Protocol C4951010 (BHV3000-404)

A Phase 4 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Rimegepant in Episodic Migraine Prevention with Multiple Dosing Regimens

Statistical Analysis Plan

Version 7

Date: 25-Oct-2024

SIGNATURE PAGE

Protocol Title: A Phase 4 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Rimegepant in Episodic Migraine Prevention with Multiple Dosing Regimens

Document Version: 7

Date: 25-Oct-2024

Author: PPD

Signature: PPD

Date: 25-Oct-2024

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).

PPD

Signature: PPD

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	Coronavirus disease 2019
CRF	Case report form
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP3A4	Cytochrome P450 3A4
DB	Double-blind
DBT	Double-blind treatment
ECG	Electrocardiogram
eDiary	Electronic diary
eGFR	Estimated glomerular filtration rate
EOD	Every other day
EOT	End of treatment
FCS	Fully conditional specification
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
LSLV	Last subject last visits
LSM	Least-squares mean
MAR	Missing at random
MDRD	Modification of diet in renal disease

Abbreviation	Definition
MNAR	Missing not at random
MSQoL	Migraine Specific Quality of Life
ODT	Orally disintegrating tablet
OL	Open-label
OLE	Open-label extension
OP	Observation Phase
P-gp	Permeability glycoprotein
PT	Preferred term
QD	Quaque die
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
TBL	Total bilirubin
TLF	Table, listing, and figure
ULN	Upper limit of normal

REVISION HISTORY

Version	Description of Change
1	Original version (13-Jul-2022) based on Protocol Version 4
2	Amended version (23-Mar-2023) based on Protocol Version 4 General: Removed "Biohaven Pharmaceuticals" throughout. Added "(C4951010)" next to BHV protocol number, and footer "Pfizer Confidential". Changed left margin from 1.25" to 1". Replaced the randomized analysis set with the full analysis set. Signature page: Removed all references to "sponsor". Replaced PPD with PPD and removed PPD Abbreviations: Added CMH, CYP3A4, eDiary, GLM, and MNAR. Removed EOS, TEAE, and US. Section 1.2: Changed "CSR" to "first", and specified that no interim analyses are planned (moved text from Section 8). Removed the last sentence. Section 2.3: Changed "CSR" to "first", and removed "and subsequent database locks". Section 2.4: Specified that SAP Version 2 is based on Protocol Version 4. Section 3.2: In the "Intercurrent Events" section, specified (1) hypothetical or composite strategy for handling study drug discontinuation for efficacy objectives, (2) 7-day cutoff on study drug discontinuation for safety objectives, and (3) nonstudy prophylactic migraine medication use before the time point of interest defining the endpoint as an intercurrent event for all objectives. Section 3.2.1: Modified the "Summary" and "Intercurrent Events" rows in Table 1. Section 3.2.2: In Table 2, modified the (1) "Summary" row for objectives #1 to 5, (2) "Efficacy Endpoint" row for objective #2, and (3) "Intercurrent Events" row for all objectives. Section 3.2.3: In Table 3, modified the (1) "Summary" row for objectives #1 to 7, and 10, (2) "Efficacy Endpoint" row for objectives #6 and 7, and (3) "Intercurrent Events" row for all objectives. Section 4.1: Removed the previous definition of the full analysis set. Removed the OL rimegepant efficacy analysis set. Section 4.2: Specified that if there are non-randomized subjects who take study drug, then the as-randomized treatment group of "not randomized" is included in the full analysis set augmented with the safety analysis set. Section 4.3: Specified randomization stratum as the only efficacy subgroup of interest. Sections 4.3.1 and 4.3.2: Removed. Sections 4.3.2.1 through 4.3.2.3: Removed. Section 5: Specified 2-sided alpha levels. Section 6.1.1.1: Removed references to safety subgroups. Section 6.1.1.2: Removed significant protocol deviations and COVID-19 visit impact codes from listings. Section 6.1.3: Modified second sentence to reference Section 6.3 for statistical methods for handling missing data in efficacy analyses. Section 6.2.1: Removed the frequency table of inclusion and exclusion from the migraine analysis set and the listing of subjects excluded from efficacy analyses. Specified that the administrative listing of randomization scheme and codes is provided for the full analysis set. Section 6.2.2: Removed the frequency tables of enrollment by age group and accrual by randomization month and year.

Version	Description of Change
	Section 6.2.3: Added the by-subject listing of subject discontinuation for the enrolled analysis set, and specified its contents.
	Section 6.2.3.1: Removed the by-subject listing of eligibility with inclusion/exclusion criteria.
	Section 6.2.3.3: Removed the by-subject listing of DBT subject disposition.
	Section 6.2.3.4: Removed the by-subject listing of OLE subject disposition.
	Section 6.2.3.5: Removed the by-subject listing of follow-up subject disposition.
	Section 6.2.3.6: Added reference to Section 6.2.3.1.
	Section 6.2.3.7; Renumbered as Section 6.2.3.6. Removed the by-subject listing of rescreen and previous study participation.
	Section 6.2.4: Moved text from Section 6.2.4.1 here.
	Sections 6.2.4.1 and 6.2.4.2: Removed.
	Section 6.2.5: Removed tables of baseline characteristics for select analysis sets. Removed the by-subject listing of cardiac and other risk factors.
	Section 6.2.5.2: Removed the parameter "diagnosed with migraines for ≥ 1 year prior to screening from the migraine history table because the parameter was added to the Core SAP. Specified that the frequency table of cardiac and other risk factors is provided only for the DBT safety analysis set. Removed select percentage parameters from the table of efficacy endpoints per week during the OP.
	Section 6.2.6.1: Modified the contents of the by-subject listing of study drug. Removed tables of DB study drug exposure by subgroups.
	Section 6.2.6.2: Changed "≤ 23" to "≥ 24" in the table of eDiary usage compliance.
	Section 6.2.6.3: Renamed section as "Non-study Concomitant Medications". Removed frequency tables of nonstudy DB or OL rimegepant concomitant and follow-up medications. Simplified the definition of migraine standard of care medications.
	Section 6.3: Removed by-subject listings of exploratory migraine and headache days per month endpoints and (2) exploratory acute migraine-specific and acute migraine medication days per month endpoints.
	Section 6.3.1: Removed the by-subject listing of eDiary headache report.
	Section 6.3.1.1: Modified the contents of the frequency table of missing efficacy data in the OP and DBT Phase.
	Section 6.3.1.2: Removed the table of values and changes from the OP in the number of migraine days per month in the DBT Phase for the DBT efficacy analysis set.
	Section 6.3.1.3: Added ", normal distribution" after "Identity link function". Removed "n (i.e., number of subjects with data)" from the GLMEM table. Removed the longitudinal plot of LSM change from OP in the number of moderate or severe migraine days per month versus month of the DBT Phase. Specified the J2R and tipping point sensitivity analyses to be on the DBT efficacy analysis set instead of the migraine analysis set. Removed the supplemental analysis of the DBT efficacy analysis set and subgroup analyses of the migraine analysis set.
	Section 6.3.2.1: Removed the frequency table of descriptive analyses, histogram, and CMH table of ≥ 50% reduction of moderate or severe pain intensity by subgroups. Specified that percentages are calculated against the number of subjects in the migraine analysis set. Removed reference to Non-evaluable = Failure.
	Section 6.3.2.2: Added ", normal distribution" after "Identity link function". Removed "change from OP in" from the description of the dependent variable. Removed "n (i.e., number of subjects with data)" from the GLMEM table.

Version	Description of Change
	Section 6.3.2.3: Described the hierarchical testing strategy for secondary endpoints. Modified table contents.
	Section 6.3.3.1: Specified that the table of values and changes has the same format as the one described in Section 6.3.1.2.
	Section 6.3.3.2: Specified that the percentage of subjects with reduction in the number of headache days during the DBT Phase is defined and assessed analogously to the percentage of subjects with reduction in the number of migraine days during the DBT Phase. Removed the frequency table of descriptive analyses. Removed reference to Non-evaluable = Failure.
	Section 6.3.3.3: Modified the calculation of migraine days per week in the OP and each week of the on-DBT efficacy analysis period. Added ", normal distribution" after "Identity link function". Removed "n (i.e., number of subjects with data)" from the GLMEM table.
	Section 6.3.3.4: Specified that analyses of headache days per week are defined analogously to those for migraine days per week. Removed the frequency table of descriptive analyses. Specified that percentages are calculated against the number of subjects in the first month migraine analysis set.
	Section 6.3.3.5: Specified that percentages are calculated against the number of subjects in the first week treated migraine analysis set. Added percentage of efficacy endpoint days in the OP to the CMH table.
	Section 6.3.3.6: Specified that the table of the number of acute migraine medication days per month in the DBT Phase has the same format as the one in Section 6.3.2.2. Removed "The corresponding CMH table has the same format.".
	Section 6.4: Removed tables during pretreatment for the enrolled analysis set by overall. Specified the slotting of measurements into analysis periods and analysis visits for tables of values and changes from baseline in safety parameters are provided for the DB or OL rimegepant safety analysis set.
	Section 6.4.1: Removed by-subject listings of SAEs, AEs leading to study drug discontinuation, and AEs of special interest.
	Section 6.4.1.1: Removed the frequency table of deaths.
	Section 6.4.1.2: Removed AE overview frequency tables during pretreatment for the enrolled analysis set and by subgroups.
	Section 6.4.1.3: Removed AE frequency tables for the enrolled analysis set.
	Section 6.4.1.4: Removed frequency tables of AEs occurring with ≥ 5% frequency, TEAEs by intensity, TEAEs occurring with ≥ 2% frequency in any rimegepant treatment group and greater than placebo after rounding, exposure-adjusted multiple occurrences of unique SAEs, exposure-adjusted multiple occurrences of SAEs related to study drug, exposure-adjusted multiple occurrences of non-SAEs with ≥ 5% frequency, and by subgroups.
	Section 6.4.1.6: Removed frequency tables of AEs occurring with ≥ 5% frequency, TEAEs by intensity, all exposure-adjusted multiple occurrences of AEs, by subgroups.
	Section 6.4.1.7: Changed reference from Section 6.4.1.6 to 6.4.1.4. Removed frequency tables of AEs by subgroups.
	Section 6.4.2: Specified that TLFs display results in SI units, if applicable. Removed by-subject listings of laboratory tests by laboratory test group and pregnancy tests. Added the by-subject listing of laboratory test results for subjects with select findings.
	Section 6.4.2.1: Removed frequency tables of laboratory test low/normal/high shift from baseline to any abnormal value for all analysis periods, laboratory test toxicity grade shift from baseline to the worst toxicity grade on OL rimegepant, and by subgroups.

Version	Description of Change
	Section 6.4.2.2: Removed frequency tables of LFT elevations during pretreatment for the enrolled analysis set, LFT ULN shifts from baseline to the worst LFT elevation on OL rimegepant, exposure-adjusted cumulative LFT elevations on OL rimegepant, and time to time to first LFT elevation on OL rimegepant. Removed eDISH plot on OL rimegepant. Replaced "treated migraine days" with "DB study drug and OL rimegepant dosing days" in the by-subject longitudinal LFT plot. Section 6.4.2.3: Replaced the table of values and changes from OL rimegepant baseline with the corresponding one from DB or OL rimegepant baseline. Section 6.4.3: Removed the by-subject listing of vital signs and physical measurements. Section 6.4.3.1: Replaced the table of values and changes from OL rimegepant baseline with the corresponding one from DB or OL rimegepant baseline. Section 6.4.3.2: Removed the frequency table on OL rimegepant. Section 6.4.4: Removed the by-subject listing of ECG results. Section 6.4.4.1: Replaced the table of values and changes from OL rimegepant baseline with the corresponding one from DB or OL rimegepant baseline. Section 6.4.4.2: Removed. Section 6.4.4.3: Renumbered as Section 6.4.4.2. Removed the frequency table on OL rimegepant. Section 6.4.5: Removed. Section 6.4.6: Renumbered as Section 6.4.5. Removed the frequency table on OL rimegepant and the by-subject listing of C-SSRS. Section 6.4.7: Renumbered as Section 6.4.6. Section 6.5: Removed reference to the OL rimegepant efficacy analysis set. Removed by-subject listings of SM and CGI-c. Specified the contents of the by-subject listing of MSQoL. Referred to the Core SAP for calculating scores and imputing missing data, and deriving categories. Section 6.5.1: Removed the table of values and changes from OL rimegepant baseline in scores for the OL rimegepant efficacy analysis set. Added a frequency table of MSQoL domain score increase from baseline categories for the DBT efficacy analysis set. Added ", normal distribution" after "Identity link function". Changed "GLMEM" to "GLM". Specified that treatment group comparisons were on subjects with paired data. Section 6.6: Removed the by-subject listing of COVID-19 impact codes by visit. Renamed the by-subject listing of COVID-19 visit impact to visits impacted by COVID-19. Section 7.1: Added the death date. Section 7.2: Removed the on-OL rimegepant efficacy, post-DBT pre-OL rimegepant efficacy, and follow-up efficacy analysis periods. Removed references to the eDiary headache report listing. Section 7.3: Modified analysis visit windows for the Screening and Pre-Randomization Visits in Table 5. Removed "Baseline #" row and corresponding footnote from Table 5. Specified how analysis visit windows are defined according to analysis period. Section 8: Removed "the CSR". Moved last sentence to Section 1.2. Section 9.1: Added studies BHV3000-406/407 to the first relevant protocol deviation bullet. Modified deviation about major depressive disorder. Changed "strong CYP3A4" to "moderate or strong CYP3A4". Section 9.3.1: Added "cl diff" to the lsmeans statement. Section 9.3.2: Renamed section as "GLM". Added "cl diff" to the lsmeans statement.
3	Amended version (21-Sep-2023) based on Protocol Version 5

Version	Description of Change
	General: Applied Pfizer Global Style Guide throughout.
	Signature page: Changed “Hospital Products” to “Infectious Disease”.
	Abbreviations: Added LSLV. Removed CMH, GLM, and GLMEM.
	General: Changed “GLMEM” to “linear mixed effects model” or “model”. Changed “GLM” to “linear regression model” or “model”. Changed “GLMEM table”, “GLM table”, and “CMH table” to “table”.
	Section 1.2: Specified that there is 1 planned database lock, LSLV database lock, which occurs when the last subject completes the Follow-up Week 8 Visit, and that the LSLV final CSR is produced after the LSLV database lock.
	Section 2.1: Specified that randomization is stratified using IWRS.
	Section 2.3: Changed “CSR” to “LSLV final CSR” and “database” to “LSLV database”.
	Section 2.4: Specified that SAP Version 3 is based on Protocol Version 5, and described protocol changes that impacted statistical analyses.
	Section 3.2: Changed “stratified CMH test” to “Mantel-Haenszel risk estimation”. Changed “change” to “mean change” and “value” to “mean value” in summary rows for continuous endpoints.
	Section 4.1: Changed “randomized analysis set” to “full analysis set”.
	Section 4.3: Specified that the randomization stratum is based on actual data, not those assigned by IWRS.
	Section 6.1.1.2: New section “Figures”.
	Section 6.1.1.3: Renumbered from 6.1.1.2. Added back the listing of significant protocol deviations from SAP Version 1.
	Section 6.2.3.1: Removed “by treatment group and overall”.
	Section 6.2.4.1: Moved text from Section 6.2.4 here. Changed “enrolled” to “full”.
	Section 6.2.4.2: Added back entire section from SAP Version 1, but changed “enrolled” to “full” and added a footnote description.
	Section 6.2.5: Modified the contents of the randomization stratum frequency table to be a cross-tabulation of each randomization stratum from IWRS versus each randomization stratum from actual data.
	Section 6.2.5.1: Specified that race and ethnicity are summarized only for subjects in the United States, and percentages are calculated against the number of subjects in the United States. Removed IWRS randomization stratum from the table of demographics and other relevant baseline characteristics.
	Section 6.2.5.2: Changed “efficacy endpoints” to “migraine-related event days”.
	Section 6.2.6.2: Changed “< 80%” to “≥ 80%” and removed the “no study drug taken for ≥ 3 days in any week” category in both treatment compliance tables. Changed “DB study drug and OL rimegepant taken on same day” to ““OL rimegepant taken during the DBT Phase” in the DB treatment compliance table.
	Section 6.3: Specified that the randomization stratum used in analyses is based on actual data, not from IWRS. For the listing of primary and key secondary efficacy endpoints, specified the reasons for exclusion from the migraine analysis set and data methods for presenting endpoints. Modified section titles throughout to be consistent with endpoints.
	Section 6.3.1.1: Changed “randomized” to “DBT efficacy”.

Version	Description of Change
	Section 6.3.1.3: Removed “Identity link function, normal distribution”. Removed “subject as a random effect” from the model. Changed “Repeated measures error structure” to “Covariance structure for repeated measures accounting for within-subject correlated errors” and modified text describing specification of the covariance structure. Changed “Denominator degrees of freedom method: Kenward-Roger” to “Standard error (SE) estimation method: Huber-White “sandwich” (refer to the Core SAP)” and “longitudinal plot” to “line plot with error bars”. Specified tipping point sensitivity analysis is not by randomization strata. Section 6.3.2.1: Changed “a CMH test stratified” with “Mantel-Haenszel risk estimation with stratification”. Specified the difference in the statistical methodology between the protocol and the SAP. Sections 6.3.2.2 and 6.3.3.3: Removed “Identity link function, normal distribution”. Removed “subject as a random effect” from the model. Changed “Repeated measures error structure” to “Covariance structure for repeated measures accounting for within-subject correlated errors” and “Denominator degrees of freedom method: Kenward-Roger” to “SE estimation method: see Section 6.3.1.3.”. Section 6.3.2.3: Changed “in the last month of” to “over the entire” for 2 secondary endpoints. Sections 6.3.3.2, 6.3.3.4, and 6.3.3.5: Changed “a CMH test stratified” with “Mantel-Haenszel risk estimation with stratification”. Section 6.4.1.2: Replaced mild, moderate, and severe AEs with “moderate or severe AE”. Section 6.4.1.6: Specified calculations for exposure-adjusted multiple occurrences of unique AEs. Section 6.5: Removed “deriving the EOT value in an outcomes research analysis period;”. Modified section titles throughout to be consistent with endpoints. Section 6.5.1: Removed EOT as a time point in descriptive analyses. Removed “Identity link function, normal distribution”. Changed “Denominator degrees of freedom method: Kenward-Roger” to “SE estimation method: see Section 6.3.1.3”. Sections 6.5.2 and 6.5.3: Removed EOT as a time point in descriptive analyses. Section 7.3: Modified analysis visit windows for screening and pre-randomization visits in Table 5. Section 8: Removed first sentence and modified second sentence as “All TLFs described in this SAP are produced for the LSLV final CSR (see Section 1.2)”. Section 9.1: Changed “more than once and assigned” to “under”. Changed “Basilar migraine or hemiplegic migraine” to “Basilar migraine, hemiplegic migraine, or retinal migraine”. For pretreatment eGFR and BMI, modified existing criteria and added new criteria to align with Protocol Version 5 Section 5.3. Changed “Use of previous medication for migraine prevention generally considered to have efficacy discrepant between IWRS and CRF data” to “Randomization stratum discrepancies between IWRS and actual data”. Removed “for the full analysis set”. Specified how to determine the protocol version to which subjects originally consented. Section 9.2.5: Defined migraine day of total pain intensity. Section 9.2.6: Defined a headache day of total pain intensity. Section 9.3.1: Modified the SAS code by adding the “empirical” option and removing “/ ddfm=kenwardroger”. Section 9.3.2: Changed “either of the last 2 secondary endpoints” to “the fifth secondary endpoint”. Defined usubjid, the unique subject identifier variable. Modified the SAS code by adding the “empirical” option, removing “/ ddfm=kenwardroger”, and adding “repeated / subject=usubjid”.

