evening report headache log or follow-up headache log; additional study medication to treat headache or during aura date/time from the evening report headache log; date of missed scheduled dosing report or evening report headache log from the medication reconciliation form; study medication date/time from the scheduled dosing report.

  ○ Study drug date/time: Study drug to treat headache or during aura date/time, imputed OL rimegepant to treat headache date/time, or complete reference time point date/time from any of the following questions: date of missed scheduled dosing report or evening report headache log from the medication reconciliation form (note that time is not collected); study medication date/time from the scheduled dosing report.

    ▪ DBT: Reference time point date/time before the IWRS Week 12 kit assigned local date/time (reference time point date before the IWRS Week 12 kit assigned local date for medication reconciliation form data) or the IWRS Week 12 kit assigned local date/time missing

    ▪ OL rimegepant: Reference time point date/time on or after the IWRS Week 12 kit assigned local date/time (reference time point date on or after the IWRS Week 12 kit assigned local date for medication reconciliation form data)

  ○ Study drug start date/time: Earliest study drug date/time.

  ○ Study drug end date/time: Latest study drug date/time.

  ○ Study drug last date/time:

    ▪ Interim database lock: Study drug end date/time date derived only for subjects who have either (1) non-missing DB completion status on the DB Subject Status CRF, not continuing to OL on the DB Subject Status CRF, and missing OL rimegepant start date/time, or (2) non-missing OL completion status on the OL Subject Status CRF.

    ▪ Final database lock: Study drug end date/time.

- ○ DBT start date/time: Earliest DBT study drug date/time. This should be equal to study drug start date/time.

- ○ DBT end date/time: Latest DBT study drug date/time.

- ○ DBT last date/time:

  - ▪ Interim database lock or snapshot prior to Week 12 Interim Analysis database lock: DBT end date/time date derived only for subjects with non-missing DB study completion status on DB Subject Status CRF.

  - ▪ Database locks at or after Week 12 Interim Analysis database lock: DBT end date/time.

- ○ OL rimegepant start date/time: Earliest OL rimegepant study drug date/time.

- ○ OL rimegepant end date/time: Latest OL rimegepant study drug date/time.

- ○ OL rimegepant last date/time:

  - ▪ Database lock or snapshot prior to final database lock: OL rimegepant end date/time date derived only for subjects with non-missing OL study completion status on OL Subject Status CRF or non-missing follow-up study completion status on the Follow-up Subject Status CRF.

  - ▪ Final database lock: OL rimegepant end date/time.

- ○ DB or OL rimegepant start date/time: Study drug start date/time for subjects whose as-treated treatment group is rimegepant; OL rimegepant start date/time for subjects whose as-treated treatment group is placebo.

- ○ DB or OL rimegepant end date/time: Study drug end date/time for subjects whose as-treated treatment group is rimegepant; OL rimegepant end date/time for subjects whose as-treated treatment group is placebo.

- ○ DB or OL rimegepant last dose date/time: Study drug last date/time for subjects whose as-treated treatment group is rimegepant; OL rimegepant last date/time for subjects whose as-treated treatment group is placebo.

- Other eDiary dates:

  - ○ Headache start date/time: Complete reference time point date/time from the headache start question from the evening report headache log.

  - ○ Headache end date/time: Complete reference time point date/time from the headache end question from the evening report headache log or follow-up headache log.

  - ○ Efficacy date: (1) Complete reference time point date from any question from the evening report headache log or follow-up headache log, or (2) non-missing OL rimegepant date on a non-scheduled day (see Sections 7.6.2.2 and 7.6.2.3).

  - ○ OP start date: Earliest reference time point date from the OP epoch.

  - ○ OP end date: Latest reference time point date from the OP epoch.

- Miscellaneous composite dates

○ Last DBT visit date: Maximum of the following: (1) latest eDiary reference time point date < OL rimegepant start date; (2) latest complete visit date from Visit Date CRF records without "follow-up" in foldername and visit date < OL rimegepant start date. This will be used to assess eDiary compliance.

