Protocol C4951012 (BHV3000-407)

BHV3000-407: A Phase 4, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Tolerability of Rimegepant for the Prevention of Migraine in Adults With a History of Inadequate Response to Oral Preventive Medications

Statistical Analysis Plan

Version 9

Date: 20-May-2025

SIGNATURE PAGE

Protocol Title:	A Phase 4, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Tolerability of Rimegepant for the Prevention of Migraine in Adults with a History of Inadequate Response to Oral Preventive Medications
Document Version:	9
Date:	20-May-2025
Author:	PPD Signature: PPD Date: ___

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
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
CTCAE	Common Technical Criteria for Adverse Events
CYP3A4	Cytochrome P450 3A4
DAIDS	Division of Acquired Immune Deficiency Syndrome
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
FDA	Food and Drug Administration
HDL	High-density lipoprotein
HIT-6	Headache Impact Test
J2R	Jump to reference
FCS	Fully conditional specification
LFT	Liver function test
LLN	Lower limit of normal
LSLV	Last subject last visit
LSM	Least-squares mean
MAR	Missing at random

Abbreviation	Definition
MDRD	Modification of diet in renal disease
MFIQ	Migraine Functional Impact Questionnaire
MIBS	Migraine Interictal Burden Scale
MNAR	Missing not at random
MSQ	Migraine-Specific Quality of Life
ODT	Orally disintegrating tablet
OP	OP
PCD	Primary completion date
PGA	Patient Global Assessment
PT	Preferred term
ROM	Recognized, orally-administered migraine-preventive
RTSM	Randomization and Trial Supply Management
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
US	United States
WPAI	Work Productivity and Activity Impairment

REVISION HISTORY

Version	Description of Change
1	Original version (04-May-2023) based on Protocol Version 4
2	Amended version (03-Oct-2023) based on Protocol Version 5 Signature page: Changed "Hospital Products" to "Infectious Disease". General: Applied Pfizer Global Style Guide throughout. Abbreviations: Added LSLV and PCD. 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" and "GLM table" to "table". Section 1.2: Specified the timing of the PCD and LSLV database locks and corresponding final CSRs. Section 2.1: Specified that randomization is stratified using an RTSM system. Section 2.4: Specified that SAP Version 2 is based on Protocol Version 5. Section 4.3: Modified randomization strata, and specified that the randomization strata are based on actual data, not those assigned by the RTSM system, Section 6.1.1.2: New section "Figures". Section 6.1.1.3: Renumbered from 6.1.1.2. Referenced the listing of significant protocol deviations. Section 6.2.3.3: Specified to use the DBT safety analysis set. Section 6.2.4.1: Moved text from Section 6.2.4 here. Changed "enrolled" to "full". Section 6.2.4.2: New section "Significant Protocol Deviations". Section 6.2.5: Modified the contents of the randomization stratum frequency table to be a cross-tabulation of each randomization stratum from the RTSM system versus each randomization stratum from actual data. Section 6.2.5.1: Removed RTSM randomization stratum from the table of demographics and other relevant baseline characteristics. Section 6.2.5.4: Added "contraindication reason not reported" to the frequency table of ROM medication failures. Added medication category to the listing of previous experience with or documented contraindication to prophylactic migraine medications. Section 6.2.6.3: Changed "reason of "contraindication"" to "due to contraindication (see Section 9.4.2)". Section 6.3: Specified that the randomization stratum used in analyses is based on actual data, not those assigned by the RTSM system. 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. Changed "on-treatment" to "on-DBT" throughout subsections. Modified section titles throughout to be consistent with endpoints. Section 6.3.1.1: Changed "full" to "DBT efficacy". Section 6.3.1.3: Removed "Identity link function, normal distribution". 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 "SE estimation method: Huber-White "sandwich" (refer to the Core SAP)" and "longitudinal plot" to "line plot with error bars". Corrected text in step 1 in the J2R sensitivity analysis. Specified tipping point sensitivity analysis is not by randomization strata.

Version	Description of Change
	Section 6.3.3.3: Removed "Identity link function, normal distribution". 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 6.4.1.2: 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 6.4.4: Removed ECG collection at Week 14. 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. 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 6.5.3.1: New section "MFIQ Monthly Average Score During the DBT Phase". Moved existing text in Section 6.5.1 about calculating the MFIQ monthly average score here. Section 6.5.3.2: New section "MFIQ Monthly Average Score Changes From Baseline Over Time". Moved existing text in Section 6.5.1 about descriptive analyses and treatment group comparisons here, Section 6.5.5.1: New section "PGA – Migraine Monthly Average Score During the DBT Phase". Moved existing text in Section 6.5.5 about calculating the PGA – Migraine monthly average score here. Section 6.5.5.2: New section "PGA – Migraine Score Changes From Baseline Over Time". Moved existing text in Section 6.5.5 about descriptive analyses and treatment group comparisons here, In descriptive analyses, removed EOT as a time point and combined results across DBT and OLE Phases into 1 table. Section 6.5.6.2: Removed EOT as a time point in descriptive analyses. Section 8.1: New section "PCD Final CSR". Specified select TLFs to be produced. Section 8.2: New section "LSLV Final CSR". Specified that all TLFs described in the SAP are produced. Section 9.1: Changed "more than once and assigned" to "under". Removed "for the full analysis set" (2 instances). Section 9.1: Changed "more than once and assigned" to "under". For pretreatment eGFR, modified existing criteria and added new criteria to align with Protocol Version 5 Section 5.3. Removed "for the full analysis set". Changed "RTSM" to "the RTSM system" where applicable. Changed "meeting either of the following criteria" to "any of the following subcategories" (2 instances). Modified deviations about randomization stratum discrepancies. 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 9.4.2: Modified the definition of medications with previous inadequate response due to contraindication.
3	Amended version (17-Apr-2024) based on Protocol Version 5 General: Applied Pfizer Global Style Guide throughout. Changed "BHV3000-407 (C4951012)" to "C4951012 (BHV3000-407)", and "BHV3000-407" to "C4951012" throughout. Abbreviations: Added CTCAE, DAIDS, FDA, and US.

Version	Description of Change
	Section 1.2: Removed "efficacy, safety, and outcomes research endpoints." (typo).
	Section 2.4: Specified that SAP Version 3 is based on Protocol Version 5.
	Section 3.2: 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. Modified the definition of acute migraine medication days.
	Sections 3.2.1: In Table 1, modified intercurrent events row.
	Sections 3.2.2.1: In Table 2, modified intercurrent events row of all objectives.
	Section 3.2.2.2: In Table 3, removed "DB or OL rimegepant" from summary row of Objective 1, and modified intercurrent events row of all objectives.
	Section 3.2.3: In Table 4, added "and number of headache days per month" to Objective 1, removed "DB or" from summary row of Objectives 12 and 14, removed "DB or OL rimegepant" from summary row of Objective 13, and modified intercurrent events row of all objectives.
	Section 4.1: Removed the COVID-19 impacted analysis set.
	Section 6.1.1.1: Removed "and pretreatment safety endpoints" and corresponding reference to Section 6.4. Specified the format of efficacy subgroup tables.
	Section 6.1.1.3: Removed "All listings except administrative listings identify subjects who are impacted by COVID-19.", and "and visits impacted by COVID-19 visit impact".
	Section 6.2.1: Removed "(excluding COVID-19 impacted)".
	Section 6.2.3: Removed "Premature study termination due to COVID-19 status" from the by-subject listing of subject discontinuation.
	Sections 6.2.3.1 and 6.2.3.2: Removed premature termination due to COVID-19.
	Section 6.2.3.3: Changed "CSR" to "PCD". Modified the algorithm for the "Did not continue to the next phase" category. Removed premature termination due to COVID-19.
	Section 6.2.3.4: Changed "CSR" to "LSLV". Modified the algorithm for the "Did not continue to the Follow-Up Phase" category. Removed premature termination due to COVID-19.
	Sections 6.2.3.5 and 6.2.3.6: Removed.
	Section 6.2.5: Removed "and in COVID-19 analyses by analysis visit (see Section 6.6)".
	Section 6.2.5.1: Removed ", and calculating age at a reference date". Removed references to age at OL rimegepant baseline and age at DB or OL rimegepant baseline.
	Section 6.2.6.1: Modified the definition of nonscheduled dosing days. Removed the administrative listing of investigational drug batch numbers.
	Section 6.2.6.2: Modified frequency table of DB treatment compliance by removing "DB study drug dosing day compliance ≥ 80%". Modified frequency table of OL rimegepant compliance by adding "OL rimegepant start on or before DB study drug end" and "OL rimegepant taken but DB study drug never taken" and removing "Odd OL rimegepant dosing day compliance ≥ 80%". Changed "DB study drug end" to "DB study drug end/OL rimegepant start".
	Section 6.2.6.3: Specified that the Concomitant Medications CRF collects indications. Modified the definitions of acute migraine and prophylactic migraine medications. Removed migraine standard or care medications.
	Section 6.3.1: Removed "data from the previous visit to the current visit".
	Section 6.3.1.1: Changed "full" to "DBT efficacy".
	Section 6.3.1.3: For the main analysis, removed text about protocol versions. For the J2R macros, specified parameters Ndraws=200 and thin=100, and that these parameters may be modified as needed.

Version	Description of Change
	Section 6.3.2.1: Removed the last paragraph. Section 6.3.2.2: 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: Added overall summary tables of treatment comparisons of all primary and key secondary efficacy endpoints during the DBT by subgroup level for all efficacy subgroups of interest described in Section 4.3. Section 6.3.3.5: Changed "DBT Phase" to "on-DBT efficacy analysis period" (2 instances). Section 6.4: Removed "Pretreatment for the safety analysis set by treatment group and overall". Section 6.4.1: Removed Sections 6.4.1.3, 6.4.1.5, and 6.4.1.9, and renumbered other subsections accordingly. Removed some tables in subsections. Changed "by intensity" to "by worst intensity" in subsections. Section 6.4.1.2: Modified the contents of the AE overview table. Section 6.4.2: Specified that TLFs display results using both SI and US units, if applicable. In subsections, removed some tables and changed some from DB or OL rimegepant to OL rimegepant. Specified separate listings of laboratory test results for each toxicity grading scale (CTCAE/DAIDS in SI units; FDA in US units), and a separate listing of pregnancy test results. Section 6.4.2.1: Specified that separate tables are provided for each toxicity grading scale: CTCAE/DAIDS using SI units; and FDA using US units.". Removed ", where shifts are based on DB or OL rimegepant baseline". Section 6.4.2.2: Specified that analyses use SI units. Removed ", where shifts are based on DB or OL rimegepant baseline". Section 6.4.2.3: Specified that a separate table is provided for each unit system (SI or US). Sections 6.4.3.2 and 6.4.4.2: Removed "using DB or OL rimegepant baseline". Section 6.5: Specified that randomization strata used in analyses are based on the actual data. Section 6.6: Removed. Section 7.1: Changed "eDiary reference date" to "eDiary measurement date". Changed "CSR" to "LSLV" in the definition of the study drug end and OL rimegepant end dates. Changed "CSR" to "PCD" in the definition of the DB study drug end date. Modified the definition of the last contact date to exclude COVID-19 visit date. Section 7.2: Removed "and to assess pretreatment safety endpoints". Removed the pre-OL rimegepant and pre-DB or OL rimegepant safety analysis periods. Modified the purpose of the on-treatment safety analysis period. Section 7.3: Removed "Rimegepant study days are used to define analysis visit windows in the on-DB or OL rimegepant safety analysis period." and "Analysis visit windows in the on-DB or OL rimegepant safety analysis period are defined analogously to those in the on-treatment safety analysis period.". Section 8.1: Changed "by intensity" to "by worst intensity". Removed "However, COVID-19 visit impact tables over time display results for all safety analysis periods.". Section 9.1: Added migraine history issue category and subcategories. For medical history, modified existing criteria, defined "present at screening", and specified the identification of active medical history status. Added subcategories to efficacy data issue during the first 28 days of the OP. Changed "DB study drug dosing issue" to "OL rimegepant dosing issue". Added "OL rimegepant start on or before DB study drug end" and "OL rimegepant taken but DB study drug never taken". Changed "study drug end" to "DB study drug end/OL rimegepant start" (2 instances)". Section 9.2.3: Modified the definition of an acute migraine medication day.