Version	Description of Change
4	Amended version (24-Apr-2024) based on Protocol Version 5
	All sections: Updated study number throughout document to reflect Pfizer numbering.
	Section 3.2: Updated definition of acute migraine medications to include those treating nonmigraine headaches on a migraine day. Added intercurrent events of (1) nonstudy acute migraine-specific medication use and (2) use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura.
	Sections 3.2.1: In Table 1, modified intercurrent events row.
	Sections 3.2.2: In Table 2, modified intercurrent events row of all objectives, and removed “DB or OL rimegepant” from summary row of Objectives 6, 7, and 8.
	Section 3.2.3: In Table 3, modified intercurrent events row of all objectives, and removed “DB or” from summary row of Objective 9.
	Section 4.1: Removed COVID-19 Impacted analysis set.
	Section 6.1.1.3: Removed listings for COVID-19 impacted patients.
	Section 6.2.1: Removed reference to COVID-19 analysis set.
	Section 6.2.3: Removed listings for COVID-19 impacted patients.
	Section 6.2.3.1: Removed subjects impacted by COVID-19 from disposition table.
	Section 6.2.3.2: Removed subjects impacted by COVID-19 from disposition table.
	Section 6.2.3.3: Removed subjects impacted by COVID-19 from disposition table. Added clarifying text about subject categorization during and after the DBT phase, including subjects with missing data.
	Section 6.2.3.4: Removed subjects impacted by COVID-19 from disposition table. Added clarifying text about subject categorization during and after the OLE phase based on LSLV database lock, including subjects with missing data.
	Section 6.2.3.5: Removed subjects impacted by COVID-19 from disposition table. Replaced “final” with “LSLV”.
	Section 6.2.3.6: Removed section (Termination due to COVID-19).
	Section 6.2.3.7: Removed section (Treatment in previous studies).
	Section 6.2.5: Removed reference to COVID-19 analyses.
	Section 6.2.5.1: Removed reference to age calculation in Core SAP. Removed references to the OL and DB rimegepant baselines.
	Section 6.2.6.1: Removed reference to administrative listing of drug batch numbers.Clarified definition of DB tablet count compliance to match OL rimegepant start date.
	Section 6.2.6.2: Removed “OL rimegepant taken during the DBT Phase”. Added 2definitions for scenarios where study drug is not taken according to protocol.
	Section 6.2.6.3: Replaced "reported" with "identified"; expanded language about Concomitant Medication CRF. Expanded definition of acute migraine medications. Removed definition of migraine standard of care medications. Clarified definition of prophylactic migraine medications.
	Section 6.3.1: Removed "data from the previous visit to the current visit".
	Section 6.3.1.3: For the J2R macros, specified parameters Ndraws=200 and thin=100, and that these parameters may be modified as needed.
	Section 6.3.2.2: Removed "data from the previous visit to the current visit". Added paragraph describing overall summary table of treatment comparisons. Replaced “Repeated measures error structure” with “Covariance structure for repeated measures accounting for within-subject correlated errors”,

Version	Description of Change
	Section 6.3.3: Changed "eDiary efficacy dates" to "eDiary efficacy data dates" in five places.
	Section 6.3.3.5: Replaced "DBT phase" with "DBT efficacy analysis period" in two places.
	Section 6.4: Removed "Pretreatment for the DBT safety analysis set by treatment group and overall". Removed tables of values and changes from baseline in safety parameters.
	Section 6.4.1.2: Removed "moderate or severe AE". Added "SAE related to study drug". Removed "Pretreatment for the safety analysis set".
	Section 6.4.1.3: Removed section (Pretreatment AEs), causing subsequent sections to be renumbered.
	Section 6.4.1.4: Changed "AEs by intensity" to "AEs by worst intensity" in two places. Removed AEs by relationship to study drug and AEs of special interest: Medication overuse headache AEs. Removed Exposure adjusted multiple occurences of unique AEs and related definitions.
	Section 6.4.1.5: Removed section.
	Section 6.4.1.6: Changed "AEs by intensity" to "AEs by worst intensity" in two places. Removed AEs by relationship to study drug. Added several categories of AEs. Removed Exposure adjusted multiple occurences of unique AEs and related definitions.
	Section 6.4.1.7: Added list of endpoints.
	Section 6.4.1.8: Changed "AEs by intensity" to "AEs by worst intensity".
	Section 6.4.1.9: Removed section (AEs across all study phases).
	Section 6.4.2: Added information about lab test results in both SI and US units and pregnancy test results in SI units.
	Section 6.4.2.1: Removed two categories from frequency tables. Removed "toxicity grade" and replaced with "abnormality". Removed DB rimegepant from second grouping in frequency table.
	Section 6.4.2.2: Renamed subsection. Removed "Pretreatment for the safety analysis set. Removed "ULN". Removed DB rimegepant from second grouping two frequency tables. Removed "On-DBT for the DBT safety analysis set". Removed "On DBT for the DBT safety set" from Time to First LFT Elevation table.
	Section 6.4.2.3: Removed the table of values and changes from DB or OL rimegepant baseline in hematology and serum chemistry tests. Added table for US units.
	Section 6.4.3.1: Removed the table of values and changes from DB or OL rimegepant baseline in vital sign and physical measurement parameters by treatment group.
	Section 6.4.3.2: Removed DB rimegepant from second grouping in the frequency table.
	Section 6.4.4.1: Removed the table of values and changes from DB or OL rimegepant baseline in ECG parameters by treatment group.
	Section 6.4.4.2: Removed DB rimegepant from second grouping in the frequency table.
	Section 6.5: Added "Randomization strata used in analyses are based on the actual data."
	Section 6.6: Removed section (COVID-19 Impact).
	Section 7.1: Replaced "CSR" with "LSLV" in four places. Modified the milestone for DB study drug last date. Removed COVID-19 reference from Last Contact Date definition.
	Section 7.2: Replaced "eDiary efficacy date" with "eDiary efficacy data date" in three places. Updated definitions of pretreatment characteristics and safety endpoints.
	Section 7.3: Removed references to on-DB or OL rimegepant and rimegepant study days.

Version	Description of Change
	Section 9.1: Defined migraine history issue. Added cluster headache to medical history. Replaced "chronic pain" with "active chronic pain". Added "present at screening" in two places and defined the term below. Added two subcategories under OL rimegepant dosing issue. Replaced “DB study drug end” with “DB study drug end/OL rimegepant start”, and “moderate or strong CYP3A4 inhibitor” with “strong CYP3A4 inhibitor”. Removed “DB study drug and OL rimegepant taken on same day” and “Select strong permeability glycoprotein (P-gp) inhibitor #”. Section 9.2.3: Updated definition of acute migraine medication day. Sections 9.3.1 and 9.3.2: Removed alpha from SAS code.
5	Amended version (25-Jun-2024) based on Protocol Version 5 Section 1: Renamed as “Background and Rationale”. Section 6.2.5: Changed "OL rimegepant baseline" and "DB or OL rimegepant baseline" to "baseline". Section 6.2.5.2: Amended categories for acute migraine-specific medication days per month and acute migraine medication days per month. Specified that categories may be redefined or combined based on the availability of the data. Section 6.2.5.4: Modified the definition of medications for migraine prevention generally considered to have efficacy. Modified the last sentence. Section 6.4.2.2: Changed “anorexia” to “decreased appetite” in frequency tables of LFT elevations. Section 6.4.6: Changed “AE” to “non-SAE” in 4 places. Reordered events.
6	Amended version (15-Oct-2024) based on Protocol Version 5. Section 6.2.5: Removed age at contact date from the OLE Phase Eligibility CRF from the listing of demographics. Section 6.2.6.1: Modified categories for DB or OL rimegepant exposure (weeks). Section 6.4.2.2: Changed “longitudinal” to “line”. Removed text about changing “anorexia” to “decreased appetite” in frequency tables of LFT elevations. Section 9.1: Removed “medical history” and “cardiovascular disease risk factor” categories, and “during pretreatment” from “finding out of range” subcategories. Changed “finding out of range” to “finding out of range during pretreatment”, “females with a positive pregnancy test on or after informed consent” to “females with a positive pregnancy test”, and “dosing error” to “dosing noncompliance” (2 instances).
7	Amended version (25-Oct-2024) based on Protocol Version 5. Section 4.3: Specified that medical history of hypertension is a safety subgroup of interest for hypertension-related safety endpoints for the DBT and OL rimegepant safety analysis sets, and referenced the Core SAP. Section 6.2.5.3: Added a frequency table of medical history of hypertension. Section 6.4.1.2: Added hypertension AE and Raynaud’s AE to AE overview tables. Section 6.4.1.3 and 6.4.1.4: Added tables of hypertension AEs, overall and for subjects with medical history of hypertension. Section 6.4.3.1: Added a table of values and changes from baseline in vital sign parameters for the safety analysis set with medical history of hypertension. Section 6.4.3.2: Added tables of vital sign abnormalities on DBT and on OL rimegepant for subjects with medical history of hypertension. Section 6.4.6: Added hypertension non-SAE and Raynaud’s phenomenon non-SAE.

1 BACKGROUND AND RATIONALE

This document presents the statistical analysis plan (SAP) for Protocol C4951010 (BHV3000-404): A Phase 4 Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Rimegepant in Episodic Migraine Prevention with Multiple Dosing Regimens.

This SAP contains the analysis details and methodology to answer the study objectives, including planned tables, listings, and figures (TLFs), which provide the basis for the results section of the clinical study report (CSR).

This SAP also references the Rimegepant/Zavegepant Core SAP, which is hereafter referred to as the "Core SAP".

1.1 Research Hypothesis

Rimegepant 75 mg orally disintegrating tablet (ODT) is safe and effective when taken daily for the prevention of migraine.

1.2 Schedule of Analyses

There is 1 planned database lock, last subject last visit (LSLV) database lock, which occurs when the last subject completes the Follow-Up Week 8 Visit. The LSLV final CSR is produced after the LSLV database lock.

No interim analyses are planned.

2 STUDY DESCRIPTION

2.1 Study Design

This is a multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of 2 different dosing regimens of rimegepant 75 mg ODT in episodic migraine prevention with an open-label extension phase.

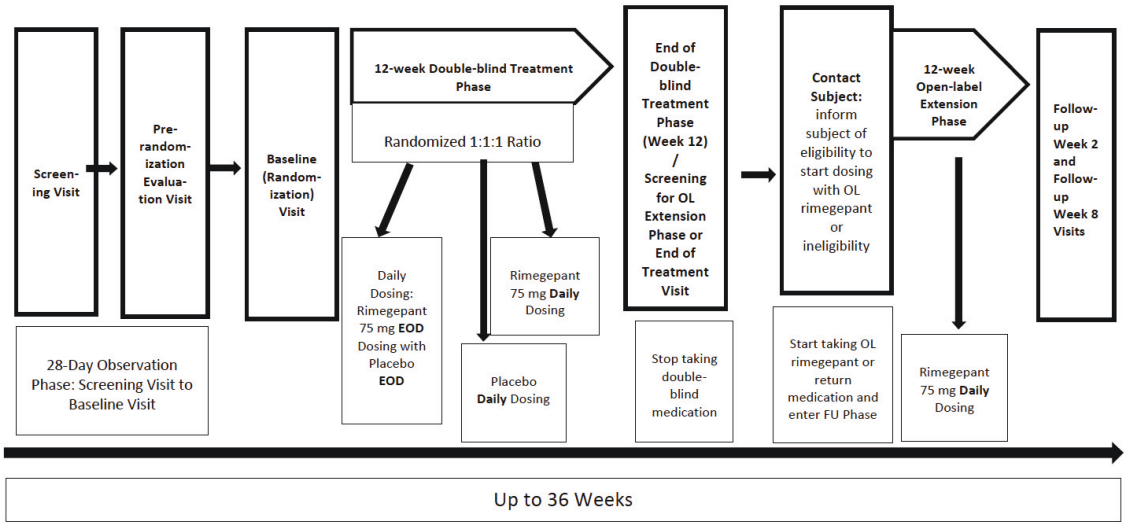
The study has 4 phases:

- Observation Phase (OP): Lasts approximately 28 days. Includes the Screening Visit and Pre-Randomization Evaluation Visit which must occur within 4 days of the Baseline Visit.
- Double-blind Treatment (DBT) Phase:
  - Lasts up to 12 weeks, and includes the Baseline Visit, and Week 2, Week 4, Week 8, Week 12, and End of Treatment (EOT) Visits.
  - Subjects are randomized 1:1:1 to one of the following 3 treatment groups at the Baseline Visit:
    - Rimegepant 75 mg dosed every other day (EOD) alternating with matching placebo EOD

    - Rimegepant 75 mg dosed daily
    - Placebo matching rimegepant 75 mg dosed daily.
  - Randomization is stratified using an Interactive Web Response System (IWRS) by use of prior prophylactic migraine medication generally considered to have efficacy (yes or no). See Section 2.2.
  - All randomized subjects who discontinue early from the DBT Phase should complete the EOT Visit. Otherwise, subjects should complete the Week 12 Visit.
- Open-label Extension (OLE) Phase:
  - Subjects who (1) complete the DBT Phase, (2) continue to meet all inclusion/exclusion criteria, and (3) have been compliant with the eDiary may enter the OLE Phase, pending review of laboratory test results.
  - Lasts up to 12 weeks, and includes the Week 14, Week 16, Week 20, Week 24, and EOT Visits.
  - Subjects take rimegepant 75 mg dosed daily.
  - All randomized subjects who discontinue early from the OLE Phase should complete the EOT Visit. Otherwise, subjects should complete the Week 24 Visit.
- Follow-Up Phase
  - Lasts up to 8 weeks, and includes Follow-up Week 2 and Follow-up Week 8 Visits primarily for safety assessments. These visits should occur approximately 2 weeks and 8 weeks, respectively, after the last visit in the last treatment phase (i.e., Week 12/EOT Visit if the subject did not enter the OLE Phase; Week 24/EOT Visit if the subject entered the OLE Phase).
  - All randomized subjects should complete both follow-up visits, regardless of completing either treatment phase.

The design of the study is shown in Figure 1. Approximately 1300 subjects are enrolled in order to randomize approximately 660 subjects.

Figure 1 Study Schematic



2.2 Treatment Assignment

The IWRS assigns a subject identifier number at the Screening Visit.

The IWRS randomizes eligible subjects to treatment groups (see Section 2.1) using permuted blocks of size 6 at the Baseline Visit. Randomization is stratified by use of prior prophylactic migraine medication generally considered to have efficacy (yes or no).

The IWRS also assigns specific container numbers for study drug to be dispensed at the Baseline Visit and subsequent visits in the DBT and OLE Phases.

2.3 Blinding and Unblinding

This study is blinded to treatment group through the LSLV database lock (see Section 1.2). Draft TLFs for the LSLV final CSR are produced with dummy treatment groups prior to LSLV database lock. Final TLFs for the LSLV final CSR are produced unblinded.

2.4 Protocol and Protocol Amendments

C4951010 SAP Versions 1 and 2 are based on C4951010 Protocol Version 4 (01-Jul-2022).

C4951010 SAP Versions 3 and 4 are based on C4951010 Protocol Version 5 (26-Jun-2023). Protocol changes that affected statistical analyses were the following: changing the sponsorship to Pfizer; stating that there is 1 planned database lock; using robust standard error (SE) estimation methods; excluding subject as a random effect from linear mixed effects models; replacing Cochran-Mantel-Haenszel test with Mantel-Haenszel risk estimation; and modifying exclusion criteria, which affects relevant protocol deviations.

C4951010 SAP Version 5 is based on C4951010 Protocol Version 5 (26-Jun-2023). This SAP makes changes to definitions and categories in Sections 6.2 and 6.4 based on project-level changes to the Core SAP.

C4951010 SAP Version 6 is based on C4951010 Protocol Version 5 (26-Jun-2023) and Rimegepant/Zavegepant Core SAP Version 7 (15-Oct-2024). This SAP incorporates program-level changes to relevant protocol deviations and certain aspects of data collection.

C4951010 SAP Version 7 is based on C4951010 Protocol Version 5 (26-Jun-2023) and Rimegepant/Zavegepant Core SAP Version 8 (21-Oct-2024). This SAP adds several tables related to hypertension AEs.

3 STUDY OBJECTIVES AND ESTIMANDS

3.1 Objectives

A month is defined as 4 weeks (28 days) for the purpose of this protocol.

3.1.1 Primary Objective

To evaluate the efficacy of EOD and daily rimegepant dosing regimens relative to placebo as a preventive treatment for episodic migraine, as measured by the mean reduction from the OP in the number of migraine days per month over the entire DBT Phase.

3.1.2 Secondary Objectives

1. To evaluate the proportion of subjects with ≥ 50% reduction from the OP in the number of moderate to severe migraine days per month over the entire DBT Phase for the EOD and daily rimegepant dosing regimens relative to placebo.

2. To evaluate the mean reduction from the OP in the number of migraine days per month in the last 4 weeks of the DBT Phase for the EOD and daily rimegepant dosing regimens relative to placebo.

3. To evaluate the mean reduction from the OP in the number of migraine days per month in the first 4 weeks of the DBT Phase for the EOD and daily rimegepant dosing regimens relative to placebo.

4. To evaluate the mean number of acute migraine-specific medication days per month over the entire DBT Phase for the EOD and daily rimegepant dosing regimens relative to placebo.

5. To evaluate the mean change from baseline in the Migraine-Specific Quality-of-Life Questionnaire v 2.1 (MSQ) restrictive role function domain score at Week 12 of the DBT Phase for the EOD and daily rimegepant dosing regimens relative to placebo.

6. To evaluate the safety and tolerability of rimegepant during the DBT and OLE Phases.

7. To evaluate the frequency of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3x upper limit of normal (ULN) concurrent with total bilirubin (TBL) > 2x ULN in subjects treated with rimegepant during the DBT and OLE Phases.

8. To evaluate the frequencies of hepatic-related adverse events (AEs) and hepatic-related AEs leading to study drug discontinuation in subjects treated with rimegepant during the DBT and OLE Phases.

3.1.3 Exploratory Objectives

1. To evaluate the mean reductions from the OP in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire DBT Phase for the EOD and daily rimegepant dosing regimens relative to placebo.

2. To evaluate the proportions of subjects with ≥ 50% reduction, ≥ 75% reduction, and 100% reduction from the OP in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire DBT Phase for the EOD and daily rimegepant dosing regimens relative to placebo.

3. To evaluate the mean reductions from the OP in the number of migraine days per week and number of headache days per week by pain intensity (total; moderate or severe) in each week of the first 4 weeks of the DBT Phase for the EOD and daily rimegepant dosing regimens relative to placebo.

4. To evaluate the proportions of subjects with ≥ 50% reduction from the OP in the number of migraine days per week and number of headache days per week by pain intensity (total; moderate or severe) in each week of the first 4 weeks of the DBT Phase for the EOD and daily rimegepant dosing regimens relative to placebo.

5. To evaluate the proportions of subjects with a migraine day and headache day by pain intensity (total; moderate or severe) on each day of the first week of the DBT Phase for the EOD and daily rimegepant dosing regimens relative to placebo.

6. To evaluate the mean number of acute migraine-specific medication days per month in each month and over the entire DBT Phase for the EOD and daily rimegepant dosing regimens relative to placebo.

7. To evaluate the mean number of acute migraine medication days per month in each month and over the entire DBT Phase for the EOD and daily rimegepant dosing regimens relative to placebo.

8. To evaluate the frequency of liver function test (LFT) elevations (AST, ALT, or TBL) based on fold changes above ULN in subjects treated with rimegepant during the DBT and OLE Phases.

9. To evaluate the frequency of ALT or AST > 3x ULN in temporal association with nausea, vomiting, anorexia, abdominal pain or fatigue in subjects treated with rimegepant during the DBT and OLE Phases.

10. To evaluate the mean changes from baseline in MSQ domain scores during the DBT and OLE Phases.

11. To evaluate the Satisfaction with Medication (SM) scale during the DBT and OLE Phases.

12. To evaluate the Clinical Global Impression – change (CGI-c) scale during the DBT and OLE Phases.

3.2 Estimands

An estimand is the target of estimation to address the scientific question of interest posed by a study objective. The 4 attributes of an estimand include the population of interest, endpoint of interest, summary of the endpoint, and specification of how intercurrent events are reflected in the scientific question of interest.

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 protocol for inclusion/exclusion criteria.

Intercurrent Events

Intercurrent events are those that occur after treatment initiation and either preclude observation of the endpoint or affect its interpretation.

Study drug discontinuation before the time point of interest defining the endpoint is considered an intercurrent event.