○ Last OLE visit date: Maximum of the following: (1) latest eDiary reference time point date ≥ OL rimegepant start date; (2) latest complete visit date from Visit Date CRF records without "follow-up" in foldername and visit date ≥ OL rimegepant start date. This will be used to assess eDiary compliance.

○ Last DB or OL rimegepant visit date: Maximum of last DBT visit date and last OLE visit date for subjects whose as-treated treatment group is rimegepant; last OLE visit date/time for subjects whose as-treated treatment group is placebo. This will be used to assess eDiary compliance.

○ Last contact date: (1) Earliest complete death date from the AE CRF, if it exists; (2) otherwise, the maximum complete date of the following: AE start/stop; COVID-19 visit only for in-person or remote visits; ECG; eDiary reference time point; informed consent; IWRS randomization; laboratory collection; menstrual period start/stop; non-study medication start/stop; physical measurement; procedure; rating scale; questionnaire; study completion/discontinuation from Subject Status CRF (DBT, OLE, follow-up); vital sign; visit.

- COVID-19 visit date: (1) Complete record date, if it exists; otherwise, complete date the visit was planned to occur for a missed visit (see Section 9.1.1).

- Death date: Last contact date derived only for subjects who died (see Section 6.5.1.1).

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

See Section 7.6.2.1 for the reference time point date/time and epoch derivations.

7.4 Analysis Periods

Analysis periods are defined as follows:

- eDiary efficacy endpoints (migraine days, rescue medication days), based on the date part of derived date/times

  ○ OP: Reference time point date in the OP epoch (see Section 7.6.2.1).

  ○ On-DBT efficacy: Reference time point date in the DBT epoch on or before the DBT last date + 1 day. This period is used to assess efficacy during the DBT phase.

  ○ Post-DBT pre-OL rimegepant efficacy: Reference time point date in the DBT epoch after the DBT last date + 1 day. This period is used only in eDiary efficacy listings.

  ○ On-OL rimegepant efficacy: Reference time point date in the OLE epoch on or before the OL rimegepant last date + 1 day. This period is used to assess efficacy during the OLE phase.

    ○ Follow-up efficacy: Reference time point date in the OLE epoch after the OL rimegepant last date + 1 day. This period is used only in eDiary efficacy listings.

- OR efficacy endpoints (MSQoL, MIDAS)

    ○ On-DBT efficacy: Measurement date after the DBT start date through the earlier of (1) DBT last date + 1 day and (2) OL rimegepant start date. This period is used to assess OR efficacy during the DBT phase for evaluable mITT subjects.

- Pre-treatment characteristics and safety endpoints

    ○ Pre-treatment: Measurement date/time on or before the study drug start date/time. Note that AEs with imputed start date equal to the study drug start date are **not** part of this period (refer to the BHV3000 Core SAP for AE start date imputation). This period is used to derive baseline values and to assess pre-treatment safety endpoints.

    ○ Pre-rimegepant: Measurement date/time on or before the DB or OL rimegepant start date/time. Note that AEs with imputed start date equal to the DB or OL rimegepant start date are **not** part of this period. This period is used to derive rimegepant baseline values and to assess pre-rimegepant safety endpoints for DB or OL rimegepant treated subjects.

    ○ On-DBT safety: Measurement date/time after the DBT start date/time through the earlier of DBT last date + 7 days and OL rimegepant start date/time. Note that AEs with imputed start date equal to the DBT start date are part of this period, while AEs with imputed start date equal to the OL rimegepant start date are **not** part of this period. This period is used to assess safety endpoints on DBT.

    ○ Post-DBT pre-OL rimegepant safety: Measurement date/time after the DBT last date + 7 days through the OL rimegepant start date/time. Note that AEs with imputed start date equal to the OL rimegepant start date are **not** part of this period. This period is used in safety listings to distinguish measurements, and to assess safety endpoints during the interim period (i.e., post-DBT pre-OL rimegepant) for interim subjects (i.e., those with > 7-day gap between DBT last date and OL rimegepant start date).

