Protocol BHV3000-309 (C4951021)

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Rimegepant for Migraine Prevention in Japanese Subjects

Statistical Analysis Plan

Version 2

Date: 23-Apr-2024

SIGNATURE PAGE

Protocol Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Rimegepant for Migraine Prevention in Japanese Subjects
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Author:	PPD PPD, Japan PPD Signature: PPD Date: 23 Apr 2024 04:55:025-0400

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
Japan PPD

Signature: PPD

Date: 23 Apr 2024 05:00:013-0400

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REVISION HISTORY

Version	Description of Change
1	Original version (22-Mar-2023) based on Protocol Version 4
2	Amended version based on Protocol Version 5 (4-AUG-2023) Signature page: Changed signatories. General: Replaced "BHV3000-309" with "C4951021" throughout. Sections 1.2 and 2.3: Updated the wordings to be consistent with those described in the Protocol version 5. Section 2.4: Added the information on the protocol amendment. 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 to 3.2.3: Updated the wordings to be consistent with those in Protocol Version 5. For binary endpoints, specified that Mantel-Haenszel risk estimation will be used. Removed DB or OL rimegepant safety analysis set from the summary for safety objectives. Section 4.1: Modified the definition of OL rimegepant efficacy analysis set. Section 4.3: Added the subgroup of historical chronic migraine according to ICHD 3rd edition. Section 6.1.1.1: Add "DB or OL Rimegepant" treatment group for the follow-up safety analysis set. Section 6.2.1: Modified the administrative listing of randomization scheme and codes. Section 6.2.3.3: Specified that summary of "continued to the next phase" and "did not continue to the next phase" is shown by subcategories of complete status of DBT phase. Section 6.2.4: Added the by-subject listing of significant protocol deviations. Changed the analysis set to be used for the by-subject listing. Section 6.2.5: Added the cross-tabulation of the number and percentage of subjects in each randomization stratum from IWRS and those from actual data. Section 6.2.5.1: Removed the OL rimegepant baseline and DB or OL rimegepant baseline. Section 6.2.5.4: Deleted the frequency tables of migraine standard of care for non-study prior medications. Section 6.2.6.1: Removed the administrative listing of IP batch numbers. Modified the formula used in the calculation of the average OL rimegepant exposure (tablets per month) and average DB or OL rimegepant exposure (tablets per month). Removed the average OL Rimegepant exposure (tablets per month) categories from parameters for OL rimegepant exposure. Section 6.2.6.2: Changed "< 80%" to "≥ 80%" for DB tablet and OL rimegepant tablet count compliance. Added the category of "OL Rimegepant taken during the DBT phase" for DB treatment compliance and category of "DB study drug never taken" for OL rimegepant treatment compliance, respectively. Change the analysis set used for the table of eDiary usage compliance. Section 6.3: Specified to use randomization stratum based on actual data, not IWRS. Added detail on the by-subject listing of primary and secondary efficacy endpoints.

Section 6.3.1.1: Changed the analysis set for the frequency table of missing efficacy data in the OP and DBT phase. SE estimation method in the linear mixed effects model for the main analysis was changed to use Huber-White robust "sandwich" estimator. Added subgroup analyses by chronic migraine according to ICHD 3rd edition. For the J2R macros, edited the description on the Ndraw and thin parameters.

Section 6.3.2.1: Specified that Mantel-Haenszel risk estimation will be used in the analyses for percentages of subjects with reduction in migraine days per month in the DBT phase. Added subgroup analyses by chronic migraine according to ICHD 3rd edition.

Section 6.3.2.2: Same changes with Section 6.3.1.1 (i.e., main analysis for the primary endpoint) are made on the model analyses. Added subgroup analyses by chronic migraine according to ICHD 3rd edition.

Section 6.3.3: Same changes with Section 6.3.1.1 and section 6.3.2.1 are made on the linear mixed effects model and binary endpoint analyses, respectively.

Section 6.3.3.5: Modified the formula for the medication days per month on planned scheduled OL rimegepant dosing/ planned non-scheduled OL rimegepant dosing days through Month 10.

Section 6.4: Removed the pretreatment safety analysis period. Removed following sections: Pretreatment AEs, Post DBT pre-OL rimegepant AEs, and AEs across all study phases combined.

Section 6.4.1: The definition of AE relatedness is specified in the study SAP. Changed "by intensity" to "by worst intensity".

Section 6.4.1.2: Added SAE related to study drug to AE overview frequency table.