Version	Description of Change
4	Amended version (05-Jun-2024) based on Protocol Version 5 Section 2.4: Specified that SAP Version 4 is based on Protocol Version 5. Section 3.2: Specified sources of PGA – Migraine during the DBT and OLE Phases. Section 4.3: Specified to use imputed randomization strata. Section 6.2.5: Removed "OL rimegepant baseline" and "DB or OL rimegepant baseline". Moved the frequency cross table of randomization stratum to Section 6.2.5.1. Section 6.2.5.1: Specified the categories in the frequency cross table of randomization stratum. Section 6.2.5.2: Modified the categories for acute migraine-specific medication days per month to be the same as those for acute migraine medication days per month. Specified that categories may be redefined or combined based on the availability of the data. Section 6.3: Specified that analyses use the imputed randomization strata. Section 6.3.2.1, 6.3.2.2, 6.3.3.5, and 6.5.6.2: Specified the calculation of percentages at all time points. Section 6.4.6: Changed "AE" to "non-SAE" for AEs leading to study drug discontinuation and AEs of special interest. Modified the order of events. Section 6.5: Specified that analyses use the imputed randomization strata. Described loss of baseline MFIQ and PGA data. Section 6.5.3.1: New section "Imputed Baseline MFIQ". Section 6.5.3.2: Renumbered from 6.5.3.1. Section 6.5.3.3: Renumbered from 6.5.3.2. Changed "baseline" to "imputed baseline". Specified to use imputed baseline in the model. Section 6.5.5.1: New section "Imputed Baseline PGA – Migraine". Section 6.5.5.2: Renumbered from 6.5.5.1. Section 6.5.5.3: Renumbered from 6.5.5.2. Changed "baseline" to "imputed baseline". Specified to use imputed baseline in the model. Section 7.3: Modified footnote of Table 7. Section 8.1: Removed the pretreatment analysis period. Section 9.1: Modified subcategories for the number of ROM medication categories with previous inadequate response, subcategory for efficacy data issue during the first 28 days of the OP, subcategories for randomization stratum discrepancies, and the definition of recognized migraine-preventive medications. Section 9.3.1: Changed "4-level" to "imputed 4-level". Section 9.4.2: Specified criteria for setting the number of ROM medication categories with inadequate response to 0 or missing.
5	Amended version (09-Sep-2024) based on Protocol Version 7 Section 1: Changed title from "Introduction and Objectives of Analysis" to "Background and Rationale". Section 2.4: Specified that SAP Version 5 is based on Protocol Version 7. Section 6.4.2.2: Changed "longitudinal LFT" to "LFT line".

Version	Description of Change
	Section 9.1: Removed "cardiovascular disease risk factor" and "medical history" 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).
6	Amended version (23-Oct-2024) based on Protocol Version 7 Section 2.4: Specified that SAP Version 6 is based on Protocol Version 7. 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 6.2.6.1: Removed references to scheduled and nonscheduled dosing days, and dosing day type. Modified the contents and sorting of the study drug listing, and changed "≥0" to ">0". Sections 6.2.6.2 and 9.1: Changed "≥1 nonscheduled DB study drug dosing day" to "consecutive DB study drug dosing days", and "≥1 nonscheduled OL rimegepant dosing day" to "consecutive OL rimegepant dosing days". Sections 6.3.1.3, 6.3.2.1, 6.3.2.2, 6.3.2.3. 6.3.3.4, 6.3.3.5, 6.5.1, and 6.5.6.2: Removed results by randomization strata from the same table as the overall results. 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 6.4.7: Added hypertension non-SAE and Raynaud's phenomenon non-SAE. Section 6.5.2: Removed "Domain" from the section title. Section 9.5: Removed references to scheduled and nonscheduled dosing days, and dosing day type. Changed "consecutive" to "sequential" (2 instances). Defined consecutive study drug dosing days. and added a corresponding column to the second table. Corrected entries in the second table. Specified that subject had 3 consecutive study drug dosing days in the second example.
7	Amended version (14-Jan-2025) based on Protocol Version 7 Section 2.4: Specified that SAP Version 7 is based on Protocol Version 7. Sections 4.1 and 6.3.3.5: Modified the definition of the first week EOD treated migraine analysis set. Section 6.1.1: Specified that country is based on a site/country external file provided by the data management vendor. Section 6.2.5.4: Modified the display of medications in the table of ROM medication failures. Specified medication category order is per Section 9.4.1. Section 6.2.6.2: Changed "maxdate" to "DB maxdate" (typo). Section 6.3.2.2: Changed "statistics" to "model estimates". Removed "n (i.e., number of subjects with data)". Section 6.4.6: Added PT of drug induced liver injury to select hepatic-related non-SAEs.

Version	Description of Change
	Sections 6.5.1 through 6.5.6: Specified that analyses of treatment group comparisons are based on the evaluable DBT efficacy analysis set, and defined evaluable subjects. Added the number of evaluable subjects in each treatment group to tables of treatment group comparisons using linear mixed effects model.
8	Amended version (05-Feb-2025) based on Protocol Version 7 Section 2.4: Specified that SAP Version 8 is based on Protocol Version 7. Section 6.2.5.4: Specified that the frequency table of the nonstudy previous prophylactic migraine medications is provided by preferred name without therapeutic class. Section 6.2.6.1: Modified the derivation of average study drug exposure (3 instances). Section 6.2.6.3: Modified the derivation of tablet count compliance (2 instances). Section 9.1: Changed "migraine-preventive" to "prophylactic migraine" (2 instances), and added a reference to Section 6.2.6.3.
9	Amended version (20-May-2025) based on Protocol Version 7 Section 2.4: Specified that SAP Version 9 is based on Protocol Version 7. Section 5: Modified the last sentence. Section 6.2.5.1: Added geographic region and randomization stratum 2 subcategories to the table of demographics and other relevant baseline characteristics. Section 6.2.5.4: Added "lack of efficacy and prior intolerance within 10 years of the Screening Visit" as a previous inadequate response category in the table of ROM medication failures. Section 6.4.1: Changed "AEs of special interest" to "significant AEs". Section 6.4.1.5: Changed "DB or OL rimegepant end" to "last contact" in last sentence. Section 6.4.6: Modified text based on the latest version of the C495/C530 Core SAP. Section 9.4.2: Added 1 criterion for setting the number of ROM medication categories with previous inadequate response to be 0.

1 BACKGROUND AND RATIONALE

This document presents the statistical analysis plan (SAP) for Protocol C4951012 (BHV3000-407): A Phase 4, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Tolerability of Rimegepant for the Prevention of Migraine in Adults With a History of Inadequate Response to Oral Preventive Medications.

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 has a favorable benefit risk profile in the prevention of migraine in adults who have previously experienced inadequate response, within 10 years of the Screening Visit, to recognized, orally-administered, migraine-preventive (ROM) medications where at least 1 example of prior inadequate response is due to lack of efficacy or prior intolerance (not contraindication).

1.2 Schedule of Analyses

There are 2 planned database locks: (1) primary completion date (PCD) database lock, which occurs after the last subject completes the Week 12/End of Treatment (EOT) Visit of the Double-Blind Treatment (DBT) Phase; and (2) last subject last visit (LSLV) database lock, which occurs after the last subject completes the Follow-Up Week 2 Visit.

The PCD final CSR is produced after the PCD database lock. Analyses focus on efficacy and safety endpoints during the DBT Phase.

The LSLV final CSR is produced after the LSLV database lock. All endpoints are assessed.

No interim analyses are planned.

2 STUDY DESCRIPTION

2.1 Study Design

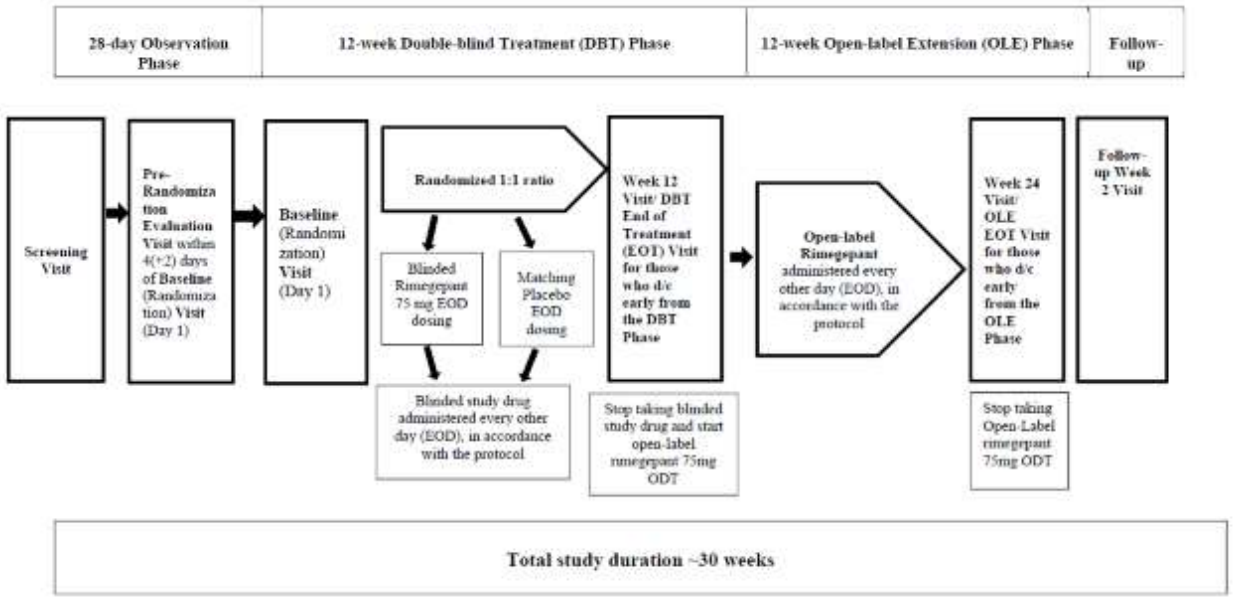
This is a multicenter, randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of rimegepant 75 mg orally disintegrating tablet (ODT) taken every other day (EOD) for prophylaxis in adults with a history of inadequate response to a variety of available oral migraine-preventive medications from different mechanistic classes.

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.
- DBT Phase:
  - Lasts up to 12 weeks, and includes the Baseline Visit, and Week 2, Week 4, Week 8, Week 12, and DBT EOT Visits.
  - Subjects are randomized 1:1 to 1 of the following 2 treatment groups at the Baseline Visit:
    - Rimegepant 75 mg dosed EOD
    - Placebo matching rimegepant 75 mg dosed EOD.
  - Randomization is stratified using a Randomization and Trial Supply Management (RTSM) system by (1) the number of migraine days reported to have occurred during the 28-day OP (4 to 7 or 8 to 14); and (2) the number of ROM medication categories with previous inadequate response (2 or 3 to 4). See Section 2.2.
    - Previous inadequate response is defined as lack of efficacy within 10 years of the Screening Visit, prior intolerance within 10 years of the Screening Visit, or contraindication.
  - All randomized subjects who discontinue early from the DBT Phase should complete the DBT EOT Visit. Otherwise, subjects should complete the Week 12 Visit.
- Open-label Extension (OLE) Phase:
  - Subjects who complete the DBT Phase and are in good standing may enter the OLE Phase. Subjects who (1) discontinue early from the DBT Phase or (2) have already entered the Follow-up Phase are not eligible to enter the OLE Phase.
  - Lasts up to 12 weeks, and includes the Week 14, Week 24, and OLE EOT Visits.
  - Subjects take rimegepant 75 mg dosed EOD.
  - All randomized subjects who discontinue early from the OLE Phase should complete the OLE EOT Visit. Otherwise, subjects should complete the Week 24 Visit.
- Follow-up Phase
  - Lasts up to 2 weeks, and includes the Follow-up Week 2 Visit primarily for safety assessments. The visit should occur approximately 2 weeks after the last visit in the last treatment phase, i.e., (i.e., Week 12/DBT EOT Visit if the subject did not enter the OLE Phase; Week 24/OLE EOT Visit if the subject entered the OLE Phase).
  - All randomized subjects should complete the Follow-up Week 2 Visit, regardless of completing the DBT or OLE Phase, except those who discontinue early from the DBT or OLE Phase due to withdrawal of consent, death, or lost to follow-up.