    ○ On-OL rimegepant safety: Measurement date/time after the OL rimegepant start date/time through the study drug last date + 7 days. Note that AEs with imputed start date equal to the OL rimegepant start date are part of this period. This period is used in safety listings to distinguish measurements, and to assess safety endpoints for OL rimegepant treated subjects in the blinded 90-Day Safety Update.

    ○ On-DB or OL rimegepant safety: Measurement date/time after the DB or OL rimegepant start date/time through the DB or OL rimegepant last date + 7 days. Note that AEs with imputed start date equal to the DB or OL rimegepant start date are part of this period. This period is used to assess safety endpoints on DB or OL rimegepant treatment for DB or OL rimegepant treated subjects.

    ○ On-treatment safety: Measurement date/time after the study drug start date/time through the study drug last date + 7 days. Note that AEs with imputed start date equal to the study drug start date are part of this period. This period is the on-DBT and on-OL rimegepant safety periods combined, and will be used to assess safety endpoints for treated subjects in the blinded 90-Day Safety Update.

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

- Non-efficacy OR endpoints (see Section 6.6)

  ○ DBT OR: Measurement date after the DBT start date to the OL rimegepant start date. This period is used to assess OR during the DBT phase.

  ○ OL rimegepant OR: Measurement date after the OL rimegepant start date. This period is used to assess OR during the OLE phase.

See Section 7.3 for derived dates for determining analysis periods.

If measurement time is missing or not collected for a parameter, then the measurement date will be compared to the derived date.

7.5   Analysis Visit Windows

Refer to BHV3000-305 Protocol Section 4.3 (Tables 1 and 2) for the schedule of assessments.

Randomization days are calculated from randomization as follows:

- Measurement date – IWRS randomization date + 1, if measurement date ≥ IWRS randomization date

- Measurement date – IWRS randomization date, if measurement date < IWRS randomization date.

Study days are calculated from study drug start as follows:

- Measurement date – study drug start date + 1, if measurement date ≥ study drug start date

- Measurement date – study drug start date, if measurement date < study drug start date.

Rimegepant study days are calculated from DB or OL rimegepant start as follows:

- Measurement date – DB or OL rimegepant start date + 1, if measurement date ≥ DB or OL rimegepant start date

- Measurement date – DB or OL rimegepant start date, if measurement date < DB or OL rimegepant start date.

Follow-up days are calculated from the study drug last as follows:

- Measurement date – study drug last date + 1, if measurement date/time ≥ study drug last date

- Measurement date – study drug last date, if measurement date < study drug last date.

Analysis visit windows presented in Table 4 below are based on study days (see Section 7.4).

Table 4:   Analysis Visit Windows for Non-Efficacy Endpoints

Analysis Period / Analysis Visit	Abbreviation in Listings	Analysis Day / Analysis Visit Window	Target Day
Pre-Treatment	**PRETRT**	**Randomization Day**	
Screening		≤ -7 or missing	
Pre-Randomization	Prerand	-6 to -1	
Randomization	Rand	1	
Post-Randomization	Postrand	≥ 2	
OR/On-Treatment Safety *	**OR: DBT or OLRMG** **Safety: DBT, INT, or OLRMG**	**Study Day**	
Week 2		1 to 21	14
Week 4		22 to 42	28
Week 8		43 to 70	56
Week 12		71 to 91	84
Week 14		92 to 105	98
Week 16		106 to 126	112
Week 20		127 to 154	140
Week 24		155 to 182	168
Week 28		183 to 210	196
Week 32		211 to 238	224
Week 36		239 to 266	252
Week 40		267 to 294	280
Week 44		295 to 322	308
Week 48		323 to 350	336
Week 52		351 to 378	364
Week 56		379 to 406	392
Week 60		407 to 434	420
Week 64		435 to 462	448
Extension #	Ext	≥ 463	476
Follow-up Safety	**FU**	**Follow-up Day**	
Follow-up Week 2	FU Week 2	8 to 21	14
Follow-up Week 8	FU Week 8	22 to 70	56
Follow-up Extension #	FU Ext	≥ 71	84