- For efficacy objectives assessed with a continuous endpoint during the DBT Phase, study drug discontinuation is handled with a "hypothetical strategy," i.e., the hypothetical scenario is that had subjects not discontinued DB study drug, their efficacy would have been similar to the efficacy of subjects from the same treatment group and randomization stratum who did not discontinue DB study drug. All observed values of the endpoint of interest are excluded after DB study drug discontinuation (see Section 7.2), and statistical methods are used to estimate the treatment effect that would have been seen had the intercurrent event not occurred.
- For efficacy objectives assessed with a binary endpoint during the DBT Phase, DB study drug discontinuation is handled with a "composite strategy," i.e., the occurrence of the intercurrent event is integrated as a component of the endpoint. All observed values of the endpoint of interest are excluded after DB study drug discontinuation (see Section 7.2), and subjects with missing data are considered failures.
- For safety objectives, study drug discontinuation is 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 are used prior to study drug discontinuation plus 7 days (see Section 7.2 and the Core SAP).

- For outcomes research and other objectives, study drug discontinuation is handled with a "treatment policy strategy", i.e., the occurrence of the intercurrent event is considered irrelevant, such that all observed values of the endpoint of interest are used regardless of study drug discontinuation.

Nonstudy prophylactic migraine medication use before the time point of interest defining the endpoint is also considered an intercurrent event. For all objectives, this intercurrent event is handled with a treatment policy strategy, such that all observed values of the endpoint of interest are used. Note that the use of prophylactic migraine medications is prohibited during the study.

Nonstudy acute migraine-specific medication use before the time point of interest defining the endpoint is also considered an intercurrent event, except for efficacy objectives based on acute migraine-specific medication days or acute migraine medication days.

- For efficacy objectives based on migraine days or headache days, this intercurrent event is handled with a composite strategy, such that acute migraine-specific medication use is part of the endpoint definition of migraine days and headache days.
- For safety and outcomes research objectives, this intercurrent event is handled with a treatment policy strategy, such that all observed values of the endpoint of interest are used.

Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura before the time point of interest defining the endpoint is also considered an intercurrent event, except for the efficacy objective based on acute migraine medication days.

- For efficacy objectives based on headache days, this intercurrent event is handled with a composite strategy, such that medication use is part of the endpoint definition of headache days.
- For all other efficacy, safety, and outcomes research objectives, this intercurrent event is handled with a treatment policy strategy, such that all observed values of the endpoint of interest are used.

See Section 4.1 for analysis sets that are used to assess endpoints.

Data Sources for Endpoints

Migraine days, acute migraine-specific medication days, acute migraine medication days, headache days, and SM categories are derived from eDiary data from the external source YPrime. Acute migraine-specific medications are triptans and ergotamine. Acute migraine medications are triptans, ergotamine, and other protocol-allowed medications to treat headache (migraine or nonmigraine) or aura, taken on a migraine day.

AEs are determined from AE CRFs.

Grade 3 to 4 laboratory test abnormalities are determined from laboratory test values graded using standardized criteria. Laboratory test results are from an external central laboratory and local laboratory test CRFs.

C-SSRS parameters, MSQ scores, and CGI-c categories are derived from their respective CRFs.

3.2.1 Primary Objective Estimand

The estimand corresponding to the primary endpoint is shown in Table 1.

Table 1 Primary Objective Estimand

Objective	Mean reduction from the OP in the number of migraine days per month over the entire DBT Phase
Efficacy Endpoint	Mean change from the OP in the number of migraine days per month over the entire DBT Phase (Weeks 1 to 12)
Summary	Mean change from the OP by treatment group using descriptive statistics and linear mixed effects model with repeated measures, and difference between treatment groups from model for the migraine analysis set
Intercurrent Events	Study drug discontinuation: hypothetical strategy
	Nonstudy prophylactic migraine medication use: treatment policy strategy
	Nonstudy acute migraine-specific medication use: composite strategy
	Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy

3.2.2 Secondary Objective Estimands

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

Table 2 Secondary Objective Estimands

Objective 1	**Proportion of subjects with ≥ 50% reduction from the OP in the number of moderate or severe migraine days per month over the entire DBT Phase**
Efficacy Endpoint	Proportion of subjects with ≥ 50% reduction from the OP in number of moderate or severe migraine days per month over the entire DBT Phase (Weeks 1 to 12)
Summary	Percentage by treatment group and difference in percentages between treatment groups using Mantel-Haenszel risk estimation for the migraine analysis set
Intercurrent Events	Study drug discontinuation: composite strategy
	Nonstudy prophylactic migraine medication use: treatment policy strategy
	Nonstudy acute migraine-specific medication use: composite strategy
	Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy
Objective 2	**Mean reduction from the OP in the number of migraine days per month in the last 4 weeks of the DBT Phase**

Efficacy Endpoint	Mean change from the OP in the number of migraine days per month in the last 4 weeks (Weeks 9 to 12) of the DBT Phase
Summary	Mean change from the OP by treatment group using descriptive statistics and linear mixed effects model with repeated measures, and difference between treatment groups from model for the migraine analysis set
Intercurrent Events	Study drug discontinuation: hypothetical strategy
	Nonstudy prophylactic migraine medication use: treatment policy strategy
	Nonstudy acute migraine-specific medication use: composite strategy
	Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy
Objective 3	**Mean reduction from the OP in the number of migraine days per month in the first 4 weeks of the DBT Phase**
Efficacy Endpoint	Mean change from the OP in the number of migraine days per month in the first 4 weeks (Weeks 1 to 4) of the DBT Phase
Summary	Mean change from the OP by treatment group using descriptive statistics and linear mixed effects model with repeated measures, and difference between treatment groups from model for the migraine analysis set
Intercurrent Events	Study drug discontinuation: hypothetical strategy
	Nonstudy prophylactic migraine medication use: treatment policy strategy
	Nonstudy acute migraine-specific medication use: composite strategy
	Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy
Objective 4	**Mean number of acute migraine-specific medication days per month over the entire DBT Phase**
Efficacy Endpoint	Mean number of acute-migraine-specific days per month on treatment over the entire DBT Phase (Weeks 1 to 12)
Summary	Mean value by treatment group using descriptive statistics and linear mixed effects model with repeated measures, and difference between treatment groups from model for the migraine analysis set
Intercurrent Events	Study drug discontinuation: hypothetical strategy
	Nonstudy prophylactic migraine medication use: treatment policy strategy
	Nonstudy acute migraine-specific medication use: not applicable
	Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy
Objective 5	**Mean change from baseline in the MSQ restrictive role function domain score at Week 12 of the DBT Phase**
Outcomes Research Endpoint	Mean change from baseline in the MSQ restrictive role function domain score at Week 12 of the DBT Phase
Summary	Mean change from baseline by treatment group using descriptive statistics and linear regression model, and difference between treatment groups from model for the DBT efficacy analysis set
Intercurrent Events	Study drug discontinuation: treatment policy strategy
	Nonstudy prophylactic migraine medication use: treatment policy strategy

	Nonstudy acute migraine-specific medication use: treatment policy strategy Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy
Objective 6	**Safety and tolerability of rimegepant during the DBT and OLE Phases**
Safety Endpoint	Number and percentage of subjects with AEs by intensity, serious adverse events (SAEs), AEs leading to study drug discontinuation, and grade 3 to 4 laboratory test abnormalities on treatment
Summary	• AEs: Frequency by treatment group for the DBT and OL rimegepant safety analysis sets • Laboratory test abnormalities: Frequency by treatment group for the DBT and OL rimegepant safety analysis sets with laboratory test data on treatment
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy Nonstudy prophylactic migraine medication use: treatment policy strategy Nonstudy acute migraine-specific medication use: treatment policy strategy Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy
Objective 7	**Frequency of ALT or AST > 3x ULN concurrent with TBL > 2x ULN in subjects treated with rimegepant during the DBT and OLE Phases**
Safety Endpoint	Number and percentage of subjects with AST or ALT > 3x ULN concurrent (i.e., on the same laboratory collection date) with TBL > 2x ULN on treatment
Summary	Frequency by treatment group for the DBT and OL rimegepant safety analysis sets with LFT data on treatment
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy Nonstudy prophylactic migraine medication use: treatment policy strategy Nonstudy acute migraine-specific medication use: treatment policy strategy Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy
Objective 8	**Frequencies of hepatic-related AEs and hepatic-related AEs leading to study drug discontinuation in subjects treated with rimegepant during the DBT and OLE Phases**
Safety Endpoint	Number and percentage of subjects with hepatic-related AEs and hepatic-related AEs leading to study drug discontinuation on treatment
Summary	Frequency by treatment group for the DBT and OL rimegepant safety analysis sets
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy Nonstudy prophylactic migraine medication use: treatment policy strategy Nonstudy acute migraine-specific medication use: treatment policy strategy Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy

3.2.3 Exploratory Objective Estimands

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

Table 3 Exploratory Objective Estimands

Objective 1	**Mean reduction from the OP in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire DBT Phase**
Efficacy Endpoint	Mean changes from the OP in the number of migraine days per month and number of headache days per month during DBT (1) over time by month and (2) overall DBT, by pain intensity (total; moderate or severe)
Summary	Mean changes from the OP by treatment group using descriptive statistics and linear mixed effects model with repeated measures, and difference between treatment groups from model for the migraine analysis set
Intercurrent Events	Study drug discontinuation: hypothetical strategy Nonstudy prophylactic migraine medication use: treatment policy strategy Nonstudy acute migraine-specific medication use: composite strategy Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy for migraine days; composite strategy for headache days
Objective 2	**Proportions of subjects with ≥ 50% reduction, ≥ 75% reduction, and 100% reduction from the OP in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire DBT Phase**
Efficacy Endpoint	Proportions of subjects with ≥ 50% reduction, ≥ 75% reduction, and 100% reduction from the OP in the number of migraine days per month and number of headache days per month during DBT (1) over time by month and (2) overall DBT, by pain intensity (total; moderate or severe)
Summary	Percentages by treatment group, and difference in percentages between treatment groups using Mantel-Haenszel risk estimation for the migraine analysis set
Intercurrent Events	Study drug discontinuation: composite strategy Nonstudy prophylactic migraine medication use: treatment policy strategy Nonstudy acute migraine-specific medication use: composite strategy Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy for migraine days; composite strategy for headache days
Objective 3	**Mean reduction from the OP in the number of migraine days per week and number of headache days per week by pain intensity (total; moderate or severe) in each week of the first 4 weeks of the DBT Phase**
Efficacy Endpoint	Mean changes from the OP in the number of migraine days per week and number of headache days per week over time by week during the first 4 weeks of DBT, by pain intensity (total; moderate or severe)
Summary	Mean changes from the OP by treatment group using descriptive statistics and linear mixed effects model with repeated measures , and difference between treatment groups from model for the first month migraine analysis set
Intercurrent Events	Study drug discontinuation: hypothetical strategy Nonstudy prophylactic migraine medication use: treatment policy strategy Nonstudy acute migraine-specific medication use: composite strategy

	Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy for migraine days; composite strategy for headache days
Objective 4	**Proportions of subjects with ≥ 50% reduction from the OP in the number of migraine days per week and number of headache days per week by pain intensity (total; moderate or severe) in each week of the first 4 weeks of the DBT Phase**
Efficacy Endpoint	Proportions of subjects with ≥ 50% reduction from the OP in the number of migraine days per week and number of headache days per week over time by week during the first 4 weeks of DBT, by pain intensity (total; moderate or severe)
Summary	Percentages by treatment group, and difference in percentages between treatment groups using Mantel-Haenszel risk estimation for the first month migraine analysis set
Intercurrent Events	Study drug discontinuation: composite strategy Nonstudy prophylactic migraine medication use: treatment policy strategy Nonstudy acute migraine-specific medication use: composite strategy Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy for migraine days; composite strategy for headache days
Objective 5	**Proportions of subjects with a migraine day and headache day by pain intensity (total; moderate or severe) on each day of the first week of the DBT Phase**
Efficacy Endpoint	Proportions of subjects with a migraine day and headache day on each day of the first week of the DBT Phase, by pain intensity (total; moderate or severe)
Summary	Percentages by treatment group, and difference in percentages between treatment groups using Mantel-Haenszel risk estimation for the first week treated migraine analysis set
Intercurrent Events	Study drug discontinuation: not applicable due to definition of the first week treated migraine analysis set Nonstudy prophylactic migraine medication use: treatment policy strategy Nonstudy acute migraine-specific medication use: composite strategy Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy for migraine days; composite strategy for headache days
Objective 6	**Mean number of acute migraine-specific medication days per month in each month and over the entire DBT Phase**
Efficacy Endpoint	Mean number of acute migraine-specific medication days per month during DBT (1) over time by month and (2) overall DBT
Summary	Mean values by treatment group using descriptive statistics and linear mixed effects model with repeated measures, and difference between treatment groups from model for the migraine analysis set
Intercurrent Events	Study drug discontinuation: hypothetical strategy Nonstudy prophylactic migraine medication use: treatment policy strategy Nonstudy acute migraine-specific medication use: not applicable Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy

Objective 7	**Mean number of acute migraine medication days per month in each month and over the entire DBT Phase**
Efficacy Endpoint	Mean number of acute migraine medication days per month during DBT (1) over time by month and (2) overall DBT
Summary	Mean values by treatment group using descriptive statistics and linear mixed effects model with repeated measures, and difference between treatment groups from model for the migraine analysis set
Intercurrent Events	Study drug discontinuation: hypothetical strategy Nonstudy prophylactic migraine medication use: treatment policy strategy Nonstudy acute migraine-specific medication use: not applicable Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: not applicable
Objective 8	**Frequency of LFT elevations based on fold changes above ULN in subjects treated with rimegepant during the DBT and OLE Phases**
Safety Endpoint	Number and percentage of subjects with LFT elevations (ALT, AST, or TBL) based on fold changes above ULN on treatment
Summary	Frequency by treatment group for the DB and OL rimegepant, and DB or OL rimegepant safety analysis sets with LFT data on treatment
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy Nonstudy prophylactic migraine medication use: treatment policy strategy Nonstudy acute migraine-specific medication use: treatment policy strategy Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy
Objective 9	**Frequency of ALT or AST > 3x ULN in temporal association with nausea, vomiting, anorexia, abdominal pain or fatigue in subjects treated with rimegepant during the DBT and OLE Phases**
Safety Endpoint	Number and percentage of subjects in the DBT safety analysis set with ALT or AST > 3x ULN concurrent with nausea, vomiting, anorexia, abdominal pain or fatigue on treatment
Summary	Frequency by treatment group for the DB and OL rimegepant safety analysis sets with LFT data on treatment
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy Nonstudy prophylactic migraine medication use: treatment policy strategy Nonstudy acute migraine-specific medication use: treatment policy strategy Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy
Objective 10	**Mean changes from baseline in MSQ domain scores during the DBT and OLE Phases**
Outcomes Research Endpoint	Mean changes from baseline in the (1) MSQ restrictive role function, preventive role function, and emotional function domain scores at Week 12 of the DBT Phase and Week 24 of the OLE Phase

Summary	(1) Mean changes from baseline at Week 12 in each domain score by treatment group using descriptive statistics and linear model, and difference between treatment groups from model for the DBT efficacy analysis set; (2) mean changes from baseline at Week 24 in each domain score by treatment group using descriptive statistics for the DBT efficacy analysis set
Intercurrent Events	Study drug discontinuation: treatment policy strategy Nonstudy prophylactic migraine medication use: treatment policy strategy Nonstudy acute migraine-specific medication use: treatment policy strategy Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy
Objective 11	**SM scale during the DBT and OLE Phases**
Outcomes Research Endpoint	Number and percentage of subjects in each of 7 satisfaction categories (completely satisfied to completely dissatisfied) of study medication at Weeks 12 and 24
Summary	Frequency over time by treatment group for the DBT efficacy analysis set with SM data
Intercurrent Events	Study drug discontinuation: treatment policy strategy Nonstudy prophylactic migraine medication use: treatment policy strategy Nonstudy acute migraine-specific medication use: treatment policy strategy Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy
Objective 12	**CGI-c scale during the DBT and OLE Phases**
Outcomes Research Endpoint	Number and percentage of subjects in each of 7 improvement categories (very much improved to very much worse) relative to investigator's past experience with other patients with the same diagnosis at Weeks 12 and 24
Summary	Frequency over time by treatment group for the DBT efficacy analysis set with CGI-c data
Intercurrent Events	Study drug discontinuation: treatment policy strategy Nonstudy prophylactic migraine medication use: treatment policy strategy Nonstudy acute migraine-specific medication use: treatment policy strategy Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy

4 ANALYSIS SETS, TREATMENT GROUPS, AND SUBGROUPS

4.1 Analysis Sets

The following analysis sets are evaluated and used for presentation and analysis of the data:

- Enrolled: Subjects who sign an informed consent form and are assigned a subject identification number, i.e., nonmissing informed consent date. This analysis set is used mainly to assess study population and in by-subject listings.

- Full: subjects in the enrolled analysis set who receive a randomized treatment assignment from the IWRS, i.e., nonmissing IWRS randomization date. This analysis set is used mainly to assess study population.
- Safety: subjects in the enrolled analysis set who take ≥ 1 dose of study drug (DB rimegepant, OL rimegepant, or placebo), i.e., nonmissing study drug start date. This analysis set is used to assess study population and produce select by-subject listings.
  - DBT safety: subjects in the safety analysis set who take ≥ 1 dose of DB study drug (rimegepant or placebo), i.e., nonmissing DB study drug start date. This analysis set is used to assess study population, exposure, and on-DBT safety.
  - OL rimegepant safety: subjects in the safety analysis set who take ≥ 1 dose of OL rimegepant, i.e., nonmissing OL rimegepant start date. This analysis set is used to assess study population, exposure, and on-OL rimegepant safety.
    - Interim safety: subjects in the OL rimegepant safety analysis set with OL rimegepant start date – DB study drug last date > 7 days. This analysis set is used to assess post-DBT pre-OL rimegepant safety.
  - Double-blind (DB) or OL rimegepant safety: subjects in the safety analysis set who take ≥ 1 dose of DB or OL rimegepant, i.e., nonmissing DB or OL rimegepant start date. This analysis set is used to assess study population, exposure, and on-DB or OL rimegepant safety.
  - Follow-up safety: subjects in the safety analysis set whose last contact date is in the follow-up safety analysis period. This analysis set is used to assess follow-up safety.
- DBT efficacy: subjects in the full analysis set who are randomized only once and take ≥ 1 dose of DB study drug (rimegepant or placebo). This analysis set is used to analyze outcomes research during the DBT Phase.
  - Migraine: subjects in the DBT efficacy analysis set with ≥ 14 days of eDiary efficacy data (not necessarily consecutive) in both the OP and ≥ 1 month (4-week interval) in the DBT Phase (see Section 6.3.1). This analysis set is used to assess migraine days, acute migraine-specific medication days, acute migraine medication days, and headache days.
  - First month migraine: subjects in the DBT efficacy analysis set with ≥ 24 days of eDiary efficacy data (not necessarily consecutive) in both the OP and in first month (4-week interval) of the DBT Phase (see Section 6.3.3.3). This analysis set is used to assess efficacy endpoints per week.
  - First week treated migraine: subjects in the DBT efficacy analysis set with (1) ≥ 24 days of eDiary efficacy data in the OP (not necessarily consecutive), (2) 7 consecutive days of eDiary efficacy data in the first week of the DBT Phase, and (3) 7 consecutive days of DB study drug dosing in the first week of the DBT Phase (see Section 6.3.3.5). This analysis set is used to assess efficacy endpoints per day.

See Section 7.1 for derived dates and Section 7.2 for analysis periods.

4.2 Treatment Groups

Treatment groups in the DBT Phase are rimegepant 75 mg EOD/placebo EOD, rimegepant 75 mg daily (i.e., quaque dia [QD]), and placebo QD. The safety analysis sets are assessed by as-treated treatment group (i.e., actual treatment received), the randomized, full, efficacy, and migraine analysis sets are assessed by as-randomized treatment group, and the enrolled analysis set is assessed overall.

If a subject takes ≥ 1 dose of planned randomized DB study drug, then that subject is considered to have as-treated treatment group equal to as-randomized treatment group (see Section 6.2.6.2).

If there are non-randomized subjects who take study drug, then the as-randomized treatment group of "not randomized" is included in the full analysis set augmented with the safety analysis set.