The design of the study is shown in Figure 1. Approximately 1000 subjects are enrolled in order to randomize approximately 600 subjects.

Figure 1 Study Schematic



2.2 Treatment Assignment

The RTSM system assigns a subject identifier number at the Screening Visit.

The RTSM system randomizes eligible subjects to treatment groups (see Section 2.1) using permuted blocks of size 6 within each of the 4 randomization strata at the Baseline Visit. Randomization is stratified by (1) the number of migraine days reported to have occurred during the 28-day OP (4 to 7 or 8 to 14); and (2) the number of ROM medication categories with previous inadequate response (2 or 3 to 4).

The RTSM system 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 PCD database lock (see Section 1.2). Draft TLFs for the PCD Final CSR are produced with dummy treatment groups prior to the PCD database lock. Otherwise, TLFs for the PCD Final CSR and LSLV Final CSR are produced unblinded.

2.4 Protocol and Protocol Amendments

C4951012 SAP Version 1 is based on C4951012 Protocol Version 4 (01-Mar-2023). Note that Protocol Version 4 added the OLE Phase. The study was originally designed with the Observation, DBT, and Follow-Up Phases.

C4951012 SAP Versions 2, 3, and 4 are based on C4951012 Protocol Version 5 (09-Aug-2023). Protocol changes that affected statistical analyses were the following: changing the sponsorship to Pfizer; removing ECG collection at Week 14; stating that there are 2 planned database locks and 2 final CSRs; 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.

C4951012 SAP Version 5, 6, 7, 8, and 9 are based on C4951012 Protocol Version 7 (31-Aug-2024).

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 compare the efficacy of rimegepant to placebo as an EOD dosing regimen for prophylaxis in adults with a history of inadequate response to agents across 2 to 4 categories of ROM medications 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

3.1.2.1 Key Secondary Objectives

1. To compare the proportion of subjects with ≥50% reduction from the OP in the number of migraine days of moderate or severe headache pain intensity per month over the entire DBT Phase (Weeks 1 to 12) between rimegepant and placebo.

2. To compare the mean reduction from the OP in the number of migraine days per month in the first 4 weeks of the DBT Phase between rimegepant and placebo.

3. To compare the mean reduction from the OP in the number of migraine days per month in the last 4 weeks of the DBT Phase between rimegepant and placebo.

4. To compare 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 between rimegepant and placebo.

5. To compare the mean change from baseline in Migraine Interictal Burden Scale (MIBS) score at Week 12 of the DBT Phase between rimegepant and placebo.

3.1.2.2 Other Secondary Objectives

1. To evaluate the frequencies of adverse events (AEs) by intensity, serious adverse events (SAEs), AEs leading to study drug discontinuation, and Grade 3 to 4 laboratory test abnormalities during the DBT and OLE Phases.

2. To evaluate the proportion of subjects with ≥ 50% reduction from the OP in the number of migraine days (regardless of headache pain intensity) per month over the entire DBT Phase (Weeks 1 to 12) in rimegepant and placebo.

3. To evaluate the mean number of acute migraine medication days per month in each month and over the entire DBT Phase in rimegepant and placebo.

4. To evaluate the mean change from baseline in Migraine Interictal Burden Scale (MIBS) score over time in the DBT Phase in rimegepant and placebo.

5. To evaluate the mean change from baseline in MSQ domain scores (restrictive role function domain, preventive role function domain and emotional function domain) over time in the DBT Phase in rimegepant and placebo.

6. To evaluate the mean change from baseline in the Migraine Functional Impact Questionnaire (MFIQ) scores (physical function, usual activities, social function, overall impact on usual activities, and emotional function) over time in the DBT Phase in rimegepant and placebo.

7. To evaluate the mean change from baseline in the Work Productivity and Activity Impairment (WPAI) − Migraine scores (absenteeism, presenteeism, work productivity loss, and activity impairment) over time in the DBT Phase in rimegepant and placebo.

8. To evaluate the mean change from baseline in the Patient Global Assessment (PGA) − Migraine score over time in the DBT Phase in rimegepant and placebo.

3.1.1 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 headache pain intensity (total; moderate or severe) in each month and the entire course of the DBT Phase in rimegepant and placebo.

2. To evaluate the proportions of subjects with ≥30% reduction, ≥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 headache pain intensity (total; moderate or severe) in each month and over the entire DBT Phase in rimegepant and 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 headache pain intensity (total; moderate or severe) in each week of the first 4 weeks of the DBT Phase in rimegepant and 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 headache pain intensity (total; moderate or severe) in each week of the first 4 weeks of the DBT Phase in rimegepant and placebo.

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

6. To evaluate the median time to ≥30% reduction and ≥50% reduction from the OP in the number of migraine days per month and number of headache days per month by headache pain intensity (total; moderate or severe) in the DBT Phase in rimegepant and placebo.

7. To evaluate the mean number of acute migraine medication days per month in each month and over the entire DBT Phase in rimegepant and placebo.

8. To evaluate the mean change from baseline in the Headache Impact Test (HIT-6) score over time in the DBT Phase in rimegepant and placebo.

9. To evaluate the proportion of subjects with ≥5-point reduction from baseline in the HIT-6 score over time in the DBT Phase in rimegepant and placebo.

10. To evaluate the mean changes from baseline in the MSQ domain, MIBS, WPAI − Migraine, HIT-6 and PGA scores over time in the OLE Phase.

11. To evaluate the proportion of subjects with ≥5-point reduction from baseline in the HIT-6 score over time in the OLE Phase.

12. To evaluate the frequencies of hepatic-related AEs and hepatic-related AEs leading to study drug discontinuation during the DBT and OLE Phases.

13. To evaluate the frequency of liver function test (LFT) elevations (AST, ALT, or total bilirubin) based on fold changes above ULN during the DBT and OLE Phases.

14. To evaluate the Columbia-Suicide Severity Rating Scale (C-SSRS) 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, study drug discontinuation is handled with a "hypothetical strategy," i.e., the hypothetical scenario is that had subjects not discontinued 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 study drug. All observed values of the endpoint of interest are excluded after study drug discontinuation plus 1 day (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 or time-to-event endpoint, 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 study drug discontinuation plus 1 day (see Section 7.2). Subjects with missing data are considered failures for binary endpoints. Subjects who achieve the response criteria before study drug discontinuation are considered to have an event for time-to-event endpoints.
- 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 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, in general, that nonstudy prophylactic migraine medication use 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, MFIQ scores, and PGA – Migraine scores during the DBT Phase are derived from electronic diary (eDiary) data from the external source YPrime. Acute migraine-specific medications are triptans, ergotamine, lasmiditan, or ubrogepant. Acute migraine medications are acute migraine-specific medications 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 (see Section 6.4.2 for more details). Laboratory test results are from an external central laboratory and local laboratory test CRFs.

Endpoints based on other rating scale and questionnaires (i.e., C-SSRS, HIT-6, MIBS, MSQ, WPAI − Migraine, PGA − Migraine during the OLE Phase) are derived from their respective CRFs.

3.2.1 Primary Objective Estimand

The estimand corresponding to the primary objective 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 linear mixed effects model with repeated measures, and difference in mean changes 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

3.2.2.1 Key Secondary Objective Estimands

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

Table 2 Key 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 of subjects 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 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 in mean changes 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 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 in mean changes 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 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 mixed effects model with repeated measures, and difference in mean changes 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 5	**Mean change from baseline in the MIBS score at Week 12 of the DBT Phase**
Outcomes Research Endpoint	Mean change from baseline in the MIBS score at Week 12 of the DBT Phase
Summary	Mean change from baseline by treatment group using descriptive statistics and linear mixed effects model with repeated measures, and difference in mean changes 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

3.2.2.2 Other Secondary Objective Estimands

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

Table 3 Other Secondary Objective Estimands

Objective 1	**Frequencies of AEs by intensity, SAES, AEs leading to study drug discontinuation, and Grade 3 to 4 laboratory test abnormalities during the DBT and OLE Phases**
Safety Endpoint	Number and percentage of subjects with AEs by intensity, SAES, AEs leading to study drug discontinuation, and Grade 3 to 4 laboratory test abnormalities on treatment during the DBT and OLE Phases
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 2	**Proportion of subjects with ≥50% reduction from the OP in the number of migraine days per month over the entire DBT Phase in rimegepant and placebo**
Efficacy Endpoint	Proportion of subjects with ≥50% reduction from the OP in number of total 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 3	**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 per month and 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 in mean values 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 4	**Mean change from baseline in MIBS score over time in the DBT Phase in rimegepant and placebo**

Outcomes Research Endpoint	Mean change from baseline in the MIBS score at Weeks 4, 8, and 12 of the DBT Phase
Summary	Mean change from baseline by treatment group using descriptive statistics and linear mixed effects model with repeated measures, and difference in mean changes 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 5	**Mean change from baseline in MSQ domain scores over time in the DBT Phase in rimegepant and placebo**
Outcomes Research Endpoint	Mean change from baseline in the MSQ domain scores (restrictive role function domain, preventive role function domain and emotional function domain) at Weeks 4, 8, and 12 of the DBT Phase
Summary	Mean change from baseline by treatment group using descriptive statistics and linear mixed effects model with repeated measures and difference in mean changes 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	**Mean change from baseline in the MFIQ scores over time in the DBT Phase in rimegepant and placebo**
Outcomes Research Endpoint	Mean change from baseline in the MFIQ scores (physical function, usual activities, social function, overall impact on usual activities, and emotional function) in each month of the DBT Phase
Summary	Mean change from baseline by treatment group using descriptive statistics and linear mixed effects model with repeated measures, and difference in mean changes 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 7	**Mean change from baseline in the WPAI − Migraine scores over time in the DBT Phase in rimegepant and placebo**
Outcomes Research Endpoint	Mean change from baseline in the WPAI − Migraine scores (absenteeism, presenteeism, work productivity loss, and activity impairment) at Weeks 4, 8, and 12 of the DBT Phase
Summary	Mean change from baseline by treatment group using descriptive statistics and linear mixed effects model with repeated measures, and difference in mean changes 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 8	**Mean change from baseline in the PGA−Migraine score over time in the DBT Phase in rimegepant and placebo**
Outcomes Research Endpoint	Mean change from baseline in the PGA−Migraine score in each month of the DBT Phase
Summary	Mean change from baseline by treatment group using descriptive statistics and linear mixed effects model with repeated measures, and difference in mean changes 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

3.2.3 Exploratory Objective Estimands

The estimands corresponding to the exploratory objectives are shown in Table 4.