* OR includes the DBT and OL rimegepant OR analysis periods; on-treatment safety includes the DBT, interim, and OL rimegepant safety analysis periods.
# Denotes an extended visit in the analysis period and is displayed only in listings

Study days are used to define analysis visit windows in all analysis periods except on-rimegepant and follow-up safety. Rimegepant study days are used to define analysis visit windows in the on-DB or OL rimegepant safety analysis period. Follow-up days are used to define analysis visit windows in the follow-up safety analysis period.

Analysis visit windows in the on-DB or OL rimegepant safety analysis period are defined analogously to those in the on-treatment safety analysis period.

7.6   Domain-Specific Derivations

7.6.1   Adverse Events

Refer to the BHV3000 Core SAP for exposure-adjusted multiple occurrences of unique AEs.

Exposure-adjusted multiple occurrences of unique AE calculations will be based on the following reference dates according to safety analysis period:

- On-DBT: reference start date is DBT start date, reference end date is DBT end date, and reference last date is earlier of (1) DBT last date + 7 days and (2) OL rimegepant start date – 1 day.

- On-OL rimegepant: reference start date is OL rimegepant start date, reference end date is OL rimegepant end date, and reference last date is OL rimegepant last date + 7 days.

- On-DB or OL rimegepant: reference start date is DB or OL rimegepant start date, reference end date is DB or OL rimegepant end date, and reference last date is DB or OL rimegepant last date + 7 days.

- On-treatment: reference start date is the study drug start date, reference end date is study drug end date, and reference last date is study drug last date + 7 days.

7.6.2   eDiary

7.6.2.1   eDiary Reference Time Point Date and Epoch
Reference Time Point Date Derivation

Reference time point date/time and epoch will only be derived for records with non-missing standard format character result/finding values.

- Evening report headache log

  o Select headache-related characteristics and non-study medication parameters with the same finding date/time: The reference time point date/time will be set to the headache start date/time, if not missing.

    ▪ Parameters will include the following: headache (yes, no); headache start date/time; aura only event (yes, no); headache last at least 30 minutes (yes, no); severity (none, mild, moderate, severe); unilateral (yes, no); pulsate (yes, no); worsen or avoid physical activity (yes, no); nausea (yes, no); vomiting (yes, no); photophobia (yes,

no); phonophobia (yes, no); aura (yes, no); triptan (yes, no); ergotamine (yes, no); other medication (yes, no).

- o Headache end date/time and headache end (ended, still continuing) parameters with the same finding date/time: The reference time point date/time will be set to headache end date/time, if the headache end date/time is not missing.

- o Study medication for headache or aura parameters with the same finding date/time: The reference time point date/time will be set to the study medication for headache or aura date/time, if not missing.

  - ▪ Parameters will include the following: study medication for headache or aura (yes, no); study medication for headache or aura date/time; number of tablets taken; confirm number of tablets taken (yes, no).

- o Additional study medication for headache or aura parameters with the same finding date/time: The reference time point date/time will be set to additional study medication for headache date/time, if not missing.

  - ▪ Parameters will include the following: additional study medication for headache (yes, no); additional study medication for headache or aura date/time; number of additional tablets taken; confirm number of additional tablets taken (yes, no).

- Follow-up headache log

  - o Headache end date/time and headache continuing (yes, no) parameters with the same finding date/time: The reference time point date/time will be set to headache end date/time, if not missing.

  - o Non-study medication triptan and ergotamine parameters: The reference time point date/time will be set to the last non-missing headache start date/time from evening report headache logs with finding date/time ≤ 24 hours at or before the follow-up headache log finding date/time.

  - o Study medication for headache parameters with the same finding date/time: The reference time point date/time will be set to the study medication for headache or aura date/time, if not missing.