4.3 Subgroups

Subgroup tables present results by subgroup level and overall for subjects with nonmissing subgroup level data.

The following efficacy subgroups are of interest for the migraine analysis set:

- Randomization stratum – use of previous prophylactic migraine medication generally considered to have efficacy: yes, no (see Section 6.2.5.4).

Randomization strata are based on the actual data, not those assigned by IWRS.

Medical history of hypertension is a safety subgroup of interest for hypertension-related safety endpoints for the DBT and OL rimegepant safety analysis sets (see Section 6.2.5.3). Refer to the Core SAP for the subgroup definition.

5 SAMPLE SIZE, POWER, AND TYPE 1 ERROR

The study randomizes approximately 220 subjects per arm. Based on data from study C4951025 (BHV3000-305), we estimate that this results in roughly 200 subjects per arm in the migraine analysis set. Assuming rimegepant provides roughly a 1.1-day advantage over placebo on the primary endpoint, a common standard deviation (SD) of 3.5 days, and a 2-sided alpha level of 0.025, then the study has roughly 80% power on the primary endpoint.

In study C4951025 (BHV3000-305), rimegepant provided a 0.8-day advantage over placebo. With daily dosing, we expect the treatment effect to increase. Using the data from study BHV3000-305, the SD of the primary endpoint was estimated to be roughly 3.5 days.

Type 1 error is controlled using a 2-sided alpha level of 0.025 and hierarchical testing. The significance of the primary endpoint is evaluated at a 2-sided alpha level of 0.025 for each rimegepant dosing regimen versus placebo. If the primary endpoint is significant for a rimegepant dosing regimen, then the secondary efficacy and outcomes research endpoints are tested hierarchically, each at a 2-sided alpha level of 0.025, in the order specified in Section

3.2.2. Thus, for a rimegepant dosing regimen, a secondary efficacy or outcomes research endpoint is tested only if the preceding secondary endpoint in the hierarchy is determined to be significant (i.e., p-value ≤ 0.025). If a test in the hierarchy is not significant, then any further tests on endpoints in the sequence have p-values presented only for descriptive purposes, and no conclusions are drawn from those results. Note that secondary safety endpoints are not tested.

For exploratory endpoints, no attempt is made to adjust for multiplicity. Any exploratory endpoints for which p-values are produced are evaluated at an unadjusted, 2-sided alpha level of 0.025 and presented only for descriptive purposes.

6 STATISTICAL ANALYSES

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

6.1 General

6.1.1 Programmed Output

A list of TLFs and corresponding templates are presented separately in a mock TLF document corresponding to this SAP.

Refer to the Core SAP for additional details about programmed output.

6.1.1.1 Tables

Treatment Group Presentation

Treatment group presentation in tables by analysis set is shown in

Table 4. Exceptions are specified in subsequent sections as needed.

Table 4 Treatment Group Presentation in Tables by Analysis Set

Analysis Set	Number of Columns	Abbreviated Treatment Group
Enrolled	1	Overall
Full, DBT efficacy, migraine, safety, DBT safety, interim safety by treatment group and {overall}	3 to 4	RMG EOD/PBO EOD RMG QD PBO QD {Overall}
OL rimegepant safety, DB or OL rimegepant safety by treatment group/OL rimegepant and overall	4	DB RMG EOD/PBO EOD/OL RMG DB RMG QD/OL RMG DB PBO QD/OL RMG Overall

Analysis Set	Number of Columns	Abbreviated Treatment Group
Follow-up safety by treatment group/OL rimegepant status and overall	6	DB RMG EOD/PBO EOD/OL RMG DB RMG QD/OL RMG DB PBO QD DB PBO QD to OL RMG DB PBO QD No OL RMG Overall

"DB PBO QD to OL RMG" denotes as-treated DB placebo QD subjects in the OL rimegepant safety analysis set, and "DB PBO QD No OL RMG" denotes as-treated DB placebo QD subjects not in the OL rimegepant safety analysis set; note that these 2 placebo groups add to the "DB PBO QD" group.

Results for study population and pretreatment safety endpoints also include overall treatment group (see Sections 6.2 and 6.4).

6.1.1.2 Figures

Refer to the Core SAP for additional details.

6.1.1.3 Listings

Unless otherwise specified, by-subject listings are sorted by randomization status (randomized, not randomized), site-subject ID, and additional variables such as time points, as applicable. Listings display as-randomized treatment group abbreviated as (1) "RMG/PBO", "RMG", and "PBO" for subjects in the full analysis set, and (2) "NRND" for subjects not in the full analysis set.

Listings of significant protocol deviations, exposure, safety parameters, outcomes research parameters include the following: abbreviated name of the analysis period in which the measurement was slotted (i.e., PRETRT, DBT, INT, OLRMG, FU; this does not apply to exposure parameters); analysis visit in which the measurement was slotted (this does not apply to exposure or AEs); measurement date/time; study day derived from the measurement date, and rimegepant study day ≥ 1 derived from the measurement date for as-randomized placebo QD subjects (see Section 7.3).

6.1.2 Statistical Methods

Refer to the Core SAP for descriptive statistics in tables, counting rules in frequency tables, and rounding rules in frequency tables.

6.1.3 Missing Data

All analyses are based on observed data unless otherwise specified. See Section 6.3 for statistical methods for handling missing data in efficacy analyses.

6.2 Study Population

Refer to the Core SAP for TLF contents.

6.2.1 Analysis Sets

The frequency table of analysis sets described in Section 4.1 displays results by treatment group (as-randomized for the full, efficacy and migraine analysis sets; as-treated for the safety and follow-up safety analysis sets), not randomized, and overall.

The by-subject listing of analysis sets is provided for the enrolled analysis set.

The administrative listing of randomization scheme and codes is provided for the full analysis set.

6.2.2 Enrollment

The frequency table of enrollment by country and site is provided for the enrolled analysis set, and also displays results for the full and DBT safety analysis sets.

6.2.3 Subject Disposition

The by-subject listing of subject discontinuation is provided for the enrolled analysis set and displays a separate record for each study phase (i.e., DBT, OLE and Follow-Up) that is discontinued (i.e., completed or not completed) corresponding to each type of subject status CRF. The listing includes the following:

- Relevant reference dates: last contact date*, IWRS randomization date
- Study phase: DBT, OLE, or Follow-Up. For each study phase:
  - Last visit date. Derived from visit dates from the Visit Date and Unscheduled Visit Checklist CRFs as follows:
    - DBT Phase: latest visit date in the pretreatment or on-DBT safety analysis period
    - OLE Phase: latest visit date in the OL rimegepant safety analysis period
    - Follow-Up Phase: latest visit date in the follow-up safety analysis period
  - Phase completion status: “completed”; or “not completed” concatenated with the reason for noncompletion (see Sections 6.2.3.1, 6.2.3.2, 6.2.3.3, 6.2.3.4, and 6.2.3.5)
  - Next phase continuation status: “continued” concatenated with the name of the next phase (OLE or Follow-Up); or “not continued” concatenated with the reason for noncontinuation (see Sections 6.2.3.2, 6.2.3.3, and 6.2.3.4). This does not apply to the Follow-Up Phase.

A footnote describes the derivation of the last contact date as “* Derived as the death date (if it exists); otherwise, the maximum date collected across study population, efficacy safety, and outcomes research parameters”. See Section 7.1 for derived dates and Section 7.2 for analysis periods.

6.2.3.1 Subject Disposition From Enrollment to Randomization

The frequency table of subject disposition from enrollment to randomization is provided for the enrolled analysis set based on the DB Subject Status CRF, and displays the following categories:

- Randomized (identified as subjects with nonmissing IWRS randomization date)
- Not randomized (identified as subjects with missing IWRS randomization date)
    - Reasons for discontinuation (i.e., not completing the DBT Phase), including not reported. For subjects whose reason is screen failure due to inclusion/exclusion criteria, the reasons for screen failure from the Inclusion/Exclusion CRF are also displayed as subcategories.

6.2.3.2 Subject Disposition From Randomization to Treatment

The frequency table of subject disposition from randomization to treatment is provided by treatment group and overall for the full analysis set based on the DB Subject Status CRF, and displays the following categories:

- Treated with study drug (identified as subjects with nonmissing study drug start date)
- Not treated with study drug (identified as subjects with missing study drug start date)
    - Reasons for discontinuation (i.e., not completing the DBT Phase), including not reported

6.2.3.3 Subject Disposition During the DBT Phase

The frequency table of subject disposition during the DBT Phase is provided by treatment group and overall for the DBT safety analysis set based on the DB Subject Status CRF, and displays the following categories:

- Ongoing in the DBT Phase. These are identified as subjects with (1) missing response to the question “Did the subject complete the DBT Phase?” and (2) missing DB study drug last date. This category only exists before all subjects have discontinued the DBT Phase (a milestone identified by the sponsor study management team); otherwise, subjects with missing response are categorized as “Did not complete the DBT Phase”.
- Completed the DBT Phase. These are identified as subjects with (1) “yes” response to the question “Did the subject complete the DBT Phase?” and (2) nonmissing DB study drug last date)
- Did not complete the DBT Phase. These are identified as subjects with (1) “no” or missing response to the question “Did the subject complete the DBT Phase?” and (2) nonmissing DB study drug last date.
    - Reasons for not completing the DBT Phase, including not reported
- Continued to the next phase. These are identified as subjects with “yes” response to the question “Will the subject continue into the next phase of the study?”.
    - Next phase, i.e., OLE or Follow-Up

- Did not continue to the next phase. These are identified as subjects with "no" response to the question "Will the subject continue into the next phase of the study?". Subjects with missing response to this question are included only after all subjects have discontinued the DBT Phase.
    - Reasons for not continuing to the next phase, including not reported.

6.2.3.4 Subject Disposition During the OLE Phase

The frequency table of subject disposition during the OLE Phase is provided by treatment group/OL rimegepant and overall for the OL rimegepant safety analysis set based on the OLE Subject Status CRF, and displays the following categories:

- Ongoing in the OLE Phase. These are identified as subjects with (1) missing response to the question "Did the subject complete the OLE Phase?" and (2) missing OL rimegepant last date. This category only exists before the LSLV database lock; otherwise, subjects with missing response are categorized as "Did not complete the OLE Phase".
- Completed the OLE Phase. These are identified as subjects with (1) "yes" response to the question "Did the subject complete the OLE Phase?" and (2) nonmissing OL rimegepant last date)
- Did not complete the OLE Phase. These are identified as subjects with (1) "no" response to the question "Did the subject complete the OLE Phase?" and (2) nonmissing OL rimegepant last date. Subjects with missing response to this question are included only after the LSLV database lock.
    - Reasons for not completing the OLE Phase, including not reported
- Continued to the Follow-Up Phase. These are identified as subjects with "yes" response to the question "Will the subject continue to the Follow-Up Phase?".
- Did not continue to the Follow-Up Phase. These are identified as subjects with "no" response to the question "Will the subject continue to the Follow-Up Phase?"). Subjects with missing response to this question after the LSLV database lock are also included.
    - Reasons for not continuing to the next phase, including not reported.

6.2.3.5 Subject Disposition During the Follow-Up Phase

The frequency table of subject disposition during the Follow-Up Phase is provided by treatment group/OL rimegepant status and overall for the follow-up safety analysis set based on the Follow-Up Subject Status CRF, and displays the following categories:

- Did not formally enter the Follow-Up Phase. These are identified as subjects with missing response to the question "Did the subject complete the Follow-Up Phase?", and either of the following:
    - "No" response to the question "Will the subject continue to the Follow-Up Phase?" on the OLE Subject Status CRF

- "No" response to the question "Will the subject continue into the next phase of the study?" on the DB Subject Status CRF.

A footnote explains that these are subjects with data in the follow-up safety analysis period who did not continue to the Follow-Up Phase as per DB or OLE Subject Status CRF.

- Ongoing in the Follow-Up Phase. These are identified as subjects with missing response to the question "Did the subject complete the Follow-Up Phase?" and who are not already categorized as "Did not formally enter the Follow-Up Phase".

  This category only exists before the LSLV database lock. After the LSLV database lock, these subjects are categorized as "Did not complete the Follow-Up Phase".
- Completed the Follow-Up Phase. These are identified as subjects with "yes" response to the question "Did the subject complete the Follow-Up Phase?"
- Did not complete the Follow-Up Phase. These are identified as subjects with "no" response to the question "Did the subject complete the Follow-Up Phase?".
  - Reasons for not completing the Follow-Up Phase, including not reported.

6.2.4 Protocol Deviations

6.2.4.1 Relevant Protocol Deviations

The frequency table of relevant protocol deviations is provided by treatment group and overall for the full analysis set by deviation type (eligibility, subject management), category, and subcategory in the order specified in Section 9.1. Results for all relevant protocol deviation categories and subcategories are displayed, even those with 0 counts, unless otherwise specified.

The by-subject listing of relevant protocol deviations is provided for the full analysis set. This includes deviation type, category, and subcategory, which are additional sorting variables.

6.2.4.2 Significant Protocol Deviations

The by-subject listing of significant protocol deviations is provided for the full analysis set, and is based on the Protocol Deviations CRF. This includes date deviation occurred, violation code, inclusion/exclusion number, and description, which are additional sorting variables. Significant protocol deviations are defined as those with a "yes" response to the question "Is the deviation significant?". A footnote describes the raw data source and how significant protocol deviations are identified as "Significant protocol deviations are those reported as significant by sites on the Protocol Deviations CRF.".

6.2.5 Baseline Characteristics

Baseline characteristics include (1) demographics and other relevant baseline characteristics, (2) baseline disease characteristics (i.e., migraine history, cardiac and other risk factors, and efficacy during the OP), (3) medical history, and (4) nonstudy prior medications. These are detailed in Sections 6.2.5.1 through 6.2.5.4, respectively.

Tables of baseline characteristics are provided for the following analysis sets:

- Migraine analysis set: baseline characteristics (1) and (2) by treatment group and overall to support efficacy
- DBT safety analysis set: baseline characteristics (1) through (4) by treatment group and overall to support DBT safety
- OL rimegepant safety analysis set: demographics and other relevant baseline characteristics by treatment group/OL rimegepant and overall to support OL rimegepant safety
- DB or OL rimegepant safety analysis set: demographics and other relevant baseline characteristics by treatment group/OL rimegepant and overall to support DB or OL rimegepant safety

The frequency cross table of randomization stratum (i.e., use of previous prophylactic migraine medication generally considered to have efficacy [yes, no]) from IWRS versus actual data is provided for the full analysis set by treatment group and overall. See Section 6.2.5.4.

Baseline for a parameter (e.g., weight) is defined according to analysis set; refer to the Core SAP for details, including handling of ties on the same measurement date (entry date/time is the "earliest data creation time" variable in the raw CRF datasets). Note that the baseline value of a parameter is independent of the baseline analysis visit defined in Table 5; the latter is used only in by-subject listings that display visit.

By-subject listings are provided for the enrolled analysis set for the following: demographics; medical history; and migraine history.

6.2.5.1 Demographics and Other Relevant Baseline Characteristics

Refer to the Core SAP for the table of demographics and other relevant characteristics. Other relevant characteristics also include the following:

- Previous study participation (e.g., any study, BHV3000-301, BHV3000-302, BHV3000-303, etc.)
- Randomization stratum based on actual data – use of previous prophylactic migraine medication generally considered to have efficacy: yes, no (see Section 6.2.5.4).

Note that race and ethnicity are summarized only for subjects in the United States of America, and percentages are calculated against the number of subjects in the United States of America.

6.2.5.2 Baseline Disease Characteristics

Migraine History

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

Cardiac and Other Risk Factors

Refer to the Core SAP for the frequency table of cardiac and other risk factors. This table is provided only for the DBT safety analysis set.

Migraine-Related Event Days During the OP

The table of migraine-related event days per month during the OP is provided only for the migraine analysis set, and summarizes the following efficacy parameters descriptively as continuous or categorical variables during the OP analysis period:

- Migraine days per month by pain intensity (total; moderate or severe). Categories are < 6, ≥ 6 to < 8, ≥ 8 to < 12, ≥ 12.
- Headache days per month by pain intensity (total; moderate or severe). Categories are same as for migraine days per month above.
- Acute migraine-specific medication days per month. Categories are 0, > 0 to < 2, ≥ 2 to < 4, ≥ 4 to < 6, ≥ 6 to < 8, ≥ 8 to ≤ 14, > 14. Acute migraine medication days per month. Categories are the same as for acute migraine-specific medication days per month, listed above. The table of migraine related event days per week during the OP is provided only for the first month migraine analysis set, and summarizes the following efficacy parameters descriptively as continuous or categorical variables during the OP analysis period:
- Migraine days per week by pain intensity (total; moderate or severe). Categories are < 1, ≥ 1 to < 2, ≥ 2 to < 3, ≥ 3.
- Headache days per week by pain intensity (total; moderate or severe). Categories are same as for migraine days per week above.

See Section 6.3.1 for migraine days per month, Section 6.3.3.1 for headache days per month, Section 6.3.3.3 for migraine days per week and headache days per week, Section 6.3.2.2 for acute migraine-specific medication days per month, Section 6.3.3.6 for acute migraine medication days per month, and Section 7.2 for the OP analysis period.

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

6.2.5.3 Medical History

The frequency table of medical history is provided by system organ class (SOC) and preferred term (PT), and is displayed in descending order of overall frequency within SOC and PT.

The frequency table of medical history of hypertension by SOC and PT is also provided.

6.2.5.4 Nonstudy Prior Medications

Frequency tables of the following nonstudy medications are provided by therapeutic class and preferred name:

- Previous medications for migraine prevention generally considered to have efficacy
- Previous prophylactic migraine medications
- Current medications: all; acute migraine

Medications are displayed in descending order of overall frequency within therapeutic class and preferred name. See also Section 6.2.6.3 for the definitions of acute migraine and prophylactic migraine medications.

Medications for migraine prevention generally considered to have efficacy are defined as nonstudy medications with preferred names containing any preferred name listed in the latest version of the sponsor-provided file Medications for Migraine Prevention Generally Considered to Have Efficacy.xlsx or equivalent.

Refer to the Core SAP for the definitions of previous and current medication types.

6.2.6 Exposure

See Section 7.1 for derived dates.

6.2.6.1 Study Medication

Study drug is dispensed in a wallet-type blister card with a unique wallet ID. Each wallet has 8 tablets. During the DBT Phase, each wallet contains only rimegepant, only matching placebo, or alternating rimegepant and matching placebo depending on the randomization. During the OLE Phase, each wallet contains only rimegepant. Sites report the wallet ID, study medication start date, study medication end date, and number of tablets taken per day on the IP Dosing CRF.

The kit type identifier associated with a wallet ID is DB rimegepant EOD/placebo EOD, DB rimegepant QD, DB placebo QD, or OL rimegepant, and is obtained by merging the IP Dosing CRF data with the DB study drug kit list file data and OL rimegepant kit list file data by wallet ID. Wallet IDs are 5 digits for DB study drug and 6 digits for OL rimegepant.

The by-subject listing of study drug is provided for the safety analysis set, and presents study medication start date, study medication end date, study day derived from study medication start date, number of tablets taken per day ≥ 0, wallet ID, and kit type identifier. The listing also displays DB study drug start and end dates, OL rimegepant start and end dates , displays rimegepant exposure parameters (time on DBT, time on OL rimegepant, time on DB or OL rimegepant), and identifies invalid wallet IDs. Valid DB wallet IDs are those in the DB study drug kit list file. Valid OL wallet IDs are those in the OL rimegepant kit list file. The listing is sorted by site-subject ID, study medication start date, study medication end date, and wallet ID.

DB Study Drug Exposure

The table of DB study drug exposure is provided by treatment group for the DB study drug safety analysis set, and summarizes the following parameters descriptively as continuous or categorical variables:

- Time on DB study drug (weeks), derived as (DB study drug end date – DB study drug start date + 1)/7
- Time on DB study drug (weeks) categories: < 2, ≥ 2 to < 4, ≥ 4 to < 6, ≥ 6 to < 8, ≥ 8 to < 10, ≥ 10 to < 12, ≥ 12
- Cumulative DB study drug exposure (mg), derived by summing {number of days × number of tablets taken per day × dose} across records with complete study medication start date and valid DB wallet ID.
    - Number of days for a record is derived as imputed study medication end date – study medication start date + 1.
    - If the kit type identifier is DB rimegepant EOD/placebo EOD, then the dose is 37.5 mg.
    - If the kit type identifier is DB rimegepant QD, then the dose is 75 mg.
    - Otherwise, the dose is 0.
- Average DB study drug exposure (mg per day), derived as cumulative DB study drug exposure/time on DB study drug (days)
- Total DB study drug exposure (tablets) summed across all subjects, derived by summing cumulative DB exposure across all subjects
- Total DB study drug exposure (patient-years), derived by summing (DB study drug end date – DB study drug start date + 1)/365.25 across all subjects.