Table 4 Exploratory Objective Estimands

Objective 1	**Mean reductions from the OP in the number of migraine days per month and number of headache days per month by headache pain intensity (total; moderate or severe) in each month and the entire course of the DBT Phase in rimegepant and placebo**
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 headache pain intensity (total; moderate or severe)
Summary	Mean changes from the OP by treatment group using descriptive statistics and model, and difference in mean changes 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 ≥30% reduction, ≥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 headache pain intensity (total; moderate or severe) in each month and over the entire DBT Phase in rimegepant and placebo**

Efficacy Endpoint	Proportions of subjects with ≥30% reduction, ≥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 headache pain intensity (total; moderate or severe)
Summary	Percentages of subjects 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 headache 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 headache pain intensity (total; moderate or severe)
Summary	Mean changes from the OP by treatment group using descriptive statistics and model, and difference in mean changes 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 headache 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 headache pain intensity (total; moderate or severe)
Summary	Percentages of subjects 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 headache 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 headache pain intensity (total; moderate or severe)
Summary	Percentages of subjects by treatment group, and difference in percentages between treatment groups using Mantel-Haenszel risk estimation for the first week EOD treated migraine analysis set
Intercurrent Events	Study drug discontinuation: not applicable 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	**Median time to ≥30% reduction and ≥50% reduction from the OP in the number of migraine days per month and number of headache days per month by headache pain intensity (total; moderate or severe) in the DBT Phase in rimegepant and placebo**
Efficacy Endpoint	Median time to ≥30% reduction and ≥50% reduction from the OP in the number of migraine days per month and number of headache days per month during DBT by headache pain intensity (total; moderate or severe)
Summary	Using the migraine analysis set for each endpoint by headache pain intensity: • Descriptive statistics by treatment group, and by randomization stratum within treatment group: (1) estimated median (months) with measures of variance; (2) Kaplan-Meier estimated cumulative probabilities through Month 3; and (3) hazard ratio between treatment groups from Cox proportional hazards model
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 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 value by treatment group using descriptive statistics and linear mixed effects model with repeated measures, and difference in mean values 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	**Mean change from baseline in the HIT-6 score over time in the DBT Phase in rimegepant and placebo**
Outcomes Research Endpoint	Mean change from baseline in the HIT-6 score at Weeks 4, 8, and 12 of the DBT Phase
Summary	Mean change from baseline by treatment group using descriptive statistics and linear mixed effects model with repeated measures, and difference in mean changes 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 9	**Proportion of subjects with ≥ 5-point reduction from baseline in the HIT-6 score over time in the DBT Phase in rimegepant and placebo**
Outcomes Research Endpoint	Proportion of subjects with ≥ 5-point reduction from baseline in the HIT-6 score at Weeks 4, 8, and 12 of the DBT Phase
Summary	Percentage by treatment group, and difference in percentages between treatment groups using Mantel-Haenszel risk estimation 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 10	**Mean changes from baseline in the MSQ domain, MIBS, WPAI – Migraine, HIT-6 and PGA − Migraine scores over time in the OLE Phase**
Outcomes Research Endpoint	Mean changes from baseline at Weeks 14 and 24 of the OLE Phase
Summary	Mean change from baseline over time 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	**Proportion of subjects with ≥ 5-point reduction from baseline in the HIT-6 score over time in the OLE Phase**
Outcomes Research Endpoint	Proportion of subjects with ≥ 5-point reduction from baseline in the HIT-6 score at Week 24 of the OLE Phase
Summary	Percentage of subjects by treatment group 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 12	**Frequencies of hepatic-related AEs and hepatic-related AEs leading to study drug discontinuation 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 during the DBT and OLE Phases
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
Objective 13	**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 during the DBT and OLE Phases
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 14	**C-SSRS during the DBT and OLE Phases**
Safety Endpoint	Number and percentage of subjects with suicidal ideation, suicidal behavior, or non-suicidal self-injurious behavior on treatment during the DBT and OLE Phases
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

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 RTSM system, i.e., nonmissing RTSM 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.
    - 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 and OLE Phases.
    - 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 EOD treated migraine: subjects in the DBT efficacy analysis set with (1) ≥24 days of eDiary efficacy data (not necessarily consecutive) in the OP, (2) 7 consecutive days of eDiary efficacy data in the first week of the DBT Phase, and (2) EOD 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 in the first week of the DBT Phase.

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

The following efficacy subgroups are of interest for the migraine analysis set (see Section 6.2.5.1):

- Imputed randomization stratum 1 – number of migraine days in the 28-day OP: <8, ≥8
- Imputed randomization stratum 2 – number of ROM medication categories with previous inadequate response: <3, ≥3
- Imputed 4-level randomization stratum:
  - <8 migraine days in the 28-day OP and <3 ROM medication categories with previous inadequate response
  - <8 migraine days in the 28-day OP and ≥3 ROM medication categories with previous inadequate response
  - ≥8 migraine days in the 28-day OP and <3 ROM medication categories with previous inadequate response
  - ≥8 migraine days in the 28-day OP and ≥3 ROM medication categories with previous inadequate response.

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 300 subjects per treatment group. Based on data from study C4951025 (BHV3000-305) and subgroup analysis from the galcanezumab Phase 3 program,[1,2,3] we estimate that rimegepant provides roughly a 1.0-day advantage over placebo on the primary endpoint, and assuming a common standard deviation (SD) of 3.6 days. Assuming that roughly 280 subjects per treatment group contribute to the final migraine analysis dataset, the study has roughly 90% power on the primary endpoint at a 2-sided alpha level of 0.05.

In study C4951025 (BHV3000-305), rimegepant dosed EOD provided a 1.0-day advantage over placebo dosed EOD in subjects who were not taking prophylactic migraine medication through randomization. Using the data from study C4951025 (BHV3000-305), the SD of the primary endpoint was estimated to be roughly 3.6 days for these subjects.

Type 1 error is controlled using a 2-sided alpha level of 0.05 and hierarchical testing. First, the significance of the primary endpoint is evaluated at the 2-sided alpha level of 0.05 for rimegepant versus placebo. If the primary endpoint is not significant (i.e., p-value > 0.05), then any further tests on key secondary endpoints will have p-values presented only for descriptive purposes. If the primary endpoint is significant (i.e., p-value ≤ 0.05), then the key secondary endpoints are tested hierarchically, each at a 2-sided alpha level of 0.05, in the order specified in Section 3.2.2.1. Thus, a key secondary endpoint is tested only if the preceding key secondary endpoint in the hierarchy is determined to be significant (i.e., p-value ≤ 0.05). 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.

For testing of other secondary or exploratory endpoints, no attempt is made to adjust for multiplicity. These endpoints are evaluated at an unadjusted, 2-sided alpha level of 0.05, and p-values are 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.

Country is based on a site/country external file provided by the data management vendor.

6.1.1.1 Tables

Treatment Group Presentation

Treatment group presentation in tables by analysis set is shown in Table 5. Exceptions are specified in subsequent sections as needed.

Table 5 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}	2 to 3	Rimegepant 75 mg Placebo {Overall}
OL rimegepant safety, DB or OL rimegepant safety by treatment group/OL rimegepant and overall	3	DB RMG/OL RMG DB PBO/OL RMG Overall
Follow-up safety by treatment group/OL rimegepant status and overall	5	DB RMG/OL RMG DB PBO DB PBO to OL RMG DB PBO No OL RMG Overall

Results for study population also include overall treatment group (see Section 6.2).

Subgroup tables of efficacy endpoints have the same format as the main efficacy tables, but display each subgroup level in a separate row, and page break by subgroup level. A separate table is produced for each efficacy subgroup of interest.

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”, 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, and 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 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, and Section 6.5 for statistical methods for handling missing data in outcomes research 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 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. The table also displays results for the full and safety analysis sets.

6.2.3 Subject Disposition

The by-subject listing of subject discontinuation is provided for the enrolled analysis set, and is based on the DB Subject Status CRF. This includes the following:

- Relevant reference dates: last contact date*, IWRS randomization date
- Study phase: DBT or OLE. 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

- Phase completion status: "completed"; or "not completed" concatenated with the reason for non-completion (see Sections 6.2.3.1, 6.2.3.2, 6.2.3.3, and 6.2.3.4)
- 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 non-continuation (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 see 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 RTSM randomization date)
- Not randomized (identified as subjects with missing RTSM 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 Criteria 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 the PCD database lock; 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 study, including not reported
- Continued to the next phase. These are identified as subjects with "yes" response to the question "Is the subject continuing to the next phase?".
  - 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 "Is the subject continuing to the next phase?". Subjects with missing response to this question after the PCD database lock are also included.
  - Reasons for not continuing to the next phase, including not reported. These are based on reasons for not continuing to the next phase.

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 missing response to the question "Did the subject complete the OLE Phase?". 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 "yes" response to the question "Did the subject complete the OLE Phase?"
- Did not complete the OLE Phase. These are identified as subjects with "no" response to the question "Did the subject complete the OLE Phase?".
  - 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.

6.2.4 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 a protocol deviation external file provided by the data management vendor from a clinical trial management system. This includes deviation date, category, subcategory, and description, which are additional sorting variables. Significant protocol deviations are defined as those reported with major severity. A footnote describes the raw data source and how significant protocol deviations are identified, e.g., "Significant protocol deviations are those reported with major severity by the data management vendor in the clinical trial management system.".

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 migraine-related endpoints 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.

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. Note that the baseline value of a parameter is independent of the baseline analysis visit defined in Table 6; 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 table of demographics and other relevant characteristics. Other relevant characteristics also include the following categorical variables:

- Geographic region: Australia/Europe, North America
  - North America is defined as Canada, Mexico, or United States of America.
- Previous study participation (e.g., any study, BHV3000-301, BHV3000-302, BHV3000-303, etc.)
- Randomization stratum 1 based on actual data – number of migraine days in the 28-day OP: <8, ≥8. These are based on absolute (not prorated) number of migraine days of total headache pain intensity during the 28-day OP analysis period (see Sections 7.2 and 9.2.5).
- Imputed randomization stratum 1 – number of migraine days in the 28-day OP: <8, ≥8.
  - If the randomization stratum 1 value based on actual data is missing, then it is imputed as follows:
    - "<8" if the randomization stratum 1 value from the RTSM system is "4 to 7",
    - "≥8" if the randomization stratum 1 value from the RTSM system is "8 to 14".
  - Otherwise, the imputed randomization stratum value 1 is equal to the randomization stratum 1 value based on actual data.
- Randomization stratum 2 based on actual data – number of ROM medication categories with previous inadequate response: <3, ≥3 (see Section 9.4.2). Subcategories include 0, 1, 2, 3, 4, 3 to 4, 5, etc.
- Imputed randomization stratum 2 – number of ROM medication categories with previous inadequate response: <3, ≥3.
  - If the randomization stratum 2 value based on actual data is missing, then it is imputed as follows:
    - "<3" if the randomization stratum 2 value from the RTSM system is "2"
    - "≥3" if the randomization stratum 2 value from the RTSM system is "3 or 4".
  - Otherwise, the imputed randomization stratum value 2 is equal to the randomization stratum 2 value based on actual data.
- 4-level randomization stratum based on actual data. Categories are based on randomization strata 1 and 2 based on actual data:
  - <8 migraine days in the 28-day OP and <3 ROM medication categories with previous inadequate response

  - <8 migraine days in the 28-day OP and ≥3 ROM medication categories with previous inadequate response
  - ≥8 migraine days in the 28-day OP and <3 ROM medication categories with previous inadequate response
  - ≥8 migraine days in the 28-day OP and ≥3 ROM medication categories with previous inadequate response.
  - Missing if either randomization stratum 1 or 2 value is missing.
- Imputed 4-level randomization stratum. This is derived based on imputed randomization strata 1 and 2.

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

The frequency cross table of randomization stratum (i.e., randomization stratum 1, randomization stratum 2) from the RTSM system versus actual data is provided for the full analysis set by treatment group and overall. Categories are as follows:

- Number of migraine days in the 28-day OP
  - RTSM value of "4 to 7" and 4≤ eDiary value ≤7
  - RTSM value of "4 to 7" and eDiary value ≤3, ≥8, or missing
  - RTSM value of "8 to 14" and 8≤ eDiary value ≤14
  - RTSM value of "8 to 14" and eDiary value ≤7, ≥15, or missing
- Number of ROM medication categories with previous inadequate response
  - RTSM value of "2" and CRF value = 2
  - RTSM value of "2" and CRF value ≤1, ≥3, or missing
  - RTSM value of "3 or 4" and CRF value = 3 or 4
  - RTSM value of "3 or 4" and CRF value ≤2, ≥5, or missing.

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, which 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 parameters descriptively as continuous or categorical variables during the OP analysis period:

- Migraine days per month by headache pain intensity (total; moderate or severe). Categories are <4, ≥4 to <8, ≥8 to <14, ≥14.
- Headache days per month by headache 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 same as for acute migraine-specific medication days per month 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 parameters descriptively as continuous or categorical variables during the OP analysis period:

- Migraine days per week by headache pain intensity (total; moderate or severe). Categories are <1, ≥1 to <2, ≥2 to <3, ≥3.
- Headache days per week by headache 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

ROM Medication Failures

A frequency table of ROM medication failures displays medications by previous inadequate response category, medication category (e.g., valproic acid), and preferred name in descending order of overall frequency within preferred name. These are based on the Previous Experience

With or Documented Contraindication to Prophylactic Migraine Medications CRF (see Section 9.4.1).

Medication categories are ordered as specified in Section 9.4.1.