    - ▪ Parameters will include the following: study medication for headache or aura (yes, no); study medication for headache or aura date/time; number of tablets taken; confirm number of tablets taken (yes, no).

- Scheduled dosing report parameters with the same finding date/time: The reference time point date/time will be set to the study medication date/time, if not missing.

- ▪ Parameters will include the following: took study medication today (yes, no); study medication date/time; number of tablets taken; confirm number of tablets taken (yes, no).

- Medication reconciliation form date missed and number of tablets taken parameters with the same finding date/time: The reference time point date/time will be set to the date missed, if not missing. Note that time will be missing.

Otherwise, the reference time point date/time will be set to the eDiary finding date/time.

Epoch Derivation

Epoch is defined based on the date part of derived date/times, as follows:

- OP: Reference time point date before the DBT start date or DBT start date missing

- DBT: (1) Reference time point date on or after the DBT start date and before the OL rimegepant start date, or (2) reference time point date on or after the DBT start date, if OL rimegepant start date missing

- OLE: Reference time point date on or after the OL rimegepant start date.

7.6.2.2   eDiary Migraine Days

For migraine day analyses, a day of efficacy data is defined as any non-missing eDiary efficacy date (see Section 7.3).

A migraine day is defined as a day of efficacy data with either (1) or (2):

1) Qualified migraine headache based on the following criteria per BHV3000-305 Protocol Appendix 3:

   o "Yes" response to the question about having a headache# with complete reference time point date/time#, or non-missing headache start date/time# (see Section 7.3)

   o Lasting for ≥ 30 minutes, defined as any of the following:

     ▪ "Yes" response to the question about the headache lasting ≥ 30 minutes#

     ▪ Headache end date/time# – headache start date/time# ≥ 30 minutes, where headache end date/time and headache start date/time have the same finding date/time

     ▪ Finding date/time# – headache start date/time# ≥ 30 minutes and headache end status is still continuing#, where headache start date/time and headache end status have the same finding date/time

     ▪ Headache end date/time@ – headache start date/time# ≥ 30 minutes, where headache end date/time is from the follow-up headache log with earliest finding date/time ≤ 24 hours on or after the finding date/time of a still continuing headache from the evening report headache log

   o Meeting at least one of the following criteria (a or b):

   a. ≥ 2 of the following pain features based on "yes" response to questions with the same finding date/time:

   i. Unilateral location#,

   ii. Pulsating quality (throbbing)#,

   iii. Moderate or severe pain intensity#

   iv. Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)#

   b. ≥ 1 of the following associated symptoms based on "yes" response to questions with the same finding date/time:

   i. Nausea#

   ii. Vomiting#

   iii. Both photophobia# and phonophobia#

2) No qualified migraine headache but meeting either of the following criteria:

   a. Non-missing date/time of (1) study drug to treat headache or during aura#@ during the on-DBT efficacy analysis period, or (2) OL rimegepant on a non-scheduled day during the on-OL rimegepant efficacy analysis period (see Sections 7.3 and 7.6.2.3).

   b. "Yes" response to the question about taking triptan to treat headache or during aura #@ or question about taking ergotamine to treat headache or during aura #@, along with complete reference time point date/time#@, in the on-DBT efficacy or on-OL rimegepant efficacy analysis period.

Date/time parameters and questions marked with "#" are identified from the evening report headache log. Date/time parameters and questions marked with "@" are identified from the follow-up headache log.

Migraine dates are determined from complete reference date/times based on eDiary parameters above.

Only unique days of efficacy data are included in analyses. If there are multiple responses on the same day, then the most severe migraine will be chosen.

7.6.2.3   *Scheduled and Non-Scheduled Days in the OLE Phase*

All days in the on-OL rimegepant efficacy analysis period are classified as either scheduled or non-scheduled days. Scheduled days are defined as days in the planned EOD dosing schedule. All other days are considered to be non-scheduled days.

For each OL rimegepant treated subject, the initial planned EOD dosing schedule pattern is classified as even or odd with respect to the OL rimegepant start date as follows:

- Calculate planned OL rimegepant day = scheduled report date – OL rimegepant start date for each scheduled report date in the on-OL rimegepant efficacy analysis period.