Section 6.4.1.3: Removed following AE frequency tables: medication-overuse headache AEs, and exposure-adjusted multiple occurrences of unique AEs.

Section 6.4.1.4: Added following AE frequency tables: hepatic-related AEs, hepatic-related AEs leading to study drug discontinuation, potential drug abuse AEs, cardiovascular AEs, and suicidality AEs.

Section 6.4.1.5: Specified the AE frequency tables: AEs by worst intensity, SAEs, and exposure-adjusted multiple occurrences of unique AEs.

Section 6.4.2: Specified the laboratory test criteria used for toxicity grading.

Section 6.4.2.1: Removed laboratory test worst abnormalities tables for interim analysis set and DB or OL Rimegepant analysis set. Changed the analysis set for laboratory test shift from baseline to the worst abnormality for each graded laboratory test from DB or OL rimegepant safety analysis set to OL rimegepant safety analysis set.

Section 6.4.2.2: Removed frequency table of LFT elevations for pretreatment safety analysis period. Changed the analysis set for frequency tables of LFT shifts from baseline to worst elevation and eDISH plot from DB or OL rimegepant safety analysis set to OL rimegepant safety analysis set. Removed the tables of exposure-adjusted cumulative LFT elevations and time to first LFT elevation for DBT safety analysis set.

Sections 6.4.2.3, 6.4.3.1, and 6.4.4.1: Removed the changes from baseline table using DB or OL Rimegepant baseline for laboratory test, vital sign and physical measurement, and ECG.

Sections 6.4.3.2 and 6.4.4.2: Changed the analysis set from DB or OL rimegepant safety analysis set to OL rimegepant safety analysis set for frequency tables of vital sign and physical measurement abnormalities and ECG abnormalities.

Section 6.4.5: Changed the analysis set from DB or OL rimegepant safety analysis set to OL rimegepant safety analysis set for frequency table of C-SSRS suicidality.

Section 6.4.6: Modified the event of special interest provided in the safety narrative

	subject identifiers. Section 6.5 Removed the results in EOT from the tables for outcomes research endpoints. SE estimation method in the linear regression model is changed to use Huber-White robust "sandwich" estimator. Section 7.2: Removed pre-OL rimegepant and Pre-DB or OL Rimegepant safety analysis periods. Modified the purpose of the pretreatment analysis period. Section 7.3: Modified the analysis visit window for "screening" and "pre-randomization". Removed the description on the DB or OL Rimegepant safety analysis period to define analysis visit windows. Section 8: Modified the content of analyses for each report. Section 9.1: Changed "more than once and assigned" to "under". Removed subcategories for cardiovascular disease risk factor. Modified the subcategories for medical history. Modified the subcategory of headache days for the efficacy data issue. Modified the description on the prohibited non-study medications. Section 9.2.3: Changed the definition of acute migraine medication day. Section 9.3: Modified the SAS codes in accordance with the change in the analysis defined in sections 6.3.1.1 and 6.5.1.

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
CRF	Case report form
CSR	Clinical study report
DB	Double-blind
DBT	Double-blind treatment
eDiary	Electronic diary
eDISH	Evaluation of drug-induced serious hepatotoxicity
eGFR	Estimated glomerular filtration rate
EOD	Every other day
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels
FCS	Fully conditional specification
GLM	Generalized linear model
GLMEM	Generalized linear mixed effect model
IP	Investigational product
IWRS	Interactive web response system
LFT	Liver function test
LSM	Least-squares mean
MDRD	Modification of diet in renal disease
MSQoL	Migraine Specific Quality of Life
ODT	Orally disintegrating tablet
OL	Open-label
OLE	Open-label extension
PCD	Primary completion date
P-gp	Permeability glycoprotein
PRN	Pro re nata

PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SE	Standard error
SI	Systeme Internationale
SOC	System organ class
TBL	Total bilirubin
TLF	Table listing figure
ULN	Upper limit of normal
VAS	Visual analog scale

1 BACKGROUND AND RATIONALE

This document presents the statistical analysis plan (SAP) for Protocol C4951021: A Phase 3 Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Rimegepant for Migraine Prevention in Japanese Subjects.

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 is a safe and effective treatment for the prevention of migraine in the Japanese subjects.