Previous inadequate response categories are ordered as follows: any, defined as previous inadequate response due to lack of efficacy within 10 years of the Screening Visit, prior intolerance within 10 years of the Screening Visit, or contraindication; lack of efficacy or prior intolerance within 10 years of the Screening Visit; lack of efficacy within 10 years of the Screening Visit; prior intolerance within 10 years of the Screening Visit; lack of efficacy and prior intolerance within 10 years of the Screening Visit (displayed without medication category and preferred name); contraindication; contraindication due to hypersensitivity; contraindication due to other reason; and contraindication reason not reported. See Section 9.4.2 for more details.

The by-subject listing of previous experience with or documented contraindication to prophylactic migraine medications is provided for the enrolled analysis set. This listing has a format similar to the nonstudy medication listing where applicable (refer to the Core SAP), with the following additional parameters: number of ROM medication categories within previous inadequate response (see Section 9.4.2); migraine-preventive medication category (recognized oral, other); medication category (e.g., valproic acid); previous inadequate response reasons (lack of efficacy, prior intolerance, contraindication) comma-space concatenated; and contraindication reason (hypersensitivity; other with specify reason colon-concatenated). Medications with previous inadequate response due to lack of efficacy or prior intolerance within 10 years of the Screening Visit are flagged. Nonstudy medication type (e.g., previous, current) is not displayed.

Prior Medications

The frequency table of the nonstudy previous prophylactic migraine medications is provided by preferred name without therapeutic class.

Frequency tables of the following nonstudy current medications are provided by therapeutic class and preferred name: all; acute migraine.

Medications are displayed in descending order of overall frequency within therapeutic class and preferred name.

See Section 6.2.6.3 for the definitions of acute migraine and prophylactic migraine medications. Refer to the Core SAP for the definitions of previous and current nonstudy 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 number. Each wallet has 8 tablets. During the DBT Phase, each wallet contains only DB rimegepant or matching

placebo depending on the randomization. During the OLE Phase, each wallet contains only OL rimegepant. Sites report the wallet number and the number of tablets taken on each day on IP Dosing Wallet 1 to 4 and Replacement IP Dosing Wallet 1 to 4 CRFs. The wallet type associated with a wallet number is DB rimegepant, DB placebo, or OL rimegepant, and is obtained by merging the dosing CRF data with the study drug wallet list file data by wallet number.

The by-subject listing of study drug is provided for the safety analysis set, and displays the following: DB study drug start and end dates, OL rimegepant start and end dates, rimegepant exposure parameters (time on DB study drug, time on OL rimegepant, time on DB or OL rimegepant), dosing date, study day derived from the dosing date, number of tablets taken ≥1, wallet number, and wallet type. The listing also identifies invalid wallet numbers. Valid wallet numbers are those in the study drug wallet list file. The listing is sorted by site-subject ID, dosing date, and wallet number.

DB Study Drug Exposure

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

- Time on DB study drug (weeks), derived as (study drug end date – 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 exposure (tablets), derived by summing the number of tablets taken per day across records with complete dosing date and wallet type identifier of DB rimegepant or DB placebo
- Average DB exposure (tablets per month), derived as (1) cumulative DB exposure (tablets) if time on DB study drug <2 weeks, or (2) 4 × cumulative DB exposure/{time on DB study drug} if time on DB study drug ≥2 weeks
- Total DB 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 (tablets), derived by summing the number of tablets taken per day across records with complete dosing date and valid OL wallet number
- Average OL rimegepant exposure (tablets per month), derived as (1) cumulative OL rimegepant exposure (tablets) if time on OL rimegepant <2 weeks, or (2) 4 × cumulative OL rimegepant exposure/{time on OL rimegepant} if time on OL rimegepant ≥2 weeks
- 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: ≤12, >12
- 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 (tablets), derived by summing number of tablets taken per day across records with complete study medication start date and wallet type identifier of DB rimegepant or OL rimegepant.
- Average DB or OL rimegepant exposure (tablets per month), derived as (1) cumulative DB or OL rimegepant exposure (tablets) if time on DB or OL rimegepant <2 weeks, or (2) 4 × cumulative DB or OL rimegepant exposure/{time on DB or OL rimegepant} if time on DB or OL rimegepant ≥2 weeks
- 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 treatment compliance parameters in separate columns: average exposure (tablets per month; see Section 6.2.6.1) for DB, OL rimegepant, and DB or OL rimegepant;

percentage for tablet count compliance and odd study drug dosing day 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 DBT Phase visit or DB study drug end/OL rimegepant start. Tablet count compliance is derived as 100 × cumulative exposure/required exposure, where
  - Cumulative DB exposure is defined in Section 6.2.6.1.
  - Required DB exposure is derived as integer((n + 1)/2)), where n = DB maxdate – DB study drug start date + 1.
    - 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.
- Average DB exposure (tablets per month) categories:
  - >16.8 (>20% above EOD dosing)
  - >15.4 (>10% above EOD dosing)
  - ≥12.6 to ≤15.4 (± 10% of EOD dosing)
  - ≥11.2 to ≤16.8 (± 20% of EOD dosing)
  - ≥12.6 (≥90% compliant with EOD dosing)
  - ≥11.2 (≥80% compliant with EOD dosing)

  Average DB exposure is defined in Section 6.2.6.1.
- DB tablets taken per month for 3 consecutive months categories: ≥12, ≥13, and ≥14
  - Tablets per month are assessed by the number of 4-week (28-day) intervals in which a subject exceeded select DB tablet counts from the DB study drug start date to the DB study drug end date, where the number of 4-week intervals are consecutive (see Section 6.3.1 for months). For example, suppose a subject takes 14 DB tablets through 4 weeks, 12 DB tablets after 4 weeks to 8 weeks, and 15 DB tablets after 8 weeks to 12 weeks. Thus, this subject is considered to have taken ≥12 and ≥13 (but not ≥14) DB tablets per month for 3 consecutive months.
- >1 DB tablet taken on any 1 day. This is determined from the derived number of DB tablets taken per day, which takes overlapping records into account (see Section 9.5).

- Consecutive DB study drug dosing days (see Section 9.5)
- 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:
    - Randomized to rimegepant who took (1) ≥1 tablet from a DB placebo wallet, and (2) no tablets from a DB rimegepant wallet
    - Randomized to placebo who took (1) ≥1 tablet from a DB rimegepant wallet, and (2) no tablets from a DB placebo wallet.
  - At least once. Defined as any of the following:
    - Randomized to rimegpant who took ≥1 tablet from a DB placebo wallet
    - Randomized to placebo who took ≥1 tablet from a DB rimegepant 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 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 × cumulative exposure/required exposure, where
  - Cumulative OL rimegepant exposure is defined in Section 6.2.6.1.
  - Required OL rimegepant exposure is derived as integer((n + 1)/2)), where n = OL maxdate – OL rimegepant start date + 1.
    - OL maxdate is defined as the latest of the (1) scheduled Week 14 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.
- Average OL rimegepant exposure (tablets per month) categories:
  - >16.8 (> 20% above EOD dosing)
  - >15.4 (> 10% above EOD dosing)
  - ≥12.6 to ≤15.4 (± 10% of EOD dosing)
  - ≥11.2 to ≤16.8 (± 20% of EOD dosing)
  - ≥12.6 (≥90% compliant with EOD dosing)
  - ≥11.2 (≥80% compliant with EOD dosing)

  Average OL rimegepant exposure is defined in Section 6.2.6.1.

- OL rimegepant tablets taken per month for 3 consecutive months categories: ≥12, ≥13, and ≥14
    - Tablets per month are assessed by the number of 4-week (28-day) intervals in which a subject exceeded select OL rimegepant tablet counts from the OL rimegepant start date to the OL rimegepant end date, where the number of 4-week intervals are consecutive (see Section 6.3.1 for months).
- >1 OL rimegepant tablet taken on any 1 day. This is determined from the derived number of OL rimegepant tablets taken per day, which takes overlapping records into account (see Section 9.5).
- Consecutive OL rimegepant dosing days (see Section 9.5)
- 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.

eDiary Usage Compliance During the OP and DBT Phase

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

eDiary DBT usage compliance is derived as follows:

- 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 study drug start date to the DB maxdate)/(total number of days from the 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. Medications with previous inadequate response due to contraindication (see Section 9.4.2) and missing medication type are excluded.

Thes following conventions apply to nonstudy medications:

- Nonstudy medications are identified from those identified from the (1) Previous Experience With or Documented Contraindication to Prophylactic Migraine Medications CRF and (2) Concomitant Medications CRF. The Concomitant Medications CRF collects indications, and links medical history and AE terms respectively to the Medical History and AE CRFs.
- Prophylactic migraine medications are defined as nonstudy medications either (1) from the Previous Experience With or Documented Contraindication to Prophylactic Migraine Medications CRF, or (2) with an indication of "prophylactic migraine medication" from the Concomitant Medications CRF.
- 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.

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 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/OL rimegepant 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 the RTSM system, but analyses use imputed randomization strata, which are based primarily on actual data (see Section 6.2.5.1). The rationale for using the actual data in analyses is that sites may erroneously report the wrong strata in the RTSM system. Hence, treatment group comparisons of continuous efficacy endpoints are *adjusted* by the imputed randomization strata, whereas treatment group comparisons of binary efficacy endpoints are *stratified* by the imputed randomization strata (except in subgroup analyses). If there are sparse data within a stratum, then results may be presented unstratified. Note that the phrase "randomization stratum" refers to the imputed randomization stratum throughout this section.

For binary efficacy endpoints, CIs are based on a normal approximation to the binomial distribution using asymptotic standard error (ASE). For continuous efficacy endpoints, CIs 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, and includes the reason 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, whereas results for binary endpoints incorporate missing data imputation. Subjects with ≥14 days of eDiary 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 (i.e., triptan, ergotamine, lasmiditan, ubrogepant, or other) 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 data 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 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 summaries parameters descriptively as continuous variables (including 2-sided normal 95% CIs for mean change) by treatment group and by headache pain intensity in each month of the DBT Phase and overall DBT. Headache 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; treatment group, 4-level 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 95% CI by month and overall DBT for each treatment group
- Difference in LSM changes from OP between rimegepant and placebo (rimegepant – placebo), SE, 95% CI, and p-value at each month and overall DBT. Results in the overall DBT support the primary objective, results in the first month support key secondary objective #2, results in the last month support key secondary objective #3, and results in the second month support exploratory objective #1.

See Section 9.3.1 for example SAS code.

These main analyses are repeated for moderate or severe headache pain intensity to support exploratory objective #1. All variables in the model are the same, except change from the OP in number of moderate or severe migraine days per month is the dependent variable. 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 95% 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.[4,5]
   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 rimegepant and placebo.
   c) The imputation model uses the following variables: age, sex, race, 4-level 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 = 100 for 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, 95% 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 the DBT efficacy analysis set if the p-value ≤ 0.05 for the treatment group comparison for the main analysis of the overall DBT.

The analysis is performed using the following steps:

1) A shift parameter of $\delta = 0$ is selected.
   a) Data are imputed under the missing not at random (MNAR) assumption for the rimegepant treatment group with a shift adjustment and the missing at random (MAR) assumption for the placebo treatment group using SAS proc mi for n = 30 data sets.[4,5]
      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, age, sex, race, 4-level 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, 95% CI, and p-value using SAS proc mianalyze.

2) The p-value for the treatment group comparison of the overall DBT is compared to 0.05.

a) If p-value ≤ 0.05, then δ is incremented by 0.1, and step 1 is repeated.

b) If p-value > 0.05, 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. 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 Reductions 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 (≥30%, ≥50%, ≥75%, and 100%), the percentages of subjects with reductions from the OP in the number of migraine days per month are compared between rimegepant and placebo using Mantel-Haenszel risk estimation (e.g., SAS proc stdrate) with stratification by 4-level randomization stratum. Percentages are calculated against the number of subjects in the migraine analysis set at all time points.

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

- Response rate (i.e., "n/N" and percentage), ASE, and 95% CI for each treatment group
- Stratified percentage difference between rimegepant and placebo (rimegepant – placebo), ASE, 95% CI, and p-value.

Results for the endpoint of ≥50% reduction of moderate or severe pain intensity in the overall DBT support key 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

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, and are prorated to account for missing migraine reports. 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 data dates in the on-DBT efficacy analysis period.

The number of acute migraine-specific medication days per month in the DBT Phase are 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, 4-level 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: 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 95% CI by month and overall DBT for each treatment group
- Difference in LSMs between rimegepant and placebo (rimegepant – placebo), SE, 95% CI, and p-value at each month and overall DBT. Results support other secondary objective #3.