- o A scheduled report date is a complete eDiary finding date from a "yes" response to either (1) question about having already taken study medication today to treat headache from the scheduled dosing report, or (2) question about taking a scheduled dose of study medication today from the scheduled dosing report.

- If the first planned OL rimegepant day is an even number or missing, then the initial planned EOD dosing schedule pattern is even.

- If the first planned OL rimegepant day is an odd number, then the initial planned EOD dosing schedule pattern is odd.

It is expected that scheduled days follow the initial planned EOD dosing schedule for the entire OLE phase. Thus, if the initial planned EOD dosing schedule pattern is even, then it is expected that scheduled days are all even planned OL rimegepant days 0, 2, 4, etc. Otherwise, if the initial planned EOD dosing schedule pattern is odd, then it is expected that scheduled days are all odd planned OL rimegepant days 1, 3, 5, etc.

However, in rare cases, the eDiary may reset at scheduled report dates and switch planned EOD dosing schedule patterns. For example, the planned EOD dosing schedule may start as even, switch to odd, and then switch back to even. A switch date is defined as a scheduled report date with an odd number of days between it and the previous scheduled report date. Switch dates define blocks of days within the on-OL rimegepant efficacy analysis period as follows:

- Block 1: All days in the OL rimegepant efficacy analysis period before the first switch are considered to follow the initial planned EOD dosing pattern.

- Block 2: All days on or after the first switch but before the second switch are considered to follow the second planned EOD dosing pattern. If there is only 1 switch, then all days on or after the first switch are considered to follow the second planned EOD dosing pattern.

- Block 3: All days on or after the second switch but before the third switch are considered to follow the initial planned EOD dosing pattern. If there are only 2 switches, then all days on or after the second switch are considered to follow the initial planned EOD dosing pattern.

This iterative process continues as needed.

Example:

- Subject has 26 days in the on-OL rimegepant efficacy analysis period, i.e., OL rimegepant start date on day 0 and OL rimegepant last date + 1 on day 25.

- Scheduled report dates fall on planned OL rimegepant days 0, 2, 4, 8, 9, 11, 15, 18, 22, and 24.

  - o The initial EOD dosing schedule pattern is even.

  - o There are 2 switches: day 9 is the first switch and day 18 is the second switch.

  - o All even days from 0 to 8 inclusive (i.e., days 0, 2, 4, 6, 8) are scheduled days.

  - o All odd days from 9 to 17 inclusive (i.e., days 9, 11, 13, 15, 17) are scheduled days.

  - o All even days from 18 to 24 inclusive (i.e., 18, 20, 22, 24) are scheduled days.

    o   All other days (i.e., days 1, 3, 5, 7, 10, 12, 14, 16, 19, 21, 23, and 25) are non-scheduled days.

Note that (1) imputed OL rimegpant dates and (2) OL rimegepant dates from the scheduled dosing report can only be on scheduled days. OL rimegepant dates from the evening report headache log, follow-up headache log, or medication reconciliation form can be on scheduled or non-scheduled days.

7.6.3   Non-Study Medications

Non-study medication types will include prior, previous, current, DBT concomitant, OL rimegepant concomitant, DB or OL rimegepant concomitant, and follow-up.

Prior medications are defined as those taken before study drug start, i.e., imputed start or stop date < study drug start date. These include the following subtypes:

- Previous medications, defined as those taken before informed consent, i.e., those with an imputed start or stop date < informed consent date

- Current medications, defined as those taken on or after informed consent and before study drug start, i.e., those with (1) informed consent date ≤ imputed start or stop date < study drug start date or (2) imputed start date ≤ informed consent date < study drug start date - 1 ≤ imputed stop date.

DBT concomitant medications are defined as those taken with DBT, i.e., (1) DBT start date ≤ imputed start or stop date ≤ minimum of {DBT last date, OL rimegepant start date - 1}, or (2) imputed start date ≤ DBT start date ≤ minimum of {DBT last date, OL rimegepant start date - 1} ≤ imputed stop date.