1.2 Schedule of Analyses

There are 3 planned database locks: (1) primary completion date (PCD) database lock for the PCD final CSR, which will occur after the last subject completes the Week 12 Visit; (2) Week 24 database lock for the Week 24 final CSR, which will occur after the last subject completes the Week 24 Visit, if requested by a regulatory agency; and (3) last subject last visit (LSLV) database lock for the LSLV final CSR, which will occur after the last subject completes the Follow-up Week 2 Visit.

No interim analyses are planned.

2 STUDY DESCRIPTION

2.1 Study Design

This is a multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of rimegepant in migraine prevention in Japanese subjects.

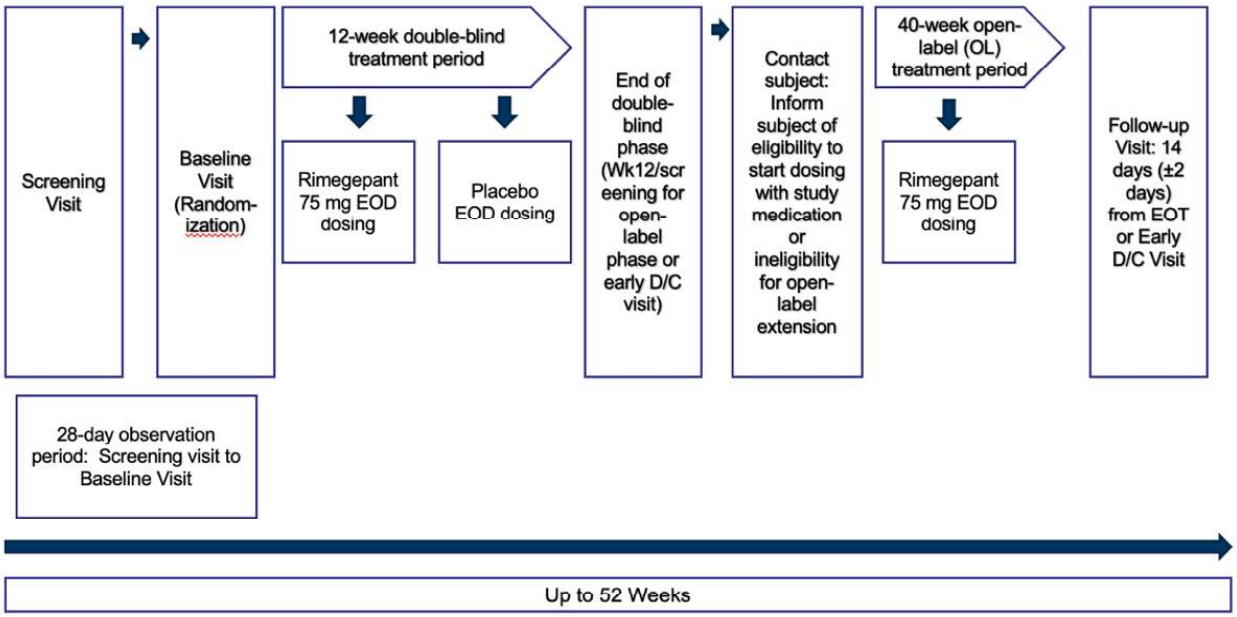
The study has 4 phases:

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

    - Placebo matching rimegepant 75 mg dosed EOD.
  - Randomization is stratified by prophylactic migraine medication use (yes or no).
  - Subjects are instructed that they can take a maximum of 1 orally disintegrating tablet (ODT) of double-blind (DB) study drug per every other calendar day.
  - All randomized subjects who discontinue early from the DBT Phase should complete the EOT Visit. Otherwise, subjects should complete the Week 12 Visit.
- Open-label Extension (OLE) Phase:
  - Subjects who (1) complete the DBT Phase, (2) continue to meet all inclusion/exclusion criteria, and (3) have been compliant with the electronic diary (eDiary) may enter the OLE Phase, pending review of laboratory test results.
  - Lasts up to 40 weeks, and includes the Week 14, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52/EOT Visits
  - Subjects are instructed that they can take a maximum of 1 open-label (OL) rimegepant 75 mg ODT (1) per every other calendar day on days they are scheduled to dose, and (2) as needed (pro re nata [PRN]) to treat a migraine on days they are not scheduled to dose.
  - All randomized subjects who discontinue early from the OLE Phase should complete the EOT Visit. Otherwise, subjects should complete the Week 52 Visit.
- Follow-up Phase:
  - Lasts up to 14 days and includes the Follow-up Week 2 Visit primarily for safety assessments. The Follow-up Week 2 Visit should occur approximately 2 weeks after the last visit in the last treatment phase (i.e., Week 12/EOT Visit if the subject did not enter the OLE Phase; Week 52/EOT Visit if the subject entered the OLE Phase).
  - All randomized subjects should complete the Follow-up Week 2 Visit, regardless of completing either treatment phase.