See Section 9.3.1 for example SAS code.

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

The 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 95% CI for each treatment group
  - Difference in LSM changes between rimegepant and placebo, 95% CI, and p-value.

  This applies to the primary endpoint and the following key secondary efficacy and outcomes research endpoints: 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); 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); MSQ restrictive role domain score mean change from baseline at Week 12 (see Section 6.5.1); and MIBS score mean change from baseline at Week 12 (see Section 6.5.2).
- Binary endpoints
  - Response rate ("n/N" and percentage) and 95% CI for each treatment group
  - Stratified percentage difference between rimegepant and placebo, 95% CI, and p-value.

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

Endpoints are displayed in the order presented in Sections 3.2.1 and 3.2.2.1. 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 (i.e., p-value ≤ 0.05; 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 0.05, in the order specified in Section 3.2.2.1. Thus, a key secondary endpoint is tested only if the preceding key secondary endpoint in the hierarchy is determined to be significant (i.e., p-value ≤ 0.05). 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 > 0.05), 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 treatment group 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 treatment group 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 are 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 change from the OP in number of total headache days per month is the dependent variable. The table has the same format as the one described in Section 6.3.1.3.

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

Results support exploratory objective #1.

6.3.3.2 Percentages of Subjects With Reductions From 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 (≥30%, ≥50%, ≥75%, and 100%), the percentages of subjects with reduction in the number of headache days per month are compared between rimegepant and placebo using Mantel-Haenszel risk estimation with stratification by 4-level randomization stratum. Percentages are calculated against the number of subjects in the migraine analysis set at all time points.

The table has the same format as the one described in Section 6.3.2.1 at each month of the DBT Phase and overall DBT by headache pain intensity.

Results support exploratory objective #2.

6.3.3.3 Migraine Days per Week and Headache Days per Week Changes From 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 95% CIs for mean change) by treatment group and headache 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; treatment group, 4-level randomization stratum, categorical 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 95% CI by week for each treatment group
- Difference in LSM changes from OP between rimegepant and placebo (rimegepant – placebo), SE, 95% CI, and p-value for each week.

See Section 9.3.1 for example SAS code.

These analyses are repeated for moderate or severe headache pain intensity. All variables in the model are the same, except change from the OP in number of moderate or severe migraine days per week is the dependent variable. 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 From OP 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.

Headache day analyses by week are defined analogously to migraine day analyses by week.

Treatment Group Comparisons

For each headache pain intensity (total; moderate or severe), the percentages of subjects with ≥50% reduction in the number of migraine days per week are compared between rimegepant and placebo using Mantel-Haenszel risk estimation with stratification by 4-level randomization stratum. Percentages are calculated against the number of subjects in the first month migraine analysis set at all time points.

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

- Response rate (i.e., "n/N" and percentage), ASE, and 95% CI for each treatment group
- Stratified percentage difference between rimegepant and placebo (rimegepant – placebo), ASE, 95% CI, and p-value.

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 EOD 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 on-DBT efficacy analysis period, and (3) EOD dosing in the first week of the on-DBT efficacy analysis period, defined as all 4 study days 1, 3, 5, and 7 being study drug dosing days and all 3 study days 2, 4, and 6 not being study drug dosing days (see Section 9.5).

Treatment Group Comparisons

Analyses are based on the first week EOD 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 rimegepant and placebo at study days 1 through 7 of the DBT Phase using Mantel-Haenszel risk estimation with stratification by 4-level randomization stratum. Percentages are calculated against the number of subjects in the first week EOD treated migraine analysis set at all time points.

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

- Response rate (i.e., "n/N" and percentage), ASE, and 95% CI for each treatment group
- Stratified percentage difference between rimegepant and placebo (rimegepant – placebo), ASE, 95% CI, and p-value.

The table also summarizes the percentage of migraine days by headache 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 Time to Percentage Reduction From OP in Number of Migraine Days and Number of Headache Days per Month Over Time on DBT

The following time-to-event endpoints are assessed by headache pain intensity (total; moderate or severe) for the migraine analysis set:

1) Time to ≥30% reduction from the OP in the number of migraine days per month
2) Time to ≥50% reduction from the OP in the number of migraine days per month.

Each time-to-event endpoint is assessed by headache pain intensity using a time-to-event distribution summary table presenting the following statistics: number and percentage of subjects with events; number and percentage of subjects censored; time to event median with 95% CI and quartiles, where the 95% CI for the median is estimated using the method of Brookmeyer and Crowley.

Each time-to-event endpoint is also assessed using a Cox proportional hazards model with the following variables: age, sex, race, 4-level randomization stratum, and treatment group. Race may be reduced to fewer levels (e.g., white versus non-white) based on the availability of data. The hazard ratio estimate (rimegepant versus placebo), 95% CI, and p-value are reported.

For a given time-to-event endpoint, subjects are considered to have an event through Month 3 based on the first month that they are evaluable and the endpoint is achieved. Otherwise, subjects

who do not have an event through Month 3 are censored at the last month they are evaluable. Subjects must have ≥14 days of eDiary efficacy data (not necessarily consecutive) in a month to be evaluable at that month.

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

Results support exploratory objective #6.

6.3.3.7 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 data dates in the on-DBT efficacy analysis period.

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

Descriptive Analyses

The table of the number of acute migraine medication days per month in the DBT analysis period is provided, and summarizes the parameter descriptively as a continuous variable (including 2-sided normal 95% CIs for mean) by treatment group at each month of the DBT Phase and overall DBT mean.

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. The corresponding table has the same format. 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 6). 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, significant AEs, 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 non-completion; 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 non-completion; death as reason for not continuing to the Follow-up Phase (see Section 6.2.3.4).

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 by SOC and PT are provided for the DBT safety analysis set for the following endpoints:

- AEs by worst intensity (other secondary objective #1)
- AEs related to study drug by worst intensity
- SAEs (other secondary objective #1)
- 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.

Frequency tables of AEs by SOC and PT display AEs in descending order of rimegepant 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 (other secondary objective #1)
- AEs related to study drug by worst intensity
- SAEs (other secondary objective #1)
- 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 = last contact date if the DB or OL rimegepant last date is missing.

6.4.1.6 Follow-Up AEs

Frequency tables of follow-up AEs by SOC and PT are provided 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 Medpace. TLFs display results in both Systeme Internationale (SI) and United States (US) units, if applicable.

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

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

Grade 3 to 4 results support other secondary objective #1.

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

Separate tables are provided for each toxicity grading scale: CTCAE/DAIDS using SI units; and FDA using US units.

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 exploratory objective #11.

Frequency tables of LFT shift from baseline to the worst (highest) 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 Section 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 9.5), 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; 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.

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 Pre-Randomization Evaluation, and 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 Follow-Up Week 2 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, QTcF, and ventricular heart rate. ECGs are measured by the external source Clario or on the ECG CRF at the following visits: Screening; Weeks 12/EOT and 24/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 the following visits: Screening; Baseline; Weeks 4, 12/EOT, 14, and 24/EOT. At the Screening Visit, the recall period for completing is (1) 12 months and lifetime for suicidal ideation and (2) 10 years and lifetime 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

Results support exploratory objective #12.

Refer to the Core SAP for calculation of C-SSRS parameters and TLF contents. Responses to lifetime questions at the Screening Visit are excluded from analyses.

6.4.6 Safety Narrative Subject Identifiers

The by-subject listing of safety narrative subject identifiers is provided for the enrolled analysis set, and displays 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

- Other significant non-SAE on DB or OL rimegepant or during follow-up for the DB or OL rimegepant safety analysis set:
  - Select hepatic-related AE, i.e., PT containing cirrhosis, drug-induced liver injury, hepatic failure, hepatitis, jaundice, or liver failure
  - Cardiovascular AE
  - Suicidality AE
  - Hypertension AE
  - Raynaud's phenomenon AE
- LFT elevation on DB or OL rimegepant or during follow-up for the DB or OL rimegepant safety analysis set:
  - 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.

Imputed randomization strata are used in analyses (see Section 6.2.5.1). Note that the phrase "randomization stratum" refers to the imputed randomization stratum throughout this section.

Outcomes research questionnaires and rating scales are as follows:

- MFIQ: Baseline and every week through Week 12 using the eDiary
- MSQ, MIBS, and HIT-6: Baseline; Weeks 4, 8, 12/EOT, and 24/EOT using CRFs
- WPAI − Migraine: Baseline; Weeks 4, 8, 12/EOT, 14, and 24/EOT using CRFs
- PGA − Migraine: Baseline and every day thereafter through Week 12 using the eDiary; Weeks 14 and 24/EOT using a CRF.

On the Baseline Visit date, sites are expected to use the YPrime portal to identify eligible subjects for the DBT Phase, and eligible subjects are expected to synchronize their eDiary with the YPrime portal. If sites and subjects fail to do these steps, then MFIQ and PGA − Migraine data are not collected that day, resulting in a loss of baseline data.

Measurements are slotted into analysis periods and analysis visits using the following steps 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 analysis visits in the analysis periods listed in the previous step. This does not apply to PGA – Migraine data from the eDiary.
   a. HIT-6, MIBS, and MSQ: Weeks 4, 8, 12, and 24 (see Table 6)
   b. WPAI − Migraine: Weeks 4, 8, 12, 14, and 24 (see Table 6)
   c. PGA − Migraine: Weeks 14 and 24 from the CRF (see Table 6)
3. MFIQ: Weeks 1, 2, …, 12 (see Table 7).

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 MSQ and MIBS is provided for the enrolled analysis set. The listing displays analysis visit, assessment date, study day derived from the assessment date, and values and changes from baseline in MSQ domain and MIBS scores.

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 MSQ Domain Score Changes From Baseline Over Time

The MSQ 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; Weeks 4, 8, and 12 of the DBT outcomes research analysis period; Week 24 in 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 MSQ domain score increase from baseline categories is provided by treatment group and overall for the DBT efficacy analysis set at the following time points: Weeks 4, 8, and 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. Refer to the Core SAP for outcomes research frequency table contents.

Results support other secondary objective #5 and exploratory objective #10.

Treatment Group Comparisons

For each domain, analyses are based on the evaluable DBT efficacy analysis set, where evaluable subjects are defined as those with nonmissing domain scores at both baseline and ≥1 scheduled

time point (i.e., Week 4, 8, or 12) during the DBT outcomes research analysis period. Treatment groups are compared using a linear mixed effects model with the following attributes:

- Variables: change from baseline in the score as the dependent variable; baseline score as a covariate; treatment group, 4-level randomization stratum, categorical week (i.e., Weeks 4, 8, and 12 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 statistics and model estimates for each domain:

- Number of evaluable subjects in each treatment group
- LSM change from baseline, SE, and 95% CI by week for each treatment group
- Difference in LSM changes from baseline between rimegepant and placebo (rimegepant – placebo), SE, 95% CI, and p-value at each week. Results for the restrictive role function domain score at Week 12 support key secondary objective #4, and results for all other domain scores or time points support other secondary objective #5.

See Section 9.3.1 for example SAS code.

6.5.2 MIBS Score Changes From Baseline Over Time

The MIBS is a 4-item, patient-administered questionnaire that measures interictal migraine-related burden in 4 domains (impairment in work or school, impairment in family and social life, difficulty making plans or commitments, and emotional/affective and cognitive distress) in the past 4 weeks on days when subjects are not having an attack.

Descriptive Analyses

The table of values and changes from baseline in the MIBS score is provided for the DBT efficacy analysis set, and has a similar format as the one described in Section 6.5.1.

Results support other secondary objective #4 and exploratory objective #10.

Treatment Group Comparisons

Analyses are based on the evaluable DBT efficacy analysis set, where evaluable subjects are defined as those with nonmissing MIBS scores at both baseline and ≥1 scheduled time point (i.e., Week 4, 8, or 12) during the DBT outcomes research analysis period. Treatment groups are compared using a model with the same attributes as the one described in Section 6.5.1. The table has a similar format.

Results at Week 12 support key secondary objective #5, and results at Weeks 4 and 8 support other secondary objective #4.