OL Rimegepant Exposure

The table of OL rimegepant exposure is provided by treatment group and overall for the OL rimegepant safety analysis set, and summarizes the following parameters descriptively as continuous or categorical variables:

- Time on OL rimegepant (weeks), derived as (OL rimegepant end date – OL rimegepant start date + 1)/7
- Time on OL rimegepant (weeks) categories: < 2, ≥ 2 to < 4, ≥ 4 to < 6, ≥ 6 to < 8, ≥ 8 to < 10, ≥ 10 to < 12, ≥ 12
- Cumulative OL rimegepant exposure (mg), derived by summing {number of days × number of tablets taken per day × 75} across records with complete study medication start date and valid OL wallet ID
- Average OL rimegepant exposure (mg per day), derived as cumulative OL rimegepant exposure/time on OL rimegepant (days)

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

DB or OL Rimegepant Exposure

The table of DB or OL rimegepant exposure is provided by treatment group and overall for the DB or OL rimegepant safety analysis set, and summarizes the following parameters descriptively as continuous or categorical variables:

- Time on DB or OL rimegepant (weeks), derived as (DB or OL rimegepant end date – DB or OL rimegepant start date + 1)/7
- Time on DB or OL rimegepant (weeks) categories: < 2, ≥ 2 to < 4, ≥ 4 to < 8, ≥ 8 to < 12, ≥ 12 to < 16, ≥ 16 to < 20, ≥ 20 to < 24, ≥ 24
- Time on DB or OL rimegepant milestone categories:
  - ≥ 3 months, defined as ≥ 11 weeks
  - ≥ 6 months, defined as ≥ 23 weeks.
- Cumulative DB or OL rimegepant exposure (mg), derived by summing {number of days × number of tablets taken per day × dose} across records with complete study medication start date and kit type identifier of DB rimegepant EOD/placebo EOD, DB rimegepant QD, or OL rimegant.
  - If the kit type identifier is DB rimegepant EOD/placebo EOD, then the dose is 37.5 mg.
  - If the kit type identifier is DB rimegepant QD or OL rimegepant, then the dose is 75 mg.
- Average DB or OL rimegepant exposure (mg per day), derived as cumulative DB or OL rimegepant exposure/time on DB or OL rimegepant (days)
- Total DB or OL rimegepant exposure (tablets) summed across all subjects, derived by summing cumulative DB exposure across all subjects
- 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.

6.2.6.2 Measurements of Treatment Compliance

The by-subject listing of treatment compliance is provided for the safety analysis set, and displays results for DB and OL rimegepant treatment compliance parameters in separate columns: percentage for tablet count compliance; flags for the other parameters (“Y” or missing).

DB Treatment Compliance

The frequency table of DB treatment compliance is provided by treatment group for the DBT safety analysis set, and displays the following categories:

- DB study drug taken but not randomized
- DB tablet count compliance ≥ 80% from DB study drug start to later of last scheduled DB study drug Phase visit or DB study drug end/OL rimegepant start. Tablet count compliance is derived as 100 × actual cumulative DB tablet count/required cumulative DB tablet count, where
  - Actual cumulative DB tablet count is derived by summing the {number of days × number of tablets taken per day} across records with complete study medication start date and kit type identifier of DB rimegepant EOD/placebo EOD, DB rimegepant QD, or DB placebo QD.
    - Number of days for a record is derived as imputed study medication end date – study medication start date + 1.
  - Required cumulative DB tablet count is derived as {DB maxdate – DB study drug start date + 1} where
    - DB maxdate is defined as the latest of the (1) scheduled Week 2, 4, 8, and 12/EOT visit dates, and (2) DB study drug end date. Scheduled visits are identified from visit labels, and therefore exclude those containing "unscheduled" in the visit label.
    - If DB maxdate ≥ OL rimegepant start date, then DB maxdate is set to OL rimegepant start date – 1 day.
- > 1 DB tablet taken on any 1 day. This is determined from either of the following:
  - Records with complete study medication start date, valid DB wallet ID, and number of tablets taken per day > 1
  - Overlapping records with valid DB wallet ID (see Section 9.4)
- Incorrect DB study drug taken
  - All the time. Defined as as-treated treatment group not equal to as-randomized treatment group, i.e., any of the following:
    - Subjects randomized to rimegpant EOD/placebo EOD who took (1) ≥ 1 tablet from a DB rimegepant QD or DB placebo QD wallet, and (2) no tablets from a DB rimegepant EOD/placebo EOD wallet
    - Subjects randomized to rimegepant QD who took (1) ≥ 1 tablet from a DB rimegepant EOD/placebo EOD or DB placebo QD wallet, and (2) no tablets from a DB rimegepant QD wallet
    - Subjects randomized to placebo QD placebo who took (1) ≥ 1 tablet from a DB rimegepant QD or DB rimegepant EOD/placebo EOD wallet, and (2) no tablets from a DB placebo QD wallet.
  - At least once. Defined as any of the following:
    - Subjects randomized to rimegpant EOD/placebo EOD who took ≥ 1 tablet from a DB rimegepant QD or DB placebo QD wallet

  - Subjects randomized to rimegepant QD who took ≥ 1 tablet from a DB rimegepant EOD/placebo EOD or DB placebo QD wallet
  - Subjects randomized to placebo QD who took ≥ 1 tablet from a DB rimegepant QD or DB rimegepant EOD/placebo EOD wallet.
- Time on DB study drug > 14 weeks.

Results for all categories are displayed, even those with 0 counts.

OL Rimegepant Treatment Compliance

The frequency table of OL rimegepant treatment compliance is provided by treatment group and overall for the OL rimegepant safety analysis set, and displays the following categories:

- OL rimegepant tablet count compliance ≥ 80% from OL rimegepant start to later of last scheduled OLE Phase visit or OL rimegepant end. Tablet count compliance is derived as 100 × actual cumulative OL rimegepant tablet count/required cumulative OL rimegepant tablet count, where
  - Actual cumulative OL rimegepant tablet count is derived by summing the {number of days × number of tablets taken per day} across records with complete study medication start date and valid OL wallet ID.
  - Required cumulative OL rimegepant tablet count is derived as {OL maxdate – OL rimegepant start date + 1} where
    - OL maxdate is defined as the latest of the (1) scheduled Week 14, 16, 20, and 24/EOT visit dates, and (2) OL rimegepant end date. Scheduled visits are identified from visit labels, and therefore exclude those containing "unscheduled" in the visit label.
- > 1 OL rimegepant tablet taken on any 1 day. This is determined from either of the following:
  - Records with complete study medication start date, valid OL wallet ID, and number of tablets taken per day > 1
  - Overlapping records with valid OL wallet ID (see Section 9.4)
- Time on OL rimegepant > 14 weeks
- OL rimegepant start on or before DB study drug end. Defined as nonmissing OL rimegepant start date ≤ DB study drug end date.
- OL rimegepant taken but DB study drug never taken. Defined as nonmissing OL rimegepant start date and missing DB study drug start date.

Results for all categories are displayed, even those with 0 counts.

eDiary Usage Compliance

The table of eDiary usage compliance is provided by treatment group for the DBT safety analysis set.

eDiary DBT usage compliance is derived as follows:

- DB study drug start to later of last scheduled DBT Phase visit or DB study drug end/OL rimegepant start: 100 × (total number of efficacy data days from the DB study drug start date to the DB maxdate)/(total number of days from the DB study drug start date to the DB maxdate), where DB maxdate is defined previously.

eDiary DBT usage compliance is summarized as a continuous variable, and in the following categories: ≥ 90% compliance; ≥ 80% compliance.

In addition, the number and percentage of subjects with ≥ 24 days of eDiary efficacy data in the first 28 days of the OP are also displayed; see Section 7.2 for the 28-day OP analysis period and Section 9.2.2 for eDiary efficacy data days.

6.2.6.3 Nonstudy Concomitant Medications

Refer to the Core SAP for the following: definitions of select nonstudy medication types (i.e., previous, current, DBT concomitant, OL rimegepant concomitant, or follow-up); counting rules in nonstudy medication frequency tables; and nonstudy medication start and end date imputation.

The by-subject listing of nonstudy medications is provided by therapeutic class and preferred name for the enrolled analysis set. Acute migraine and prophylactic migraine medications are identified, as well as medication type.

The following conventions apply to nonstudy medications:

- Nonstudy medications are identified from those identified from the Previous Prophylactic Migraine Medications and Concomitant Medication CRFs. The Concomitant Medication CRF collects indications and links medical history and AE terms respectively to the Medical History and AE CRFs.
- Acute migraine medications are defined as nonstudy medications with either (1) an indication of "acute migraine medication" from the Concomitant Medications CRF, or (2) preferred name containing triptan, ergotamine, lasmiditan, or ubrogepant.
- Prophylactic migraine medications are defined as nonstudy medications either (1) from the Previous Prophylactic Migraine Medications CRF, or (2) with an indication of "prophylactic migraine medication" from the Concomitant Medications CRF.

Nonstudy DBT Concomitant Medications

Frequency tables of the following nonstudy DBT concomitant medications are provided by treatment group for the DBT safety analysis set: all; acute migraine. Medications are displayed in descending order of rimegepant QD frequency within therapeutic class and preferred name.

Nonstudy OL Rimegepant Concomitant Medications

Frequency tables of the following nonstudy OL rimegepant concomitant medications are provided by treatment group and overall for the OL rimegepant safety analysis set: all; acute migraine. Medications are displayed in descending order of overall frequency within therapeutic class and preferred name.

6.3 Efficacy

Efficacy endpoints are assessed by as-randomized treatment group.

Randomization is stratified using IWRS, but the randomization strata used in analyses are based on actual data, i.e., use of previous prophylactic migraine medication generally considered to have efficacy (see Sections 4.3 and 6.2.5.4). The rationale for using the actual data in analyses is that sites may erroneously report the wrong stratum in IWRS. Hence, treatment group comparisons of continuous efficacy endpoints are *adjusted* by the randomization stratum, whereas treatment group comparisons of binary efficacy endpoints are *stratified* by the randomization stratum (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 are based on a normal approximation to the binomial distribution using asymptotic standard error (ASE). Otherwise, CIs for continuous efficacy endpoints are based on the normal distribution. All CIs are 2-sided.

See Sections 7.2 and 7.3 for the definition of efficacy analysis periods and study days.

The by-subject listing of primary and key secondary efficacy endpoints is provided for the full analysis set, including the reason(s) for exclusion from the migraine analysis set: randomized more than once; not treated with study drug; treated with study drug and < 14 days of eDiary efficacy data in the OP; treated with study drug and < 14 days of eDiary efficacy data in all 3 months of the DBT Phase. Results for continuous endpoints are based on observed data that support descriptive analyses, whereas results for binary endpoints incorporate missing data imputation for risk estimation. Subjects with ≥ 14 days of efficacy data (not necessarily consecutive) in the month defining the endpoint are flagged for secondary endpoints based on a single month.

6.3.1 Primary Efficacy Endpoint

Subjects are instructed to report headache occurrence, headache pain features and associated symptoms, aura occurrence, and medication used to treat headache or aura in the eDiary headache report every day in the OP and DBT Phase.

Migraine days per month are assessed as “migraine days per 4 weeks” to correspond with the 4-week visit schedule. Migraine days per month are based on 4-week intervals, and are prorated to account for missing migraine reports.

See Section 9.2.2 for the definition of eDiary efficacy data days, and Section 9.2.5 for the definition of migraine days.

The number of migraine days per month in the DBT Phase is examined relative to the number of migraine days per month in the OP for the migraine analysis set, i.e., subjects with ≥ 14 days of eDiary efficacy data in both the OP analysis period and ≥ 1 month (i.e., 4-week interval) in the on-DBT efficacy 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 are based on eDiary efficacy dates in the OP and on-DBT efficacy analysis periods.

The number of migraine days per month is prorated to 28 days and derived as follows:

- OP: 28 × (total number of migraine days in the OP analysis period)/(total number of eDiary efficacy data days in the OP analysis period). Subjects must have ≥ 14 days of eDiary efficacy data (not necessarily consecutive) in the OP to be evaluable.
- 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 eDiary efficacy data days in the month). Subjects must have ≥ 14 days of eDiary efficacy data (not necessarily consecutive) in the specified month to be evaluable.
- Overall DBT: 28 × (total number of migraine days through Month 3 in the on-DBT efficacy analysis period)/(total number of eDiary efficacy data days through Month 3 in the on-DBT efficacy analysis period).

6.3.1.1 Missing Efficacy Data

The frequency table of missing efficacy data in the OP and DBT Phase is provided for the DBT efficacy analysis set, and displays the following categories:

- Included in the migraine analysis set: ≥ 14 days of eDiary efficacy data in both the OP and ≥ 1 month (i.e., 4-week interval) of the DBT Phase
  - Month 1: ≤ 4 weeks *
  - Month 2: > 4 to ≤ 8 weeks *
  - Month 3: > 8 to ≤ 12 weeks *
- Excluded from the migraine analysis set
  - < 14 days of eDiary efficacy data in the OP
  - < 14 days of eDiary efficacy data in all 3 months of the DBT Phase.

In the categories marked with "*", subjects must have ≥ 14 days of efficacy data (not necessarily consecutive) in the specified month to be evaluable.

6.3.1.2 *Migraine Days per Month Changes From OP Over Time on DBT: Descriptive Analyses*

The table of values and changes (both absolute and percent) from the OP in the number of migraine days per month in the DBT Phase is provided for the migraine analysis set, and summarizes parameters descriptively as continuous variables (including 2-sided normal 97.5% CIs for mean change) by treatment group and by pain intensity in each month of the DBT Phase and overall DBT. Pain intensity categories are (1) total (mild, moderate, severe, or not reported) and (2) moderate or severe. The table also displays results by subgroup level for all efficacy subgroups of interest described in Section 4.3.

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

6.3.1.3 *Migraine Days per Month Changes From OP Over Time on DBT: Treatment Group Comparisons*

Analyses are based on the migraine analysis set and total pain intensity, unless otherwise specified.

Main Analysis: Migraine Analysis Set

The main analysis of the primary endpoint uses a linear mixed effects model with repeated measures and the following attributes:

- Variables: change from the OP in number of total migraine days per month as the dependent variable; number of total migraine days per month in the OP as a covariate; treatment group, randomization stratum, categorical month (i.e., Months 1 to 3 of the DBT Phase), and the month-by-treatment group interaction as fixed effects.
- Covariance structure for repeated measures accounting for within-subject correlated errors: assumed to be homogeneous across treatment groups, and initially specified as unstructured. If the model fails to converge or cannot be fit with an unstructured covariance structure, then other covariance structures are specified in the following hierarchical order: Toeplitz (which has heterogenous variances and heterogenous correlations between elements); first-order autoregressive with heterogeneous variances; and first-order autoregressive with homogeneous variances.
- SE estimation method: Huber-White "sandwich" (refer to the Core SAP).

The table displays the following model estimates:

- Least-squares mean (LSM) change from OP, SE, and 97.5% CI by month and overall DBT for each treatment group
- Difference in LSM changes from OP between each rimegepant treatment group and placebo (rimegepant$_i$ – placebo; i = 1 and 2), SE, 97.5% CI, and p-value at each month and overall DBT. Results in the overall DBT support the primary objective, results in the last month

support secondary objective #2, results in the first month support secondary objective #3, and results in the second month support exploratory objective #1.

See Section 9.3.1 for example SAS code. Model estimates by randomization stratum (yes, no) are presented in the same table, using additional models that exclude randomization stratum as a fixed effect.

These main analyses are repeated for moderate or severe pain intensity to support exploratory objective #1. All variables in the model are the same, except (1) change from the OP in number of moderate or severe migraine days per month is the dependent variable, and (2) number of moderate or severe migraine days per month in the OP is the covariate. The corresponding table has the same format.

A line plot with error bars displays the LSM change from OP in the number of total migraine days per month on the y-axis versus month of the DBT Phase on the x-axis by rimegepant treatment group. Error bars denote 97.5% CIs for LSM changes.

J2R Imputation Sensitivity Analysis: DBT Efficacy Analysis Set

A sensitivity analysis of the primary endpoint uses the same model as the main analysis, but with jump to reference (J2R) to impute missing data (i.e., change from OP in the number of total migraine days per month) in Months 1 to 3 for the DBT efficacy analysis set. Placebo is considered the "reference".

The analysis is performed using the following steps:

1) Data are imputed under J2R using specific multiple imputation SAS macros for n = 30 data sets.[1,2]
   a) Subjects with < 14 days of eDiary efficacy data in a specified month in the on-DBT efficacy analysis period have missing data imputed in that month.
   b) Data imputation is applied to each treatment group.
   c) The imputation model uses the following variables: number of total migraine days per month in the OP, age, sex, race, randomization stratum, and treatment group. Race may be reduced to fewer levels (e.g., white versus non-white) based on the availability of data.
   d) The macros are run in the following order: %part1A; %part1B using n = 200 data sets (Ndraws parameter) and n = 10 as the length of the Markov chain Monte Carlo (MCMC) chain thinning (thin parameter); %part2A; and %part2B. Note that the Ndraws and thin parameters may be modified as needed (e.g., to decrease Monte Carlo error and autocorrelation).
2) Each imputed data set in step 1 is analyzed using the same model from the main analysis (see Section 9.3.1).
3) Results from each model analysis in step 2 are combined to produce a pooled difference in LSM change, SE, 97.5% CI, and p-value using SAS proc mianalyze.

The corresponding table has the same format as the one for the main analysis.

Tipping Point Sensitivity Analysis: DBT Efficacy Analysis Set

A tipping point sensitivity analysis is performed for each rimegepant treatment group separately for the DBT efficacy analysis set, and only if the p-value ≤ 0.025 for that rimegepant treatment group comparison to placebo for the main analysis of the overall DBT.

The analysis is performed for a rimegepant$_i$ treatment group (i = 1 or 2) using the following steps:

1) A shift parameter of δ = 0 is selected.
   a) Data are imputed under the missing not at random (MNAR) assumption for the rimegepant$_i$ treatment group with a shift adjustment and the missing at random (MAR) assumption for all other treatment groups using SAS proc mi for n = 30 data sets.[1,2]
      i) Subjects with < 14 days of eDiary efficacy data in a specified month in the on-DBT efficacy analysis period have missing data imputed in that month.
      ii) Data imputation is applied to each treatment group.
      iii) The fully conditional specification (FCS) method is used with regression to impute data at Months 1 to 3.
      iv) The imputation model specifies variables in the following order: changes from OP in the number of total migraine days per month at Months 1 to 3, number of total migraine days per month in the OP, age, sex, race, randomization stratum, and treatment group. Race may be reduced to fewer levels (e.g., white versus non-white) based on the availability of data.
      v) A shift of δ is applied to imputed data only for subjects in the rimegepant$_i$ treatment group.
   b) Each imputed data set in step 1a is analyzed using the same model from the main analysis (see Section 9.3.1).
   c) Results from each model analysis in step 1b are combined to produce a pooled difference in LSM change, SE, 97.5% CI, and p-value using SAS proc mianalyze.
2) The p-value for the rimegepant$_i$ treatment group comparison to placebo of the overall DBT is compared to 0.025.
   a) If p-value ≤ 0.025, then δ is incremented by 0.1, and step 1 is repeated.
   b) If p-value > 0.025, then the iterative process stops, and the last δ used becomes the tipping point.

For each shift parameter, the same statistics are provided as those in the main analysis, but only for the overall DBT and not by randomization strata. Results across all shift parameters are displayed together in the same table.