OL rimegepant concomitant medications are defined as those taken with OL rimegepant, i.e., (1) OL rimegepant start date ≤ imputed start or stop date ≤ OL rimegepant last date, or (2) imputed start date ≤ OL rimegepant start date ≤ OL rimegepant last date ≤ imputed stop date.

DB or OL rimegepant concomitant medications are defined as those taken with DB or OL rimegepant, i.e., (1) DB or OL rimegepant start date ≤ imputed start or stop date ≤ DB or OL rimegepant last date, or (2) imputed start date ≤ DB or OL rimegepant start date ≤ DB or OL rimegepant last date ≤ imputed stop date.

Follow-up medications are defined as those taken after study drug discontinuation, i.e., study drug last date < imputed start or stop date.

Listings will display abbreviated medication types. Note that a medication may be classified into multiple types.

7.7 Age at a Reference Date

Age at a reference date (e.g., laboratory collection date) will be calculated using the birth date as follows:

- Let BD, BM, and BY respectively denote the numeric day, month, and year of the birth date.

- Let RD, RM, and RY respectively denote the numeric day, month, and year of the reference date.

- Age is defined as RY – BY, if either (1) RM > BM, or (2) RM = BM and RD ≥ BD; otherwise, age is RY – BY – 1.

Both the birth date and reference date must be complete.

Note that age at informed consent will be calculated as above by an external data management vendor, and provided in the raw demographics dataset.

8 CHANGES TO PLANNED ANALYSES IN THE PROTOCOL

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

9   APPENDICES

9.1   COVID-19 Visit Impact

Analyses are based on the COVID-19 Visit Impact CRF.

9.1.1   COVID-19 Visit Impact CRF Description

At each visit (scheduled or unscheduled), sites are required to complete the COVID-19 Visit Impact CRF, either retrospectively for visits on or after 01MAR2020 or prospectively.

Unscheduled visits are identified from folder names containing "unscheduled". Otherwise, all other visits are considered scheduled. In listings, the COVID-19 visit type is abbreviated as "U" for unscheduled visits and blank (i.e., missing) otherwise.

COVID-19 visit impact status is based on the response to the lead question "Was this visit impacted by COVID-19 related issues? (yes or no)". In listings, the COVID-19 visit impact status is abbreviated as "&" for yes and "#" for no.

If the response to the lead question is "yes", then responses to the following questions may be provided:

- COVID-19 visit impact type: What was the impact? (Indicate one):
  - Missed visit – no assessments done [abbreviated as "M" in listings]
  - In-person visit at site [abbreviated as "I" in listings]
  - Remote visit [abbreviated as "R" in listings]
- COVID-19 visit impact characteristics:
  - If missed visit, date visit planned to occur [used to derive the COVID-19 visit date]
  - If in-person visit at site: (Mark all that apply)
    - Not all assessments completed [abbreviated as "A" in listings]
    - Scheduled visit occurring earlier or delayed relative to protocol specified schedule [abbreviated as "S" in listings]
  - If remote visit, then indicate nature of contact with subject: (Indicate one)
    - Virtual visit (video/telemedicine) [abbreviated as "V" in listings]
    - Telephone contact [abbreviated as "T" in listings]
  - If remote visit, was investigational product (IP) shipped to the subject? (yes; no) [abbreviated as "Y" for yes, "N" for no in listings]
- COVID-19 visit impact relationship: How was the impact related to COVID-19? (Mark all that apply)
  - Subject diagnosed with COVID-19 or quarantined due to COVID-19 [abbreviated as "1" in listings]

- o   Site closed or access restricted due to COVID-19 [abbreviated as "2" in listings]

- o   Site open but subject unwilling or unable to come to the site due to COVID-19 [abbreviated as "3" in listings]

- o   Other [abbreviated as "4" in listings], with specify text

- COVID-19 premature study termination: If the subject is terminating the study prematurely, was the termination related to COVID-19? (yes; no; not applicable, subject continuing) [abbreviated as "X" for yes, "Z" for no, and blank otherwise in listings].