6.5.3 MFIQ

The MFIQ is a 26-item, patient-reported questionnaire developed to measure the subjective impact of migraine on physical functioning (everyday activities, physical impairment) as well as social and emotional functioning in the past 7 days. The MFIQ is administered weekly.

6.5.3.1 Imputed Baseline MFIQ

The imputed baseline MFIQ questionnaire is derived using the following steps in order to reduce the loss of baseline data (see Section 6.5):

- If the baseline MFIQ questionnaire is missing (i.e., all 26 item responses are missing at baseline), then the imputed baseline MFIQ questionnaire is set to the MFIQ questionnaire assessed on DB study drug start date + 1 day, if available.
- Otherwise, the imputed baseline MFIQ questionnaire is set to the baseline MFIQ questionnaire.

In a migraine prevention study with EOD dosing, it is not expected that MFIQ scores would change substantially after 1 dose of DB study drug.

6.5.3.2 MFIQ Monthly Average Score During the DBT Phase

For each domain and global item, the MFIQ monthly average score is derived using the following steps:

- First, MFIQ transformed scores are slotted into weekly analysis visit windows in the DBT outcomes research analysis period (see Table 7). Refer to the Core Sap for deriving MFIQ transformed scores.
- Next, 1 MFIQ transformed score is selected in each weekly analysis visit window, i.e., the weekly MFIQ transformed score. Refer to the Core SAP for handling multiple questionnaires in an analysis visit window or on the same assessment date based on eDiary data.
- Finally, the MFIQ monthly average score is calculated for each month as the mean of nonmissing weekly MFIQ transformed scores across the following weeks:
  - Month 1: Weeks 1 to 4
  - Month 2: Weeks 5 to 8
  - Month 3: Weeks 9 to 12.

For each domain and global item, subjects must have ≥2 weekly MFIQ transformed scores (not necessarily consecutive) in a month to be evaluable at that month.

6.5.3.3 MFIQ Monthly Average Score Changes From Baseline Over Time

Descriptive Analyses

The table of values and changes from imputed baseline in MFIQ monthly average score is provided by treatment group and overall for each domain (physical function, usual activities, social function, emotional function) and global item (overall impact on usual activities) for the DBT efficacy analysis set at the following time points: baseline; imputed baseline; and Months 1, 2, and 3 of the DBT outcomes research analysis period. Results for overall are displayed only at baseline and imputed baseline.

Results support other secondary objective #6.

Treatment Group Comparisons

For each domain and global item, analyses are based on the evaluable DBT efficacy analysis set, where evaluable subjects are defined as those with (1) nonmissing imputed baseline MFIQ transformed score and (2) ≥1 nonmissing MFIQ monthly average score (i.e., Month 1, 2, or 3) during the DBT outcomes research analysis period. Treatment groups are compared using a model with the same attributes as the one described in Section 6.5.1, except month replaces week and imputed baseline replaces baseline. The table has a similar format.

Results support other secondary objective #6.

6.5.4 WPAI − Migraine Changes From Baseline Over Time

The WPAI − Migraine is a 6-item, patient-administered questionnaire that is used to capture work impairment due to migraine pain.

Descriptive Analyses

The table of values and changes from baseline in the WPAI − Migraine scores (absenteeism, presenteeism, work productivity loss, and activity impairment) is provided for the DBT efficacy analysis set, and has a similar format as the one described in Section 6.5.1 plus an additional time point (i.e., Week 14 of the OL rimegepant outcomes research analysis period).

Results support other secondary objective #7 and exploratory objective #10.

Treatment Group Comparisons

For each WPAI − Migraine score, analyses are based on the evaluable DBT efficacy analysis set, where evaluable subjects are defined as those with nonmissing WPAI − Migraine scores at baseline and ≥1 scheduled time point (i.e., Week 4, 8, or 12) during the DBT outcomes research analysis period. Treatment groups are compared using a model with the same attributes as the one described in Section 6.5.1. The table has a similar format.

Results support other secondary objective #7.

6.5.5 PGA − Migraine

The PGA − Migraine is a 5-point rating scale that measures the patient's overall assessment of migraine.

6.5.5.1 Imputed Baseline PGA − Migraine

The imputed baseline PGA − Migraine value is derived using the following steps in order to reduce the loss of baseline data (see Section 6.5):

- If the baseline PGA − Migraine value is missing, then the imputed baseline PGA − Migraine value is set to the nonmissing PGA − Migraine value on DB study drug start date + 1 day, if available.
- Otherwise, the imputed baseline PGA − Migraine value is set to the nonmissing baseline PGA – Migraine value.

In a migraine prevention study with EOD dosing, it is not expected that the PGA − Migraine value would change substantially after 1 dose of DB study drug.

6.5.5.2 PGA − Migraine Monthly Average Score During the DBT Phase

The PGA − Migraine monthly average score for each month of the DBT Phase is derived using the following steps:

- First, PGA − Migraine scores are slotted into the DBT outcomes research analysis period (see Table 7).
- Next, 1 PGA − Migraine score is selected on each day. Refer to the Core SAP for handling multiple questionnaires on the same assessment date based on eDiary data.
- Finally, the PGA − Migraine monthly average score is calculated for each month as the mean of nonmissing scores across the following time points:
  - 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.

Subjects must have ≥14 days of PGA − Migraine scores (not necessarily consecutive) in a month to be evaluable in that month.

6.5.5.3 PGA − Migraine Score Changes From Baseline Over Time

Descriptive Analyses

The table of values and changes from imputed baseline in the PGA − Migraine score in the DBT Phase is provided by treatment group and overall for the DBT efficacy analysis set at the following time points: baseline; imputed baseline; Months 1, 2, and 3 of the DBT outcomes research analysis period; Week 14 and Week 24 of the OL rimegepant outcomes research

analysis period. Results at Months 1 to 3 are based on a monthly average score, whereas results at all other time points are based on a single score. Results for overall are displayed only at baseline, imputed baseline, and time points in the OL rimegepant outcomes research analysis period.

Results support other secondary objective #8 and exploratory objective #10.

Treatment Group Comparisons

Analyses are based on the evaluable DBT efficacy analysis set, where evaluable subjects are defined as those with (1) nonmissing imputed baseline PGA − Migraine score and (2) ≥1 nonmissing PGA − Migraine monthly average score (i.e., Month 1, 2, or 3) during the DBT outcomes research analysis period.

For the PGA − Migraine monthly average score, treatment groups are compared using a model with the same attributes as the one described in Section 6.5.1, except month replaces week and imputed baseline replaces baseline. The table has a similar format.

Results support other secondary objective #8.

6.5.6 HIT-6

The HIT-6 is a 6-item, patient-administered questionnaire developed to assess headache severity over the previous month and change in clinical status over time.

6.5.6.1 HIT-6 Changes From Baseline Over Time

Descriptive Analyses

The table of values and changes from baseline in the HIT-6 score is provided for the DBT efficacy analysis set, and has a similar format as the one described in Section 6.5.1.

Results support exploratory objective #8 and exploratory objective #10.

Treatment Group Comparisons

Analyses are based on the evaluable DBT efficacy analysis set, where evaluable subjects are defined as those with nonmissing HIT-6 scores at baseline and ≥1 scheduled time point (i.e., Week 4, 8, or 12) during the DBT outcomes research analysis period. Treatment groups are compared using a model with the same attributes as the one described in Section 6.5.1. The table has a similar format.

Results support exploratory objective #8.

6.5.6.2 Percentages of Subjects With HIT-6 Reductions From Baseline Over Time

Descriptive Analyses

The frequency table of ≥ 5-point reduction from baseline in the HIT-6 score is provided by treatment group and overall for the DBT efficacy analysis set at Week 24 of the OL rimegepant outcomes research analysis period. Refer to the Core SAP for outcomes research frequency table contents.

Results support exploratory objective #11.

Treatment Group Comparisons

The percentages of subjects with ≥ 5-point reduction from baseline in the HIT-6 score at each week (Weeks 4, 8, and 12) are compared between rimegepant and placebo using Mantel-Haenszel risk estimation with stratification by 4-level randomization stratum. Percentages are calculated against the number of subjects in the DBT efficacy analysis set at all time points.

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

- Response rate (i.e., "n/N" and percentage), ASE, and 95% CI for each treatment group
- Stratified percentage difference between rimegepant and placebo (rimegepant – placebo), ASE, 95% CI, and p-value.

Results support exploratory objective #9.

7 CONVENTIONS

7.1 Derived Dates

Derived dates are defined as follows:

- Screening visit date: earliest visit date containing "screening" in the visit label from the Date of Visit CRF
- eDiary measurement date: complete datepart{eDiary finding date/time} – 1 day, if from the eDiary headache log; complete datepart{eDiary finding date/time} otherwise
- eDiary efficacy data date: eDiary measurement date from the eDiary headache log
- Study drug start date: earliest complete dosing date from IP Dosing Wallet 1 to 4 and Replacement IP Dosing Wallet 1 to 4 CRF records with number of tablets taken >0. This is an analysis period reference date.
- Study drug end date: latest complete dosing date from IP Dosing Wallet 1 to 4 and Replacement IP Dosing Wallet 1 to 4 CRF records with number of tablets taken >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 of the following:
    - "no" response to the continuing to the next phase question on the DB Subject Status CRF
    - {"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 CRF
- LSLV database lock: study drug end date

This is an analysis period reference date.

- DB study drug start date: earliest complete dosing date from IP Dosing Wallet 1 to 4 and Replacement IP Dosing Wallet 1 to 4 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 complete dosing date from IP Dosing Wallet 1 to 4 and Replacement IP Dosing Wallet 1 to 4 CRF records with number of tablets taken per day >0 and valid DB wallet ID
- DB study drug last date:
  - Before the PCD database lock: DB study drug end date derived only for subjects with "yes" or "no" response to the phase completion question on the DB Subject Status or OLE Subject Status
  - PCD database lock and after: DB study drug end date

  This is an analysis period reference date.
- OL rimegepant start date: earliest complete dosing date from IP Dosing Wallet 1 to 4 and Replacement IP Dosing Wallet 1 to 4 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 complete dosing date from IP Dosing 1 to 4 and Replacement IP Dosing Wallet 1 to 4 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 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; OL rimegepant start date for subjects whose as-treated DB treatment group is placebo. 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; OL rimegepant end date for subjects whose as-treated DB treatment group is placebo
- DB or OL rimegepant last dose date: study drug last date for subjects whose as-treated DB treatment group is rimegepant; OL rimegepant last date for subjects whose as-treated DB treatment group is placebo. This is an analysis period reference date.
- OP start date: earliest of the following: screening visit date – 1 day; eDiary efficacy data date. 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:
  1. Earliest complete death date from the AE CRF, if it exists.
  2. Otherwise, the latest complete date of the following: AE start or end; ECG; eDiary finding; dosing; informed consent; RTSM randomization; laboratory test collection; nonstudy medication start or end; physical exam; physical measurement; procedure; rating scale; questionnaire; vital sign; visit.
  3. 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 baseline characteristics and relevant protocol deviations.
- On-DBT efficacy:
  - If the DB study drug last date or OL rimegepant start date is not missing: eDiary efficacy data date on or after the DB study drug start date through the earlier of {DB study drug last date + 1 day; 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 + 1 day

  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 (MSQ, MIBS, MFIQ, HIT-6, WPAI − Migraine, PGA − Migraine) *
  - 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 DBT 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 C4951012 Protocol Section 4.3 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.

General analysis visit windows are shown in Table 6. MFIQ DBT analysis visit windows are shown in Table 7.

Table 6 General 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	**On-Treatment Safety: 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 112	98
Week 24		155 to 182	168
Extension @		≥183	
Follow-Up Safety	**FU**	**Follow-Up Day**	
Follow-Up Week 2	FU Week 2	8 to 28	14
Follow-Up Extension @	FU Ext	≥29	

* 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

Table 7 MFIQ DBT Analysis Visit Windows

Analysis Visit	Study Day Analysis Visit Window	Target Day
Week 1	2 to 10	7
Week 2	11 to 17	14
Week 3	18 to 24	21
Week 4	25 to 31	28
Week 5	32 to 38	35
Week 6	39 to 45	42
Week 7	46 to 52	49
Week 8	53 to 59	56
Week 9	60 to 66	63
Week 10	67 to 73	70
Week 11	74 to 80	77
Week 12	81 to 98	84
Extension @	≥99	

@ Denotes an extended visit in the analysis period

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

See Section 1.2 for the timing of database locks and reports.