6.3.2 Secondary Efficacy Endpoints

6.3.2.1 Percentages of Subjects With Reduction From OP in Number of Migraine Days per Month Over Time on DBT

Analyses are based on the migraine analysis set with eDiary efficacy data dates in the OP and on-DBT efficacy analysis periods (see Section 7.2).

In analyses by months, subjects must (1) achieve the reduction criterion from OP in the number of migraine days per month in the specified month, (2) have ≥ 14 days of eDiary efficacy data (not necessarily consecutive) in the specified month, and (3) have ≥ 1 migraine day (absolute not prorated) of appropriate pain intensity in the OP analysis period to be classified as responders in the specified month. Otherwise, subjects are classified as failures in the specified month.

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

Treatment Group Comparisons

For each pain intensity (total; moderate or severe) and select percentage reduction (≥ 50%, ≥ 75%, and 100%), the percentages of subjects with reductions in the number of migraine days per month are compared between each rimegepant treatment group and placebo using Mantel-Haenszel risk estimation with stratification by randomization stratum (yes, no). Percentages are calculated against the number of subjects in the migraine analysis set.

The table displays the following statistics at each month of the DBT Phase and overall DBT by pain intensity:

- Response rate (i.e., "n/N" and percentage), ASE, and 97.5% CI for each treatment group
- Stratified percentage difference between each rimegepant treatment group and placebo (rimegepant$_i$ – placebo; i = 1 and 2), ASE, 97.5% CI, and p-value
- Response rate (i.e., "n/N" and percentage), ASE, and 97.5% CI by randomization stratum for each treatment group
- Percentage difference between each rimegepant treatment group and placebo (rimegepant$_i$ – placebo; i = 1 and 2), ASE, 97.5% CI, and p-value by randomization stratum.

Results for the endpoint of ≥ 50% reduction of moderate or severe pain intensity in the overall DBT support secondary objective #1. Results for all other endpoints support exploratory objective #2.

6.3.2.2 Acute Migraine-Specific Medication Days per Month Over Time on DBT

During the DBT Phase, subjects may record taking triptan, ergotamine, and other medications to treat headache or aura yesterday in the eDiary headache report.

Acute migraine-specific medication days per month are assessed as "acute migraine-specific medication days per 4 weeks" to correspond with the 4-week visit schedule. Acute migraine-specific medication days per month are based = on 4-week intervals. See Section 9.2.4 for the definition of acute migraine-specific medication days.

Analyses are based on the migraine analysis set with eDiary efficacy dates in the on-DBT efficacy analysis period.

The number of acute migraine-specific medication days per month in the DBT Phase is 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 acute migraine-specific medication days in the month)/(total number of eDiary efficacy data days in the month). Subjects must have ≥ 14 days of eDiary efficacy data (not necessarily consecutive) in the specified month to be evaluable.
- Overall DBT: 28 × (total number of acute migraine-specific medication days through Month 3 in the on-DBT efficacy analysis period)/(total number of eDiary efficacy data days through Month 3 in the on-DBT efficacy analysis period).

Descriptive Analyses

The table of the number of acute migraine-specific medication days per month in the DBT analysis period is provided, and summarizes the parameter descriptively as a continuous variable by treatment group in each month of the DBT Phase and overall DBT.

Treatment Group Comparisons

Treatment groups are compared using a linear mixed effects model with repeated measures and the following attributes:

- Variables: number of acute migraine-specific medication days per month as the dependent variable; treatment group, randomization stratum, month (i.e., Months 1 to 3 of the DBT Phase), and the month-by-treatment group interaction as fixed effects
- Covariance structure for repeated measures accounting for within-subject correlated errors : See Section 6.3.1.3.
- SE estimation method: See Section 6.3.1.3.

The table displays the following model estimates:

- LSM, SE, and 97.5% CI by month and overall DBT for each treatment group
- Difference in LSMs between each rimegepant treatment group and placebo (rimegepant$_i$ – placebo; i = 1 and 2), SE, 97.5% CI, and p-value at each month and overall DBT. Results in the overall DBT support secondary objective #4, whereas results at other time points support exploratory objective #6.

See Section 9.3.1 for example SAS code. Model estimates by randomization stratum (yes, no) are presented in the same table, using additional models that exclude randomization stratum as a fixed effect.

6.3.2.3 Overall Summary of Primary and Key Secondary Endpoints in Hierarchical Testing

An overall summary table of treatment comparisons of all primary and key secondary endpoints tested hierarchically displays the following statistics:

- Continuous endpoints involving change from OP or baseline
  - n (i.e., number of subjects in the analysis set), LSM change, and 97.5% CI for each treatment group
  - Difference in LSM changes between each rimegepant treatment group and placebo, 97.5% CI, and p-value.

  This applies to the primary endpoint and the following secondary efficacy and outcomes research endpoints: mean change in number of migraine days per month in the last month of the DBT Phase (see main analysis in Section 6.3.1.3); mean change in number of migraine days per month in the first month of the DBT Phase (see main analysis in Section 6.3.1.3); and MSQoL restrictive role domain score mean change from baseline at Week 12 (see Section 6.5.1).
- Continuous endpoints not involving change from OP or baseline
  - n, LSM, and 97.5% CI for each treatment group
  - Difference in LSMs between each rimegepant treatment group and placebo, 97.5% CI, and p-value.

  This applies to the secondary efficacy endpoint of the mean number of acute migraine-specific medication days per month over the entire DBT Phase (see Section 6.3.2.2).
- Binary endpoints
  - Response rate ("n/N" and percentage) and 97.5% CI for each treatment group
  - Stratified percentage difference between each rimegepant treatment group and placebo, 97.5% CI, and p-value.

  This applies to the secondary efficacy endpoint of percentage of subjects with ≥ 50% reduction in number of moderate or severe migraine days per month over the entire DBT Phase (see Section 6.3.2.1).

Endpoints are displayed in the order presented in Sections 3.2.1 and 3.2.2. P-values that are determined to be significant based on the testing hierarchy are flagged.

If the main analysis of the primary endpoint is significant for a rimegepant dosing regimen (i.e., p-value ≤ 0.025; see Section 6.3.1.3), then the key secondary efficacy and outcomes research endpoints are tested hierarchically, each at a 2-sided alpha level of 0.025, in the order specified in Section 3.2.2. Thus, for a rimegepant dosing regimen, a key secondary efficacy or outcomes

research endpoint is tested only if the preceding key secondary endpoint in the hierarchy is determined to be significant (i.e., p-value ≤ 0.025). If a test in the hierarchy is not significant, then any further tests on endpoints in the sequence have p-values presented only for descriptive purposes, and no conclusions are drawn from those results.

If the main analysis of the primary endpoint is not significant (i.e., p-value > 0.025), then any further tests of key secondary endpoints will have p-values presented only for descriptive purposes, and no conclusions are drawn from those results.

For a given rimegepant dosing regimen to placebo comparison of a continuous endpoint, the null hypothesis of interest H_0 is that the mean change observed on rimegepant (denoted $\mu_{rimegepant}$) is equal to the one observed on placebo (denoted $\mu_{placebo}$), i.e., H_0: $\mu_{rimegepant} = \mu_{placebo}$. The alternative 2-sided hypothesis of interest H_1 is that the mean changes observed on rimegepant and placebo differ, i.e., H_1: $\mu_{rimegepant} \neq \mu_{placebo}$. For a given rimegepant dosing regimen to placebo comparison of a binary endpoint, the hypotheses are based on percentages instead of mean changes.

The overall summary table of treatment comparisons of all primary and key secondary efficacy endpoints during the DBT Phase is also produced by subgroup level for all efficacy subgroups of interest described in Section 4.3. Separate tables are provided for each subgroup. Analyses of continuous endpoints are performed using models that exclude randomization stratum as a fixed effect, while analyses of binary endpoints are performed unstratified. P-values are presented only for descriptive purposes, and are not flagged for significance.

6.3.3 Exploratory Efficacy Endpoints

6.3.3.1 Headache Days per Month Changes From OP Over Time on DBT

The number of headache days per month is prorated to 28 days and defined analogously to migraine days per month (see Section 6.3.1).

A headache day is defined in Section 9.2.6.

Analyses are based on the migraine analysis set with eDiary efficacy data dates in the OP and on-DBT efficacy analysis periods (see Section 7.2).

Descriptive Analyses

The table of values and changes (both absolute and percent) from the OP in the number of headache days per month in the DBT Phase is provided, and has the same format as the one described in Section 6.3.1.2.

In the percent change analyses, subjects must also have ≥ 1 headache day (absolute not prorated) of appropriate pain intensity in the OP analysis period to be included.

Treatment Group Comparisons

Treatment groups are compared using a model with the same attributes as the one for the primary endpoint except that (1) change from the OP in number of total headache days per month is the dependent variable, and (2) number of total headache days per month in the OP is a covariate. The table has the same format as the one described in Section 6.3.1.3.

These analyses are repeated for moderate or severe pain intensity. All variables in the model are the same, except (1) change from the OP in number of moderate or severe headache days per month is the dependent variable, and (2) number of moderate or severe headache days per month in the OP is the covariate. The table has the same format.

Results support exploratory objective #1.

6.3.3.2 Percentage of Subjects With Reduction From the OP in Number of Headache Days per Month Over Time on DBT

Analyses are based on the migraine analysis set with eDiary efficacy data dates in the OP and on-DBT efficacy analysis periods (see Section 7.2). The percentage of subjects with reduction in the number of headache days during the DBT Phase is defined and assessed analogously to the percentage of subjects with reduction in the number of migraine days during the DBT Phase (see Section 6.3.2.1).

Treatment Group Comparisons

For each pain intensity (total; moderate or severe) and select percentage reduction (≥ 50%, ≥ 75%, and 100%), the percentages of subjects with reduction in the number of headache days per month are compared between each rimegepant treatment group and placebo using Mantel-Haenszel risk estimation with stratification by randomization stratum (yes, no). The table has the same format as the one described in Section 6.3.2.1. Results support exploratory objective #2.

6.3.3.3 Migraine Days per Week and Headache Days per Week Changes From the OP Over Time in the First Month on DBT

The number of migraine days per week in the first month (Weeks 1 to 4) of the DBT Phase is examined relative to the number of migraine days per week in the OP for the first month migraine analysis set, i.e., subjects in the DBT efficacy analysis set with ≥ 24 days of eDiary efficacy data (not necessarily consecutive) in both the OP analysis period and first month of the on-DBT efficacy analysis period.

Weeks 1 to 4 of the DBT Phase are defined as follows:

- Week 1: study days 1 to 7
- Week 2: study days 8 to 14
- Week 3: study days 15 to 21
- Week 4: study days 22 to 28.

See Sections 7.2 and 7.3 for the definition of analysis periods and study days used to define analysis visit windows.

Analyses are based on the first month migraine analysis set using eDiary efficacy data dates in the OP and on-DBT efficacy analysis periods.

The number of migraine days per week is prorated to 7 days and derived as follows:

- OP: 7 × (total number of migraine days in the OP analysis period)/(total number of eDiary efficacy data days in the OP analysis period)
- Week (7-day interval) of the on-DBT efficacy analysis period: 7 × (total number of migraine days in the week)/(total number of eDiary efficacy data days in the week).

The number of headache days per week is derived analogously.

Descriptive Analyses

The table of values and changes (both absolute and percent) from the OP in the number of migraine days per week in the first month (Weeks 1 to 4) of the DBT Phase is provided, and summarizes parameters descriptively as continuous variables (including 2-sided normal 97.5% CIs for mean change) by treatment group and pain intensity (total; moderate or severe). In the percent change analyses, subjects must also have ≥ 1 migraine day of appropriate intensity (absolute not prorated) in the OP analysis period to be included.

The table of values and changes from the OP in number of headache days per week in the first month of the DBT Phase is provided analogously.

Treatment Group Comparisons

Treatment groups are compared using a linear mixed effects model with repeated measures and the following attributes:

- Variables: change from the OP in number of total migraine days per week as the dependent variable; number of total migraine days per week in the OP as a covariate; treatment group, randomization stratum, week (i.e., Weeks 1 to 4 of the DBT Phase), and the week-by-treatment group interaction as fixed effects.
- Covariance structure for repeated measures accounting for within-subject correlated errors: See Section 6.3.1.3.
- SE estimation method: See Section 6.3.1.3.

The table displays the following model estimates:

- LSM change from OP, SE, and 97.5% CI by week for each treatment group
- Difference in LSM changes from OP between each rimegepant treatment group and placebo (rimegepant$_i$ – placebo; i = 1 and 2), SE, 97.5% CI, and p-value for each week.

See Section 9.3.1 for example SAS code. Model estimates by randomization stratum (yes, no) are presented in the same table, using additional linear mixed effects models that exclude randomization stratum as a fixed effect.

These analyses are repeated for moderate or severe pain intensity. All variables in the model are the same, except (1) change from the OP in number of moderate or severe migraine days per week is the dependent variable, and (2) number of moderate or severe migraine days per week in the OP is the covariate. The corresponding table has the same format.

All analyses described above are performed analogously for headache days per week.

Results support exploratory objective #3.

6.3.3.4 Percentages of Subjects With Reductions in Numbers of Migraine Days per Week and Headache Days per Week Over Time in the First Month on DBT

Analyses are based on the first month migraine analysis set with eDiary efficacy data dates in the OP and on-DBT efficacy analysis periods (see Section 7.2).

In analyses of migraine days per week, subjects must (1) achieve the reduction criterion from OP in the number of migraine days in the specified week, and (2) have ≥ 1 migraine day (absolute not prorated) of appropriate pain intensity in the OP analysis period to be classified as responders in the specified week. Otherwise, subjects are classified as failures in the specified week.

Analyses of headache days per week are defined analogously.

Treatment Group Comparisons

For each pain intensity (total; moderate or severe), the percentages of subjects with ≥ 50% reduction in the number of migraine days per week are compared between each rimegepant treatment group and placebo using Mantel-Haenszel risk estimation with stratification by randomization stratum (yes, no). Percentages are calculated against the number of subjects in the first month migraine analysis set.

The table displays the following statistics at each week of the DBT Phase by pain intensity:

- Response rate (i.e., "n/N" and percentage), ASE, and 97.5% CI for each treatment group
- Stratified percentage difference between each rimegepant treatment group and placebo (rimegepant$_i$ – placebo; i = 1 and 2), ASE, 97.5% CI, and p-value
- Response rate (i.e., "n/N" and percentage), ASE, and 97.5% CI by randomization stratum for each treatment group and placebo
- Percentage difference between each rimegepant treatment group and placebo (rimegepant$_i$ – placebo; i = 1 and 2), ASE, 97.5% CI, and p-value by randomization stratum.

All analyses described above are performed analogously for headache days per week.

Results support exploratory objective #4.

6.3.3.5 *Percentages of Subjects With Migraine Days and Headache Days Over Time in the First Week on DBT*

Analyses are based on the first week treated migraine analysis set, i.e., subjects in the DBT efficacy analysis set with (1) ≥ 24 days of eDiary efficacy data (not necessarily consecutive) in the OP analysis period, (2) 7 consecutive days of eDiary efficacy data in the first week (i.e., study days 1 through 7) of the DBT efficacy analysis period, and (3) 7 consecutive days of DB study drug dosing in the first week of the DBT efficacy analysis period (see Section 9.4).

Treatment Group Comparisons

Analyses are based on the first week migraine analysis set with eDiary efficacy data dates in the OP and on-DBT efficacy analysis periods (see Section 7.2).

For each pain intensity (total; moderate or severe), the percentages of subjects with a migraine day are compared between each rimegepant treatment group and placebo using Mantel-Haenszel risk estimation with stratification by randomization stratum (yes, no) at study days 1 through 7 of the DBT Phase. Percentages are calculated against the number of subjects in the first week treated migraine analysis set.

The table displays the following statistics at study days 1 through 7 by pain intensity:

- Response rate (i.e., "n/N" and percentage), ASE, and 97.5% CI for each treatment group
- Stratified percentage difference between each rimegepant treatment group and placebo (rimegepant$_i$ – placebo; i = 1 and 2), ASE, 97.5% CI, and p-value.
- Response rate (i.e., "n/N" and percentage), ASE, and 97.5% CI by randomization stratum for each treatment group
- Percentage difference between each rimegepant treatment group and placebo (rimegepant$_i$ – placebo; i = 1 and 2), ASE, 97.5% CI, and p-value by randomization stratum.

The table also summarizes the percentage of migraine days by pain intensity (total; moderate or severe) in the OP descriptively as a continuous variable as a baseline reference. For each subject, the percentage is calculated as 100 × (total number of migraine days in the OP analysis period)/(total number of eDiary efficacy data days in the OP analysis period).

All analyses described above are performed analogously for headache days.

Results support exploratory objective #5.

6.3.3.6 *Acute Migraine Medication Days per Month Over Time on DBT*

Acute migraine medication days per month are assessed analogously to acute migraine-specific medication days per month (see Section 6.3.2.2).

An acute migraine medication day is defined in Section 9.2.3.

Analyses are based on the migraine analysis set with eDiary efficacy dates in the on-DBT efficacy analysis period.

The number of acute migraine medication days per month in the DBT Phase is prorated to 28 days.

Descriptive Analyses

The table of the number of acute migraine medication days per month in the DBT Phase is provided, and has the same format as the one in Section 6.3.2.2.

Treatment Group Comparisons

Treatment groups are compared using a model with the same properties as the model specified in Section 6.3.2.2, except that the number of acute migraine medication days per month is the dependent variable. Results support exploratory objective #7.

6.4 Safety

Safety parameters include the following: deaths; AEs; laboratory tests; vital signs; physical measurements; electrocardiograms (ECGs); and Columbia-Suicidality Severity Rating Scale (C-SSRS.

Tables of safety endpoints are provided according to safety analysis period and analysis set:

- On-DBT safety for the DBT safety analysis set by treatment group
- Post-DBT pre-OL rimegepant safety for the interim safety analysis set by treatment group and overall
- On-OL rimegepant safety for the OL rimegepant safety analysis set by treatment group/OL rimegepant and overall
- On-DB or OL rimegepant safety for the DB or OL rimegepant safety analysis set by treatment group/OL rimegepant and overall
- Follow-up safety for the follow-up safety analysis set by treatment group/OL rimegepant status and overall.

Results are presented by as-treated treatment group according to Section 6.1.1.1.

Measurements are slotted into analysis periods and analysis visits using the following steps:

1) Measurements are slotted into the pretreatment, on-treatment safety, and follow-up safety analysis periods.
2) Measurements are slotted into analysis visits in the analysis periods listed in the previous step (see Table 5). This does not apply to AEs.

3) Measurements in the on-treatment safety analysis period are slotted further into the on-DBT, post-DBT pre-OL rimegepant, and on-OL rimegepant safety analysis periods.

Refer also to the Core SAP for details about measurement slotting. See Sections 6.2.5, 7.2 and 7.3 for definitions of baseline, analysis periods, and analysis visit windows, respectively.

6.4.1 Adverse Events

Refer to the Core SAP for the following: AE start and end date imputation; death date derivation; counting and rounding rules in AE frequency tables; definitions of AEs related to study drug, AEs of special interest, and exposure-adjusted multiple occurrences of unique AEs; and TLF contents.

Frequency tables of AEs by SOC and PT display AEs in descending order of overall frequency within SOC and PT, unless otherwise specified.

The by-subject listing of AEs (i.e., non-SAEs and SAEs) is provided for the enrolled analysis set.

6.4.1.1 Deaths

Deaths are identified from any of the following sources:

- AE CRF with any of the following: PT or reported term of "death"; outcome of "fatal"; "yes" response to any death-related question (e.g., "Did the AE result in death?"; "Is a death certificate available?"; "Is an autopsy report available?"); complete or partially complete death date.
- DB Subject Status CRF with any of the following: death as reason for DBT Phase noncompletion; death as reason for not continuing to the next phase (see Section 6.2.3.3)
- OLE Subject Status CRF with any of the following: death as reason for OLE Phase noncompletion; death as reason for not continuing to the Follow-Up Phase (see Section 6.2.3.4)
- Follow-up Subject Status CRF: death as reason for Follow-Up Phase noncompletion (see Section 6.2.3.5).

The by-subject listing of deaths is provided for the enrolled analysis set.