9.1.2   COVID-19 Impact

A subject is impacted by COVID-19 if there is a "yes" response to the lead question at ≥ 1 visit.

9.1.3   COVID-19 Visit Impact

A visit is impacted by COVID-19 if there is a "yes" response to the lead question at that visit (see Section 9.1.1).

A visit is not impacted by COVID-19 if there is a "no" response to the lead question at that visit.

9.1.4   COVID-19 Premature Phase Termination

An OL rimegepant treated subject terminated the OLE phase prematurely due to COVID-19 if all of the following criteria are met: "yes" response to the COVID-19 premature study termination question at ≥ 1 visit (see Section 9.1.1); did not complete the OLE phase (see Section 6.2.3.4); and missing response to the question about completing all follow-up visits on the Follow-up Subject Status CRF. Reasons for termination are based on the reasons for not completing the OLE phase.

A follow-up subject terminated the follow-up phase prematurely due to COVID-19 if all of the following criteria are met: "yes" response to the COVID-19 premature study termination question at ≥ 1 visit (see Section 9.1.1); did not complete the follow-up phase (see Section 6.2.3.5). Reasons for termination are based on the reasons for not completing the follow-up phase.

9.1.5   COVID-19 Visit Impact Code

9.1.5.1   COVID-19 Visit Impact Code Derivation

At each visit, the COVID-19 visit impact code is derived as follows:

- If the visit is impacted by COVID-19, then the value is the concatenation of the COVID-19 abbreviations described in Section 9.1.1 in the following order:

  1) Visit impact status (i.e., lead question response): "&"

  2) Visit type: "U" if unscheduled

  3) Visit impact type: "M", "I", or "R"

4) Visit impact characteristics: "A", "N", "S", "T", "V", or "Y". Multiple responses may be selected.

5) Visit impact relationship: 1, 2, 3, or 4. Multiple responses may be selected.

6) Premature study termination: "X" or "Z".

Examples:

o "&UIAS24X" if visit type is unscheduled, visit impact type is in-person visit, visit impact characteristics are "Not all assessments completed" and "Scheduled visit occurring earlier or delayed relative to protocol specified schedule", visit impact relationships are "Site closed or access restricted due to COVID-19" and "Other", and premature study termination is yes.

o "&RTY1" if visit type is scheduled, visit impact type is remote visit, visit impact characteristics are "Telephone contact" and "IP shipped to subject" , visit impact relationship is "Subject diagnosed with COVID-19 or quarantined due to COVID-19", and premature study termination is not applicable.

- If the visit is not impacted by COVID-19, then the value is the concatenation of the visit impact status "#" and the visit type ("U" if unscheduled).

- Otherwise, the value is blank (i.e., missing).

9.1.5.2   COVID-19 Visit Impact Code in Listings

Select by-subject listings of measurements over time will display all COVID-19 visit impact codes for visits impacted by COVID-19 as additional data records (see Section 9.1.3). Refer to the Mock TLF CSR document for more details.

COVID-19 measurements will be slotted into analysis periods and analysis visit windows according to the COVID-19 visit date (see Sections 7.3 through 7.5).

In the listing of COVID-19 impact codes by visit, footnotes will describe the abbreviations in the COVID-19 visit impact code, e.g., "COVID-19 visit impact code: & = Impacted; # = Not impacted; A = Not all assessments done; I = In-person visit at site; M = Missed visit; N = IP not shipped to subject; R = Remote visit; S = Scheduled visit early or late; T = Telephone; U = Unscheduled; V = Virtual; X = Premature termination due to COVID-19; Y = IP shipped to subject; Z = Premature termination not due to COVID-19; 1 = Subject dx or quar.; 2 = Site closed or restricted access; 3 = Site open but subject unwilling/unable to come to site; 4 = Other".