8.1 PCD Final CSR

The following TLFs are produced for the PCD Final CSR, which focuses on efficacy, safety, and outcomes research endpoints during the DBT Phase:

- Section 6.2 Study Population: all tables and listings
- Section 6.3 Efficacy: all tables and listings
- Section 6.3 Safety:
  - All listings, including safety narrative subject identifiers
  - On-DBT and post-DBT pre-OL rimegepant safety analysis periods: all tables and figures
  - On-OL rimegepant safety analysis period: tables of AE overview, AEs by worst intensity, AEs related to study drug by worst intensity, SAEs, AEs leading to study drug discontinuation, worst laboratory test abnormalities, and LFT elevations.

- Follow-up safety analysis period: tables of AE overview, AEs by worst intensity, and SAEs.

- Section 6.4 Outcomes Research: listing; tables of endpoints during the DBT Phase.

Tables of safety and outcomes research endpoints over time display results only during pretreatment and the DBT Phase.

8.2 LSLV Final CSR

All TLFs described in this SAP are produced for the LSLV Final CSR.

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 BHV3000-201/305/404/405/406 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 Microsoft Excel file of protocol deviations extracted from clinical trial management system (CTMS) by Sponsor Clinical Operations.
- 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
  - ≥7 nonmigraine headache days per month in the 3 months prior to screening, if originally consented to Protocol Version 4 or higher. Defined as {number of headache days per month in the 3 months prior to screening} – {number of migraine days per month of any pain intensity 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 3 or lower *

- BMI ≥35 kg/m^2, if originally consented to Protocol Version 4 or higher *
- C-SSRS suicidal ideation with active intent or plan to act, or suicidal behavior present. Defined as having a "yes" response to any of the following C-SSRS questions during pretreatment:
  - 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).

  Responses to lifetime questions at the Screening Visit are excluded from analyses.

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.

- Nonstudy medication CRF data issue with ROM medication categories with previous inadequate response, defined as any of the following subcategories:
  - Number of ROM medication categories with previous inadequate response due to lack of efficacy or prior intolerance within 10 years of the Screening Visit ≤1 or missing
  - Number of ROM medication categories ≤1 or missing
  - Number of ROM medication categories ≥5

  Medication categories based on nonstudy medication CRF data are defined in Section 9.4.2.
- Efficacy data issue during the first 28 days of the OP, defined as any of the following subcategories:
  - ≤3 or missing migraine days
  - ≥15 headache days
  - ≥7 nonmigraine headache days, if originally consented to Protocol Version 4 or higher. A nonmigraine headache day is defined as a headache day that is not a migraine day.
  - ≤23 days of eDiary efficacy data (see Sections 6.2.6.2 and 9.2.2). Subjects without any eDiary efficacy data are considered to have 0 days of eDiary efficacy data.

  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 the RTSM system and actual data, defined as any of the following subcategories:
  - Number of total migraine days during the first 28 days of the OP discrepant between the RTSM system and eDiary data. This is defined as any of the following subcategories:
    - RTSM value of "4 to 7" and eDiary value ≤3, ≥8, or missing

    - RTSM value of "8 to 14" and eDiary value ≤7, ≥15, or missing.
  - Number of ROM medication categories with previous inadequate response discrepant between the RTSM system and nonstudy medication CRF data. ROM medication categories based on nonstudy medication CRF data are defined in Section 9.4.2. This is defined as any of the following subcategories:
    - RTSM value of "2" and CRF value ≤1, ≥3, or missing
    - RTSM value of "3 to 4" and CRF value ≤2, ≥5, or missing.

  See Section 6.2.5.1.
- DB study drug dosing noncompliance, defined as any of the following subcategories (see Sections 6.2.6.2 and 9.5):
  - DB study drug taken but not randomized
  - DB tablet count compliance <80% from 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
  - Consecutive DB study drug dosing days
  - Incorrect DB study drug taken.
- OL rimegepant dosing noncompliance, defined as any of the following subcategories (see Sections 6.2.6.2 and 9.5):
  - 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
  - Consecutive OL rimegepant dosing days
  - OL rimegepant start on or before DB study drug end
  - OL rimegepant taken but DB study drug never taken.
- eDiary usage compliance <80% from study drug start to later of last scheduled DBT Phase visit or DB study drug end/OL rimegepant start (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
  - Recognized prophylactic migraine medication taken up to 30 days before informed consent or afterward #. Recognized prophylactic migraine medication is defined as prophylactic migraine medication with preferred name containing any preferred name listed in the latest version of the sponsor-provided file Recognized Migraine Prevention

Medications.xlsx or equivalent. Prophylactic migraine medication is defined in Section 6.2.6.3.

- Narcotic (barbiturate or opioid) #
- Select moderate or strong cytochrome P450 3A4 (CYP3A4) inducer #
- Select strong CYP3A4 inhibitor #.

Note that nonstudy medications with route of "topical" or "intraocular" are excluded.

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

The protocol version to which subjects consented is determined from the Inclusion/Exclusion Criteria 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)
- Lasmiditan (yes, no)
- Ubrogepant (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 data 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 triptan 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 any of the 4 questions about taking triptan, ergotamine, lasmiditan, or ubrogepant 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 5 questions about taking medications to treat headache or aura (i.e., triptan, ergotamine, lasmiditan, ubrogepant, 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
- month: month; categorical variable with levels of 1, 2, and 3
- rndstr: imputed 4-level randomization stratum; categorical variable with levels of 1, 2, 3, and 4 (see Section 4.3)
- trt: treatment group; categorical variable with levels of 1 and 2 to denote rimegepant and placebo, respectively
- usubjid: unique subject identifier; categorical variable.

Then the SAS code is as follows:

```
proc mixed empirical;
class usubjid rndstr trt month;
model mdmchg = rndstr trt month trt*month;
repeated month / subject=usubjid type=un; /* unstructured covariance */
lsmeans trt trt*month / alpha=0.05 diff cl;
run;
```

9.4 ROM Medications With Previous Inadequate Response

9.4.1 Previous Experience With or Documented Contraindication to Prophylactic Migraine Medications CRF

The Previous Experience With or Documented Contraindication to Prophylactic Migraine Medications CRF first collects migraine-preventive medication category (ROM medication; other migraine-preventive medication).

- If the migraine-preventive medication category is "recognized, orally-administered migraine-preventive medication", then the CRF collects the following parameters: medication name from a drop-down menu; other specify as free text if medication name is "other"; medication category (1 to 8; see below), which is automatically derived from the medication name in the raw database; inadequate response status (yes, no); inadequate response reasons (lack of efficacy, prior intolerance, contraindication) – note that subjects may have ≥1 reason; contraindication reason (hypersensitivity, other); start date*; end date*; dose*; units (fixed as "mg")*; route (fixed as "oral")*; and frequency*.
- If the migraine-preventive medication category is "other migraine-preventive medication", then the CRF collects the following parameters: medication name as free text; inadequate response status; inadequate response reasons; contraindication reason; start date*; end date*; dose*; units*; route*; and frequency*.

Parameters marked with "*" are collected only if (1) inadequate response status is "no", or (2) ≥1 reason for inadequate response is "lack of efficacy", or (3) ≥1 reason for inadequate response is "prior intolerance".

The 8 medication categories are: (1) valproic acid; (2) other anticonvulsant; (3) beta blocker; (4) tricyclic antidepressant; (5) serotonin-norepinephrine reuptake inhibitor; (6) calcium-channel blocker; (7) angiotensin blocker; and (8) other.

All medications in the drop-down menu and free-text are coded.

9.4.2 Number of ROM Medication Categories With Previous Inadequate Response

The number of ROM medication categories with previous inadequate response is calculated as the sum across categories in which there is ≥1 medication with previous inadequate response due to (1) lack of efficacy within 10 years of the Screening Visit, (2) prior intolerance within 10 years of the Screening Visit, or (3) contraindication.

Analyses are based on medications in the migraine-preventive medication category of "recognized orally-administered migraine-preventive medication" from the Previous Experience With or Documented Contraindication to Prophylactic Migraine Medications CRF (see Section 9.4.1).

Medications with previous inadequate response due to lack of efficacy within 10 years of the Screening Visit are those that meet both of the following criteria:

- Inadequate response reason of "lack of efficacy"
- Screening visit date – 3651 days ≤ nonstudy medication imputed start date or imputed end date ≤ screening visit date – 1 day (see Section 7.1).

Medications with previous inadequate response due to prior intolerance within 10 years of the Screening Visit are those that meet both of the following criteria:

- Inadequate response reason of "prior intolerance"
- Screening visit date – 3651 days ≤ nonstudy medication imputed start date or imputed end date ≤ screening visit date – 1 day (see Section 7.1).

Medications with previous inadequate response due to contraindication are those with either (1) inadequate response reason of "contraindication" or (2) nonmissing contraindication reason.

- Medications with previous inadequate response due to contraindication due to hypersensitivity are those with contraindication reason of "hypersensitivity".
- Medications with previous inadequate response due to contraindication due to other reason are those with contraindication reason of "other".

- Medications with previous inadequate response due to contraindication reason not reported are those with both (1) inadequate response reason of "contraindication" and (2) missing contraindication reason.

If the number of ROM medication categories with previous inadequate response is NOT ≥1, then the following apply:

- The number is set to 0 if either of the following criteria is met:
  - There is a "no" response to the CRF question "Does the subject have any experience using prophylactic migraine medication(s) for the preventive treatment of migraine, or documented contraindication to using any prophylactic migraine medication?".
  - ≥1 medication in the migraine-preventive medication category of "recognized orally-administered migraine-preventive medication" has "no" response to the CRF question "Did the subject experience inadequate response as defined in the protocol?".
  - ≥1 medication in the migraine-preventive medication category of "recognized orally-administered migraine-preventive medication" has inadequate response reason of "lack of efficacy" or "prior intolerance" with nonmissing nonstudy medication imputed end date < screening visit date – 3651 days.
- Otherwise, the number is set to missing.

9.5 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 dosing date and number of tablets taken >0 are selected. Next, records are sorted by dosing date, wallet number, and number of tablets taken. Let dosing date1 and dosing date2 denote dates from any 2 sequential records such that dosing date1 ≤ dosing date2.

- Overlapping records are defined as those with dosing date1 = dosing date2.
- Gaps between 2 sequential study drug dosing day records are defined as dosing date2 – dosing date1 ≥ 2 days. All days from the dosing date1 + 1 day to the dosing date2 – 1 day inclusive are considered days on which no study drug was taken (i.e., not study drug dosing days).
- Consecutive study drug dosing days are defined as those with dosing date1 = dosing date2 – 1 day.

A DB study drug dosing day is defined as a day with complete dose date on which ≥1 tablet of DB study drug was taken, which is determined using valid DB wallet numbers.

An OL rimegepant dosing day is defined as a day with complete dose date on which ≥1 tablet of OL rimegepant study drug was taken, which is determined using valid OL wallet numbers.

Example:

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

Dosing Date	Wallet Number	Number of Tablets Taken	Note
01JAN2022	1234	1	
01JAN2022	5678	1	Dosing date entry error; overlap with previous record
03JAN2022	1234	1	
04JAN2022	1234	2	
05JAN2022	1234	1	
07JAN2022	1234	0	Excluded from analysis
11JAN2022	5678	1	5-day gap between previous record

Then study drug start date = 01JAN2022 and study drug end date = 11JAN2022.

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

Date	Number of Tablets Taken per Day	Dosing Day Flag	> 1 Tablet Taken per Day	Consecutive Study Drug Dosing Day
01JAN2022	2	Y	Y	
02JAN2022	0			
03JAN2022	1	Y		Y
04JAN2022	2	Y	Y	Y
05JAN2022	1	Y		Y
06JAN2022	0			
07JAN2022	0			
08JAN2011	0			
09JAN2011	0			
10JAN2011	0			
11JAN2011	1	Y		

The subject has a total of 5 study drug dosing days and 7 tablets taken. The subject took >1 tablet on 2 days and had 3 consecutive study drug dosing days.

10 REFERENCES

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