6.4.1.2 AE Overviews

An AE overview frequency table displays the following categories without SOC and PT: any AE; AE related to study drug; AE leading to study drug discontinuation; SAE; SAE related to study drug; medication-overuse headache AE; hepatic-related AE; hepatic-related AE leading to study drug discontinuation; potential drug abuse AE; cardiovascular AE; suicidality AE; hypertension AE; and Raynaud's phenomenon AE.

AE overview frequency tables are provided for the following safety analysis periods and analysis sets:

- On-DBT for the DBT safety analysis set
- Post-DBT pre-OL rimegepant for the interim safety analysis set
- On-OL rimegepant for the OL rimegepant safety analysis set
- On-DB or OL rimegepant for the DB or OL rimegepant safety analysis set
- Follow-up for the follow-up safety analysis set.

6.4.1.3 On-DBT AEs

Frequency tables of on-DBT AEs are provided for the DBT safety analysis set by SOC and PT for the following endpoints:

- AEs by worst intensity (secondary objective #6)
- AEs related to study drug by worst intensity
- SAEs (secondary objective #6)
- AEs leading to study drug discontinuation
- Hepatic-related AEs (secondary objective #8)
- Hepatic-related AEs leading to study drug discontinuation
- Potential drug abuse AEs, displayed in alphabetical order by intensity and PT without SOC
- Cardiovascular AEs
- Suicidality AEs
- Hypertension AEs
- Hypertension AEs for subjects with medical history of hypertension.

Frequency tables of AEs by SOC and PT display AEs in descending order of rimegepant QD frequency within SOC and PT, unless otherwise specified.

6.4.1.4 On-OL Rimegepant AEs

Frequency tables of on-OL rimegepant AEs are provided for the OL rimegepant safety analysis set by SOC and PT for the following endpoints:

- AEs by worst intensity (secondary objective #6)
- AEs related to study drug by worst intensity
- SAEs (secondary objective #6)
- AEs leading to study drug discontinuation
- Hepatic-related AEs (exploratory objective #10)
- Hepatic-related AEs leading to study drug discontinuation (exploratory objective #10)

- Potential drug abuse AEs, displayed in alphabetical order by worst intensity and PT without SOC
- Cardiovascular AEs
- Suicidality AEs
- Hypertension AEs
- Hypertension AEs for subjects with medical history of hypertension.

6.4.1.5 On-DB or OL Rimegepant AEs

Frequency tables of on-DB or OL rimegepant AEs are provided for the DB or OL rimegepant safety analysis set by SOC and PT for the following endpoints:.

- AEs by worst intensity (other secondary objective #1)
- SAEs (other secondary objective #1)
- Exposure-adjusted multiple occurrences of unique AEs.

Calculations for on-DB or OL rimegepant exposure-adjusted multiple occurrences of unique AEs use an analysis period reference start date = DB or OL rimegepant start date, analysis period reference end date = DB or OL rimegepant last date + 7 days if the DB or OL rimegepant last date is nonmissing, and analysis period reference end date = DB or OL rimegepant end date if the DB or OL rimegepant last date is missing.

6.4.1.6 Follow-Up AEs

Frequency tables of follow-up AEs are provided by SOC and PT for the follow-up safety analysis set for the following endpoints:

- AEs by worst intensity
- SAEs.

6.4.2 Laboratory Tests

Laboratory tests are analyzed using results from local laboratory tests reported on CRFs and the external central laboratory ACM Global Laboratories. TLFs display results in both Systeme Internationale (SI) units and United States (US) units, if applicable.

Laboratory tests of clinical interest are collected at the following visits:

- Hematology: Screening; Pre-Randomization; Weeks 2, 4, 8, 12, 14, and 24; and EOT
- Serum chemistry: Screening; Pre-Randomization; Weeks 2, 4, 8, 12, 14, and 24; and EOT. Exceptions are for the following:
  - LFTs (ALT, AST, alkaline phosphatase [ALP], TBL, direct bilirubin, indirect bilirubin): All visits

  - Lipids (total cholesterol, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, triglycerides): Pre-Randomization; Weeks 12 and 24; and EOT

- Urinalysis: Pre-randomization; Weeks 12 and 24; and EOT.

The following by-subject laboratory test listings are provided for the enrolled analysis set:

- Laboratory test results using the Common Technical Criteria for Adverse Events/Division of Acquired Immune Deficiency Syndrome (CTCAE/DAIDS) toxicity grading scale (SI units). The listing displays all test results over time for subjects with grade 3 to 4 laboratory test abnormalities at any time point.
- Laboratory test results using the Food and Drug Administration (FDA) toxicity grading scale (US units). The listing displays all test results over time for subjects with grade 3 to 4 laboratory test abnormalities at any time point.
- LFT values and ratios to ULN (i.e., ALT, AST, TBL and ALP) (SI units). The listing displays all LFT results over time for subjects with select LFT elevations (ALT or AST > 3x ULN; ALP or TBL > 2x ULN) at any time point.
- Pregnancy test results (SI units). The listing displays all pregnancy test results over time for subjects with a positive pregnancy test at any time point.

Refer to the protocol for laboratory tests of clinical interest. Refer to the Core SAP for toxicity grades and TLF contents.

6.4.2.1 Laboratory Test Abnormalities

Frequency tables of the worst (highest) laboratory test abnormality for each graded laboratory test are provided for the following safety analysis periods and analysis sets:

- On-DBT for the DBT safety analysis set
- On-OL rimegepant for the OL rimegepant safety analysis set
- Follow-up for the follow-up safety analysis set.

Grade 3 to 4 results support other secondary objective #7.

Frequency tables of laboratory test shift from baseline to the worst abnormality for each graded laboratory test are provided for the following safety analysis periods and analysis sets:

- On-DBT for the DBT safety analysis set
- On-OL rimegepant for the OL rimegepant safety analysis set.

6.4.2.2 LFT Elevations

Analyses use SI units.

LFT Elevations

Frequency tables of LFT elevations are provided for the following analysis periods and analysis sets:

- On-DBT for the DBT safety analysis set
- Post-DBT pre-OL rimegepant for the interim safety analysis set
- On-OL rimegepant for the OL rimegepant safety analysis set
- On-DB or OL rimegepant for the DB or OL rimegepant safety analysis set
- Follow-up for the follow-up safety analysis set.

Results support secondary objective #7 and exploratory objectives #8 and #9.

A confidence level of 97.5% is used for CIs.

LFT Shifts From Baseline to Worst Elevation

Frequency tables of LFT shifts from baseline to the worst (highest) LFT elevation are provided for the following safety analysis periods and analysis sets:

- On-DBT for the DBT safety analysis set
- On-OL rimegepant for the OL rimegepant safety analysis set.

Exposure-Adjusted Cumulative LFT Elevations

Frequency tables of exposure-adjusted cumulative LFT elevations are provided for the following safety analysis periods and analysis sets:

- On-DB or OL rimegepant for the DB or OL rimegepant safety analysis set.

Calculations use the same analysis period reference start and end dates as corresponding exposure-adjusted AEs (see Sections 6.4.1.5).

Time to First LFT Elevation

Frequency tables of time to first LFT elevation are provided for the following safety analysis periods and analysis sets:

- On-DB or OL rimegepant for the DB or OL rimegepant safety analysis set with on-DB or OL rimegepant LFT elevations
  - Time categories are: ≤ 2, > 2 to ≤ 4, > 4 to ≤ 8, > 8 to ≤ 12, > 12 to ≤ 16, > 16 to ≤ 20, > 20 to ≤ 24, > 24 weeks.
  - Time to elevation is calculated as (LFT collection date – DB or OL rimegepant start date + 1)/7.

LFT Plots

Evaluation of drug-induced serious hepatotoxicity (eDISH) scatter plots are provided for the following safety analysis periods and analysis sets:

- On-DBT for the DBT safety analysis set by treatment group
- On-OL rimegepant for the OL rimegepant safety analysis set by treatment group/OL rimegepant.

By-subject LFT line plots are provided for the safety analysis set with select LFT elevations in any safety analysis period. Study weeks are defined as study day/7, where study day is derived from the laboratory test collection date (see Section 7.3). Each figure also displays DB study drug and OL rimegepant dosing days using symbols along the x-axis (see Section 9.4), and denotes additional study milestones (e.g., start of the on-DBT safety analysis period, start of the on-OL rimegepant safety analysis period, and start of the follow-up safety analysis period) using vertical lines with their corresponding descriptions in footnotes.

6.4.2.3 Laboratory Test Changes From Baseline Over Time

The table of values and changes from baseline in all hematology and serum chemistry laboratory tests is provided by treatment group and overall for the safety analysis set at the following time points: baseline; each scheduled visit through Week 12 and EOT in the on-DBT safety analysis period; each scheduled visit after Week 12 through Week 24 and EOT in the on-OL rimegepant safety analysis period; and each scheduled visit in the follow-up safety analysis period. Results for overall are displayed only at baseline and time points in the on-OL rimegepant and follow-up safety analysis periods.

Note that scheduled visits vary according to laboratory test.

A separate table is provided for each unit system (SI or US).

Refer to the Core SAP for (1) handling multiple values in an analysis visit window or on the same laboratory test collection date, and (2) deriving the EOT value in an on-treatment safety analysis period.

6.4.3 Vital Signs and Physical Measurements

Vital signs include systolic blood pressure, diastolic blood pressure, heart rate, temperature, and respiratory rate. Physical measurements include height, weight, and body mass index (BMI). These parameters are measured at all visits, except that height is measured only at the Screening Visit.

Refer to the Core SAP for TLF contents.

6.4.3.1 Vital Sign and Physical Measurement Changes From Baseline Over Time

The table of values and changes from baseline in vital sign and physical measurement parameters is provided by treatment group and overall for the safety analysis set at the following time points: baseline; each scheduled visit through Week 12 and EOT in the on-DBT safety analysis period;

each scheduled visit after Week 12 through Week 24 and EOT in the on-OL rimegepant safety analysis period; and each scheduled visit in the follow-up safety analysis period. Results for overall are displayed only at baseline and time points during the on-OL rimegepant and follow-up safety analysis periods.

The table of values and changes from baseline in vital sign parameters is also provided for the safety analysis set with medical history of hypertension.

Refer to the Core SAP for (1) handling multiple values in an analysis visit window or on the same measurement date, and (2) deriving the EOT value in an on-treatment safety analysis period.

6.4.3.2 Vital Sign and Physical Measurement Abnormalities

Frequency tables of vital sign and physical measurement abnormalities are provided for the following safety analysis periods and analysis sets:

- On-DBT for the DBT safety analysis set
- On-OL rimegepant for the OL rimegepant safety analysis set
- Follow-up for the follow-up safety analysis set.

Frequency tables of vital sign abnormalities are provided for the following safety analysis periods and analysis sets:

- On-DBT for the DBT safety analysis set with medical history of hypertension
- On-OL rimegepant for the OL rimegepant safety analysis set with medical history of hypertension.

6.4.4 Electrocardiograms

ECG parameters include RR, QRS, PR, QT, QTcB, QTcF, and ventricular heart rate. ECGs are measured by the external source Clario at the following visits: Screening; Pre-randomization; Weeks 2, 4, 8, 12, 14, and 24; and EOT.

Refer to the Core SAP for TLF contents.

6.4.4.1 ECG Changes From Baseline Over Time

The table of values and changes from baseline in ECG parameters is provided by treatment group and overall for the safety analysis set at the following time points: baseline; each scheduled visit through Week 12 and EOT in the on-DBT safety analysis period; and each scheduled visit after Week 12 through Week 24 and EOT in the on-OL rimegepant safety analysis period. Results for overall are displayed only at baseline and time points in the on-OL rimegepant safety analysis period.

Refer to the Core SAP for (1) handling multiple values in an analysis visit window or on the same measurement date, and (2) deriving the EOT value in an on-treatment safety analysis period.

6.4.4.2 ECG Abnormalities

Frequency tables of ECG abnormalities are provided for the following safety analysis periods and analysis sets:

- On-DBT for the DBT safety analysis set
- On-OL rimegepant for the OL rimegepant safety analysis set
- Follow-up for the follow-up safety analysis set.

ECG abnormalities are presented together with vital sign and physical measurement abnormalities in the same frequency tables (see Section 6.4.3.2).

6.4.5 C-SSRS

The C-SSRS is a clinician administered questionnaire used to help establish immediate risk of suicide. The C-SSRS is administered at EOT and all visits except Pre-Randomization and Follow-Up Week 8. At the Screening Visit, the recall period for completing is 12 months for suicidal ideation and 10 years for suicidal behavior; at all other visits, the recall period for completing the C-SSRS is since the last visit.

Frequency tables of C-SSRS suicidality are provided for the following safety analysis periods and analysis sets:

- On-DBT for the DBT safety analysis set
- On- OL rimegepant for the OL rimegepant safety analysis set
- Follow-up for the follow-up safety analysis set.

Refer to the Core SAP for calculation of C-SSRS parameters and TLF contents.

6.4.6 Safety Narrative Subject Identifiers

The by-subject listing of safety narrative subject identifiers is provided for the following select events as columns:

- Death in any analysis period for the enrolled analysis set
- SAE on DB or OL rimegepant or during follow-up for the DB or OL rimegepant safety analysis set
- Non-SAE leading to study drug discontinuation in any analysis period for the DB or OL rimegepant safety analysis set
- Event of special interest on DB or OL rimegepant for the DB or OL rimegepant safety analysis set:

- Select hepatic-related non-SAE, i.e., PT containing cirrhosis, hepatic failure, hepatitis, jaundice, or liver failure
- Cardiovascular non-SAE
- Suicidality non-SAE
- Hypertension non-SAE
- Raynaud's phenomenon non-SAE
- ALT or AST > 3x ULN
- ALT or AST > 3x ULN concurrent with TBL > 2x ULN
- ALP or TBL > 2x ULN.

Refer to the Core SAP for additional details.

6.5 Outcomes Research

Analyses are based on as-randomized treatment group for the DBT efficacy analysis set.

Randomization strata used in analyses are based on the actual data.

Outcomes research questionnaires and rating scales are MSQoL, SM, and CGI-c, and are assessed from respective CRFs. These are assessed at Baseline (MSQoL only), Week 12, Week 24, and EOT.

Measurements are slotted into analysis periods and analysis visits using the following steps:

1) Measurements are slotted into the pretreatment, DBT outcomes research, and OL rimegepant outcomes research analysis periods.
2) Measurements are slotted into the Week 12 and Week 24 analysis visits in the analysis periods listed in the previous step (see Table 5).

See Sections 6.2.5, 7.2, and 7.3 for definitions of baseline, outcomes research analysis periods, and analysis visit windows, respectively.

The by-subject listing of MSQoL is provided for the enrolled analysis set, and displays values and changes from baseline in domain scores.

A confidence level of 97.5% is used for CIs.

Refer to the Core SAP for the following: detailed descriptions of these questionnaires and rating scales; calculating scores and imputing missing data; deriving categories; handling multiple questionnaires or rating scale values in an analysis visit window or on the same assessment date; and TLF contents.

6.5.1 MSQoL Domain Score Changes From Baseline Over Time

The MSQoL consists of 14 items across the following 3 domains: (1) restrictive role function, (2) preventive role function and (3) emotional function.

Descriptive Analyses

The table of values and changes from baseline in scores is provided by treatment group and overall for each domain for the DBT efficacy analysis set at the following time points: baseline; Week 12 of the DBT outcomes research analysis period; Week 24 of the OL rimegepant outcomes research analysis period. Results for overall are displayed only at baseline and Week 24 of the OL rimegepant outcomes research analysis period.

The frequency table of MSQoL domain score increase from baseline categories is provided by treatment group and overall for the DBT efficacy analysis set at the following time points: Week 12 of the DBT outcomes research analysis period; Week 24 of the OL rimegepant outcomes research analysis period. Results for overall are displayed only at Week 24 of the OL rimegepant outcomes research analysis period.

Results support exploratory objective #10.

Treatment Group Comparisons

Analyses of each domain are based on the DBT efficacy analysis set with paired data, i.e., nonmissing domain scores at both baseline and Week 12 of the DBT outcomes research analysis period.

For each domain, treatment groups are compared using a linear regression model with the following attributes:

- Variables: Week 12 change from baseline in the score as the dependent variable; baseline score as a covariate; treatment group and randomization stratum as fixed effects.
- SE estimation method: see Section 6.3.1.3.

The table provides n (i.e., number of subjects with paired data) and the following model estimates for each domain:

- LSM change from baseline at Week 12, SE, and 97.5% CI for each treatment group
- Difference in LSM changes from baseline at Week 12 between each rimegepant treatment group and placebo (rimegepant$_i$ – placebo; i = 1 and 2), SE, 97.5% CI, and p-value.

Results for the restrictive role function support secondary objective #5, whereas results for the other domains support exploratory objective #10.

See Section 9.3.2 for example SAS code. Model estimates by randomization stratum (yes, no) are presented in the same table, using additional models that exclude randomization stratum as a fixed effect.

6.5.2 SM Categories Over Time

The SM is a 7-point rating scale that measures the patient's satisfaction with study medication to treat migraines using the eDiary.

The frequency table of SM categories is provided by treatment group and overall for the DBT efficacy analysis set at the following time points: Week 12 of the DBT outcomes research analysis period; Week 24 of the OL rimegepant outcomes research analysis period. Results for overall are displayed only at Week 24 of the OL rimegepant outcomes research analysis period.

Results support exploratory objective #11.

6.5.3 CGI-c Categories Over Time

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 frequency table of CGI-c categories is provided by treatment group and overall for the DBT efficacy analysis set at the following time points: Week 12 in the DBT outcomes research analysis period; Week 24 in the OL rimegepant outcomes research analysis period. Results for overall are displayed only at Week 24 of the OL rimegepant outcomes research analysis period.

Results support exploratory objective #12.

7 CONVENTIONS

7.1 Derived Dates

Derived dates are defined as follows:

- eDiary efficacy date: complete datepart{eDiary finding date/time} – 1 day
- Study drug start date: earliest complete study medication start date from IP Dosing CRF records with number of tablets taken per day > 0. This is an analysis period reference date.
- Imputed study medication end date: If the study medication end date is (1) noncomplete or (2) complete but before the study medication start date, then the imputed end date is set to the study medication start date. Otherwise, the imputed end date is set to the complete study medication end date. Derived only for IP Dosing CRF records with complete study medication start date and number of tablets taken per day > 0.
- Study drug end date: latest of (1) complete study medication start dates, or (2) complete study medication end dates from IP Dosing CRF records with number of tablets taken per day > 0
- Study drug last date:
    - Before the LSLV database lock: study drug end date derived only for subjects who have either (1) or (2):

  - (1) "Yes" or "no" response to the phase completion question on the DB Subject Status CRF, and {either (1a) "no" response to the continuing to the next phase question on the DB Subject Status CRF, or (1b) "Follow-up" specified as the next phase on the DB Subject Status CRF}, and missing OL rimegepant start date
  - (2) "Yes" or "no" response to the phase completion question on the OLE Subject Status or Follow-up Subject Status CRF
- LSLV database lock: study drug end date

This is an analysis period reference date.

- DB study drug start date: earliest complete study medication start date from IP Dosing CRF records with number of tablets taken per day > 0 and valid DB wallet ID. This is an analysis period reference date.
- DB study drug end date: latest of (1) complete study medication start dates, or (2) complete study medication end dates from IP Dosing CRF records with number of tablets taken per day > 0 and valid DB wallet ID
- DB study drug last date:
  - Before all subjects have discontinued the DBT Phase: DB study drug end date derived only for subjects with "yes" or "no" response to the phase completion question on the DB Subject Status, OLE Subject Status, or Follow-up Subject Status CRF
  - After all subjects have discontinued the DBT Phase: DB study drug end date

  This is an analysis period reference date.
- OL rimegepant start date: earliest complete study medication start date from IP Dosing CRF records with number of tablets taken per day > 0 and valid OL wallet ID. This is an analysis period reference date.
- OL rimegepant end date: latest of (1) complete study medication start dates, or (2) complete study medication end dates from IP Dosing CRF records with number of tablets taken per day > 0 and valid OL wallet ID
- OL rimegepant last date:
  - Before the LSLV database lock: OL rimegepant end date derived only for subjects with "yes" or "no" response to the phase completion question on the OLE Subject Status or Follow-up Subject Status CRF
  - LSLV database lock: OL rimegepant end date

  This is an analysis period reference date.
- DB or OL rimegepant start date: study drug start date for subjects whose as-treated DB treatment group is rimegepant EOD/placebo EOD or rimegepant QD; OL rimegepant start date for subjects whose as-treated DB treatment group is placebo QD. This is an analysis period reference date.

- DB or OL rimegepant end date: study drug end date for subjects whose as-treated DB treatment group is rimegepant EOD/placebo EOD or rimegepant QD; OL rimegepant end date for subjects whose as-treated DB treatment group is placebo QD
- DB or OL rimegepant last dose date: study drug last date for subjects whose as-treated DB treatment group is rimegepant EOD/placebo EOD or rimegepant QD; OL rimegepant last date for subjects whose as-treated DB treatment group is placebo QD. This is an analysis period reference date.
- OP start date: earliest of the following: screening visit date – 1 day; eDiary efficacy data date. The screening visit date is determined from the visit label from the Visit Date CRF. This is an analysis period reference date.
- OP end date:
    - If the study drug start date is nonmissing: study drug start date – 1 day
    - If the study drug start date is missing and the randomization date is nonmissing: randomization date – 1 day
    - If both study drug start date and randomization date are missing: last contact date

  This is an analysis period reference date.
- Last contact date:
    - Earliest complete death date from the AE CRF, if it exists.
    - Otherwise, the latest complete date of the following: AE start or end; ECG; eDiary finding; informed consent; IWRS randomization; laboratory test collection; nonstudy medication start or end; physical exam; physical measurement; procedure; rating scale; questionnaire; study medication start or end; vital sign; visit.
    - If the last contact date is after the most recent raw database creation date, then it is set to the most recent raw database creation date.
- Death date: refer to the Core SAP.

No imputations are performed on these derived dates unless otherwise specified.

Refer to the Core SAP for the definition of complete dates.

7.2 Analysis Periods

Measurements are slotted into analysis periods based on comparing measurement dates to analysis period reference dates (time is not applicable).

Analysis periods are defined according to endpoints as follows:

- eDiary efficacy endpoints (migraine days, acute migraine-specific medication days, acute migraine medication days, headache days)

- OP: eDiary efficacy data date on or after the OP start date through the OP end date. Note that this is a subset of the pretreatment analysis period.
- 28-day OP: eDiary efficacy data date on or after the OP start date through the earlier of {OP start date + 27 days; OP end date}. Note that this is a subset of the OP analysis period, and is used only to assess efficacy data issues during the OP as relevant protocol deviations.
- On-DBT efficacy:
  - If the DB study drug last date or OL rimegepant start date is not missing: eDiary efficacy date on or after the DB study drug start date through the earlier of {DB study drug last date; OL rimegepant start date – 1 day}
  - If the DB study drug last date and OL rimegepant start date are both missing: eDiary efficacy data date on or after the DB study drug start date

  This period is used to assess efficacy during the DBT Phase.

- Pretreatment characteristics and safety endpoints *
  - Pretreatment: This period is used to derive baseline values
  - On-DBT safety: This period is used to assess safety endpoints on DBT for the DBT safety analysis set.
  - Post-DBT pre-OL rimegepant safety: This period is used to assess safety endpoints during the interim period (i.e., post-DBT pre-OL rimegepant) for the interim safety analysis set.
  - On-OL rimegepant safety: This period is used to assess safety endpoints on OL rimegepant for the OL rimegepant safety analysis set.
  - On-DB or OL rimegepant safety: This period is used to assess safety endpoints on DB or OL rimegepant for the DB or OL rimegepant safety analysis set.
  - On-treatment safety: This period is used to derive analysis visit windows for slotting measurements and may also be used to assess blinded safety endpoints on treatment in an integrated safety report, as needed.
  - Follow-up safety: This period is used to assess safety endpoints during follow-up for the follow-up safety analysis set.
- Outcomes research endpoints (MSQoL, SM, CGI-c) *
  - DBT outcomes research: This period is used to assess outcomes research endpoints during the DBT Phase for the DBT efficacy analysis set.
  - OL rimegepant outcomes research: This period is used to assess outcomes research endpoints during the OLE Phase for the OL rimegepant efficacy analysis set.

For endpoints marked with "*", refer to the Core SAP for the definitions of analysis periods in Phase 2/3/4 multiple-dose studies with both DBT and OLE Phases. See Section 7.1 for derived dates for determining analysis periods.

7.3 Analysis Visit Windows

Refer to C4951010 Protocol Section 4.3 (Table 1) for the schedule of assessments.

Refer to the Core SAP for defining randomization days, study days, rimegepant study days, and follow-up days in Phase 2/3/4 multiple-dose studies with both DBT and OLE Phases.

Analysis visit windows are shown in Table 5.

Table 5 Analysis Visit Windows

Analysis Period **Analysis Visit**	**Abbreviation in Listings**	**Analysis Day** **Analysis Visit Window**	**Target Day**
Pretreatment	**PRETRT**	**Randomization Day**	
Screening *		≤ -7	
Pre-Randomization *	Prerand	-6 to -1	
Baseline *		1	
Post-Randomization @	Postrand	≥ 2	
Outcomes Research /On-Treatment Safety	**Outcomes Research: DBT or OLRMG/Safety: DBT, INT, OLRMG, or ONTRT**	**Study Day**	
Week 2		2 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
Extension @		≥ 169	
Follow-Up Safety	**FU**	**Follow-Up Day**	
Follow-Up Week 2	FU Week 2	8 to 35	14
Follow-Up Week 8	FU Week 8	36 to 77	56
Follow-Up Extension @	FU Ext	≥ 78	

* For subjects in the enrolled analysis set excluded from the full analysis set, the visit label is used for slotting.
@ 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 follow-up safety. Follow-up days are used to define analysis visit windows in the follow-up safety analysis period.

8 CONTENTS OF REPORTS

All TLFs described in this SAP are produced for the LSLV final CSR (see Section 1.2).

9 APPENDICES

9.1 Relevant Protocol Deviations

Relevant eligibility protocol deviations include the following categories:

- Previously treated with study drug in another multiple-dose BHV3000 study. Defined as subjects with (1) previous BHV3000 study subject identifiers from studies BHV3000-201/305/405/406/407 from the Demographics/Informed Consent CRF, and (2) who took ≥ 1 dose of study drug (e.g., rimegepant or placebo) in a multiple-dose study.
- Randomized or treated with study drug under > 1 subject identifier. These are identified from the Protocol Deviations CRF.
- Migraine history issue, defined as any of the following subcategories:
  - ≤ 3 or ≥ 15 migraine days per month of any pain intensity in the 3 months prior to screening
  - ≥ 15 headache days per month in the 3 months prior to screening.

  These are based on the Migraine History CRF.
- Finding out of range during pretreatment, defined any as any of the following subcategories:
  - Females with a positive pregnancy test (see Section 6.4.2)
  - Estimated glomerular filtration rate (eGFR) according to the re-expressed abbreviated (4-variable) Modification of Diet in Renal Disease (MDRD) Study equation ≤ 40 mL/min/1.73m^2, if originally consented to Protocol Version 4 or lower *
  - eGFR according to the re-expressed abbreviated (4-variable) MDRD Study equation < 30 mL/min/1.73m^2, if originally consented to Protocol Version 5 or higher *
  - BMI ≥ 33 kg/m^2, if originally consented to Protocol Version 4 or lower *
  - BMI > 35 kg/m^2, if originally consented to Protocol Version 5 or higher *
  - C-SSRS suicidal ideation with active intent or plan to act, or suicidal behavior present during pretreatment. Defined as having a "yes" response to any of the following C-SSRS questions:
    - Suicidal ideation question 4 (active suicidal ideation with some intent to act, without specific) or 5 (active suicidal ideation with specific plan and intent)
    - Suicidal behavior question 1 (actual attempt), 3 (interrupted attempt), 4 (aborted attempt), 5 (preparatory acts or behavior), or 6 (suicidal behavior).

  For the subcategories marked with "*", all nonmissing values during the pretreatment analysis period must meet the deviation criteria in order to be considered a deviation.

- Efficacy data issue during the first 28 days of the OP, defined as any of the following subcategories:
  - ≤ 3 migraine days
  - ≥ 15 headache days
  - ≤ 23 days of eDiary efficacy data (see Sections 6.2.6.2 and 9.2.2).

  These are assessed during the 28-day OP analysis period (see Section 7.2). Migraine days and headache days are absolute, not prorated to 28 days per month (see Sections 9.2.5 and 9.2.6), and of total pain intensity.

Relevant subject management protocol deviations include the following categories:

- Randomization stratum discrepancies between IWRS and actual data, defined as any of the following subcategories:
  - IWRS randomization stratum of yes, but no use of nonstudy previous medication for migraine prevention generally considered to have efficacy
  - IWRS randomization stratum of no, but use of nonstudy previous medication for migraine prevention generally considered to have efficacy.

  See Section 6.2.5.4 for the definition of nonstudy medication for migraine prevention generally considered to have efficacy.
- DB study drug dosing noncompliance, defined as any of the following subcategories (see Section 6.2.6.2):
  - DB study drug taken but not randomized
  - DB tablet count compliance < 80% from DB study drug start to later of last scheduled DBT Phase visit or DB study drug end/OL rimegepant start
  - > 1 DB tablet taken on any 1 day
  - Incorrect DB study drug taken
- OL rimegepant dosing noncompliance, defined as any of the following subcategories (see Section 6.2.6.2):
  - OL rimegepant tablet count compliance < 80% from OL rimegepant start to later of last scheduled OLE Phase visit or OL rimegepant end
  - > 1 OL rimegepant tablet taken on any 1 day
  - OL rimegepant start on or before DB study drug end
  - OL rimegepant taken but DB study drug never taken
- eDiary usage compliance < 80% from DB study drug start to later of last scheduled DBT Phase visit or DB study drug end (see Section 6.2.6.2)
- Prohibited nonstudy medications taken on or after informed consent (or otherwise specified), defined as any of the following subcategories:

- Atypical antipsychotic, divalproex, valproic acid, or valproate #
- Ergotamine
- Lamotrigine
- Medication for migraine prevention generally considered to have efficacy or prophylactic migraine medication taken up to 30 days before informed consent or afterward (see Sections 6.2.5.4 and 6.2.6.3) #
- Narcotic (barbiturate or opioid) #
- Select moderate or strong cytochrome P450 3A4 (CYP3A4) inducer #
- Select strong CYP3A4 inhibitor #.

For the subcategories marked with "#", preferred names are displayed alphabetically as additional subcategories. Medications taken up to *X* days before a reference date or afterward are defined as those with imputed medication start date or imputed end date ≥ reference date – *X*. Refer to the Core SAP for additional details about prohibited nonstudy medications.

The IWRS randomization date is the reference date for "randomization". If the IWRS randomization date is missing, then the study drug start date is used.

The protocol version to which subjects originally consented is determined from the Demographics/Informed Consent CRF.

9.2 eDiary Efficacy

9.2.1 Efficacy Parameters

On a given day, subjects use the eDiary to provide responses to the following efficacy parameters occurring yesterday:

- Headache (yes, no)
- If the response to headache is "yes", then responses to the following pain features and associated symptoms are collected:
  - Lasts at least 30 minutes (yes, no)
  - Pain intensity (mild, moderate, severe)
  - Unilateral (yes, no)
  - Pulsating (yes, no)
  - Worsen or avoid physical activity (yes, no)
  - Nausea (yes, no)
  - Vomiting (yes, no)
  - Photophobia (yes, no)
  - Phonophobia (yes, no)

- Aura (yes, no)
- If the response to headache or aura is "yes", then the responses to the following parameters about taking medications to treat headache or aura are collected:
  - Triptan (yes, no)
  - Ergotamine (yes, no)
  - Other medication (yes, no).

These efficacy parameters are collected together as a set with the same eDiary finding date/time for a subject. It is expected that subjects have only 1 set of efficacy parameters collected on a given eDiary finding date. Handling of multiple sets on the same date are discussed in subsequent sections.

9.2.2 eDiary Efficacy Data Day

A day of eDiary efficacy data is defined as any complete eDiary efficacy date (see Section 7.1).

9.2.3 Acute Migraine Medication Day

An acute migraine medication day is defined as either (1) or (2):

1) Acute migraine-specific medication day (see Section 9.2.4)
2) Migraine day (see Section 9.2.5) with a "yes" response to the question about taking other medications to treat headache or aura.

Thus, acute migraine medication days are a subset of migraine days (see Section 9.2.5). If there are multiple sets of efficacy parameters on the same finding date, then data from all sets are used cumulatively to assess acute migraine medication day status on that day, regardless of finding time. For example, if a subject has both "yes" and "no" responses to the question about taking triptan on that day, then the subject is considered to have taken acute migraine medication on that day.

9.2.4 Acute Migraine-Specific Medication Day

An acute migraine-specific medication day is defined as a day of eDiary efficacy data with a "yes" response to either of the 2 questions about taking triptan or ergotamine to treat headache or aura.

Thus, acute migraine-specific medication days are a subset of acute migraine medication days and migraine days (see Sections 9.2.3 and 9.2.5, respectively). If there are multiple sets of efficacy parameters on the same finding date, then data from all sets are used cumulatively to assess acute migraine-specific medication day status on that day, regardless of finding time.

9.2.5 Migraine Day

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

1) Qualified migraine headache, defined as meeting both criteria a and b:
   a. Headache lasting ≥ 30 minutes: "Yes" response to the question about lasting ≥ 30 minutes
   b. Meeting ≥ 1 of the following criteria (i or ii):
      i. ≥ 2 of the following pain features:
         1. Unilateral: "Yes" response to the question about unilateral
         2. Pulsating: "Yes" response to the question about pulsating
         3. Moderate or severe pain intensity
         4. Worsen or avoid physical activity: "Yes" response to the question about worsen or avoid physical activity
      ii. ≥ 1 of the following associated symptoms:
         1. Nausea: "Yes" response to the question about nausea
         2. Vomiting: "Yes" response to the question about vomiting
         3. Both photophobia and phonophobia: "Yes" responses to the questions about photophobia and phonophobia
2) Acute migraine-specific medication day (see Section 9.2.4).

Migraine days are a subset of headache days (see Section 9.2.6).

If there are multiple sets of efficacy parameters on the same finding date, then data from all sets are used cumulatively to assess migraine day status on that day, regardless of finding time. Migraine pain intensity is set to the greatest pain intensity on that day.

A migraine day of total pain intensity is any migraine day, regardless of pain intensity.

9.2.6 Headache Day

A headache day is defined as a day of eDiary efficacy data with either (1), (2), or (3):

1) Migraine day (see Section 9.2.5)
2) Headache that lasts ≥ 30 minutes: "Yes" response to the question about lasting ≥ 30 minutes
3) Headache of any duration for which acute headache treatment is administered: Meeting both of the following criteria (a and b):
   a) "Yes" response to the question about having a headache
   b) "Yes" response to any of the 3 questions about taking medications to treat headache or aura (i.e., triptan, ergotamine, or other medications).

If there are multiple sets of efficacy parameters on the same finding date, then data from all sets are used cumulatively to assess headache day status on that day, regardless of finding time. Headache pain intensity is set to the greatest pain intensity on that day.

A headache day of total pain intensity is any headache day, regardless of pain intensity.

9.3 SAS Code

9.3.1 Linear Mixed Effects Model With Repeated Measures

Consider the following variables used to evaluate the primary efficacy endpoint using a linear mixed effects model with repeated measures:

- mdmchg: change from the OP in migraine days per month; continuous variable
- mdmop: migraine days per month during the OP; continuous variable
- month: month; categorical variable with levels of 1, 2, and 3
- rndstr: randomization stratum; categorical variable with levels of 1 and 2 to denote yes and no, respectively
- trt: treatment group; categorical variable with levels of 1, 2, and 3 to denote rimegepant EOD/placebo EOD, rimegepant QD, and placebo QD, respectively
- usubjid: unique subject identifier; categorical variable.

Then the SAS code is as follows:

```
proc mixed empirical;
class usubjid rndstr trt month;
model mdmchg = mdmop rndstr trt month trt*month;
repeated month / subject=usubjid type=un; /* unstructured covariance */
lsmeans trt trt*month / alpha=0.025 cl diff;
run;
```

9.3.2 Linear Regression Model

Consider the following variables used to evaluate the fifth secondary endpoint using a linear regression model:

- scorechg: score change from baseline at Week 12; continuous variable
- rndstr: randomization stratum; categorical variable with levels of 1 and 2 to denote yes and no, respectively
- scorebl: baseline score; continuous variable
- trt: treatment group; categorical variable with levels of 1, 2, and 3 to denote rimegepant EOD/placebo EOD, rimegepant QD, and placebo QD, respectively
- usubjid: unique subject identifier; categorical variable.

Then the SAS code is as follows:

```
proc mixed empirical;
class usubjid rndstr trt;
model scorechg = scorebl rndstr trt;
```

```
repeated / subject=usubjid;
lsmeans trt / alpha=0.025 cl diff;
run;
```

9.4 Study Drug Dosing Day

A study drug dosing day is defined as a day on which ≥ 1 tablet of study drug was taken.

For each subject, study drug dosing days and the number of tablets per day are determined for every day in the interval defined from the study drug start date to the study drug end date inclusive.

First, study medication records with complete study medication start date, complete imputed study medication end date, and number of tablets taken per day > 0 are selected. Imputed study medication end date, study drug start date, and study drug end date are derived (see Section 7.1).

Next, records are sorted by study medication start date, imputed study medication end date, wallet ID, and number of tablets taken per day.

Let [study medication start date1, imputed study medication end date1] and [study medication start date2, imputed study medication end date2] denote any 2 records.

Overlapping records are defined as maximum(study medication start date1; study medication start date2) ≤ minimum(imputed study medication end date1; imputed study medication end date2). All days from the maximum to the minimum inclusive are considered overlapping study drug dosing days on which the number of tablets taken per day > 1. Note that overlapping records need not be consecutive.

Gaps between 2 consecutive records are defined as study medication start date2 – imputed study medication end date1 ≥ 2 days. All days from the imputed study drug end date1 + 1 day to the study medication start date2 – 1 day inclusive are considered days on which no study drug was taken (i.e., not study drug dosing days).

A DB study drug dosing day is defined as a day on which ≥ 1 tablet of DB study drug was taken. DB study drug dosing days are determined using valid DB wallet IDs.

An OL rimegepant dosing day is defined as a day on which ≥ 1 tablet of OL rimegepant study drug was taken. OL rimegepant dosing days are determined using valid OL wallet IDs.

Example:

Suppose study medication data are as follows for a given subject:

Study Medication Start Date	Study Medication End Date	Imputed Study Medication End Date	Number of Tablets Taken per Day	Note
01JAN2022	03JAN2022	03JAN2022	1	
04JAN2022	05JAN2022	05JAN2022	0	Excluded from analysis
06JAN2022	09JAN2022	09JAN2022	1	
09JAN2022	11JAN2022	11JAN2022	2	1-day overlap with previous record
13JAN2022		13JAN2022	1	1-day gap between previous record

Then study drug start date = 01JAN2022 and study drug end date = 13JAN2022.

Study drug dosing days and number of tablets per day are derived as follows for the subject, taking overlaps and gaps into account:

Date	Number of Tablets per Day	Study Drug Dosing Day Flag
01JAN2022	1	Y
02JAN2022	1	Y
03JAN2022	1	Y
04JAN2022	0	
05JAN2022	0	
06JAN2022	1	Y
07JAN2022	1	Y
08JAN2022	1	Y
09JAN2022	3	Y
10JAN2022	2	Y
11JAN2022	2	Y
12JAN2022	0	
13JAN2022	1	Y

The subject has a total of 10 study drug dosing days and 14 tablets taken.

10 REFERENCES

1. Reference-based MI via multivariate normal RM (the “five macros” and MIWithD) from the Drug Information Association scientific working group on estimands and missing data. London School of Hygiene and Tropical Medicine, 2021. at https://www.lshtm.ac.uk/research/centres-projects-groups/missing-data#dia-missing-data.)

2. Carpenter JR, Roger JH, Kenward MG. Analysis of longitudinal trials with protocol deviation: a framework for relevant, accessible assumptions, and inference via multiple imputation. Journal of Biopharmaceutical Statistics 2013;23:1352-71.