The design of the study is shown in Figure 1. Approximately 1064 subjects are screened to randomize up to approximately 490 subjects. It is estimated that approximately 400 subjects will enter the OLE Phase.

Figure 1 Study Schematic



2.2 Treatment Assignment

The Interactive Web Response System (IWRS) assigns a subject identifier number at the Screening Visit.

The IWRS randomizes eligible subjects to treatment groups (see Section 2.1) at the Baseline Visit. Randomization is stratified by prior prophylactic migraine medication use (yes or no).

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

2.3 Blinding and Unblinding

This study is blinded through the PCD database lock (see Section 1.2). Draft TLFs produced for the PCD final CSR are produced with dummy treatment groups prior to the PCD database lock. Otherwise, TLFs for the PCD final CSR, Week 24 final CSR, and LSLV final CSR are produced unblinded.

2.4 Protocol and Protocol Amendments

C4951021 SAP Version 1 is based on C4951021 Protocol Version 4 (27-Feb-2023).

C4951021 SAP Version 2 is based on C4951021 Protocol Version 5 (04-Aug-2023). Protocol changes that affected statistical analyses were the following: changing the sponsorship to Pfizer; stating that there are 3 planned database locks and 3 final CSRs; using robust standard error (SE) estimation methods; excluding subject as a random effect from linear mixed effects models; and replacing Cochran-Mantel-Haenszel test with Mantel-Haenszel risk estimation.

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 relative to placebo as a preventive treatment for migraine as measured by the mean reduction from baseline in the number of migraine days per month in the last 4 weeks of the DBT Phase.

3.1.2 Secondary Objectives

1. To compare the efficacy of rimegepant to placebo on the proportion of the subjects that have ≥ 50% reduction from baseline in the number of moderate to severe migraine days per month in the last 4 weeks of the DBT Phase.

2. To compare the efficacy of rimegepant to placebo on the mean reduction from baseline in the number of migraine days per month over the entire course of the DBT Phase.

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

4. To compare the efficacy of rimegepant to placebo on the mean number of acute migraine-specific medication (i.e., triptans and ergotamine) days per month in the last 4 weeks of the DBT Phase.

5. To compare the change from baseline in the Migraine-Specific Quality-of-Life Questionnaire v 2.1 (MSQoL v2.1) role function - restrictive domain score at Week 12 of the DBT Phase between rimegepant and placebo.

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

7. To compare the change from baseline in the EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) visual analog scale (VAS) score at Week 12 of the DBT Phase between rimegepant and placebo.

8. To evaluate the frequencies of AEs by intensity, SAEs, AEs leading to study drug discontinuation, and grade 3 to 4 laboratory test abnormalities in subjects treated with rimegepant during the DBT and OLE Phases.

9. To evaluate the frequency of ALT or AST > 3x ULN concurrent with total bilirubin > 2x ULN in subjects treated with rimegepant during the DBT and OLE Phases.

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

3.1.3 Exploratory Objectives

1. To evaluate the efficacy of rimegepant to placebo on the mean reduction from baseline in the number of migraine days per month by pain intensity (total; moderate or severe) in each month and the entire course of the DBT Phase.

2. To evaluate the efficacy of rimegepant to placebo on the proportion of the subjects that have ≥ 50% reduction, ≥ 75% reduction, and 100% reduction from baseline in the number of migraine days per month by pain intensity (total; moderate or severe) in each month and the entire course of the DBT Phase.

3. To evaluate the efficacy of rimegepant to placebo on the mean reduction from baseline in the number of migraine days per week by pain intensity (total; moderate or severe) in each week of the first 4 weeks of the DBT Phase.

4. To evaluate the mean reduction in the number of migraine days per month by pain intensity (total; moderate or severe) in each month and the entire course of the OLE Phase.

5. To evaluate the proportion of the subjects that have ≥ 50% reduction, ≥ 75% reduction, and 100% reduction from baseline in the number of migraine days per month by pain intensity (total; moderate or severe) in each month and the entire course of the OLE Phase.

6. To evaluate the efficacy of rimegepant to placebo on the mean number of acute migraine-specific medication (i.e., triptans and ergotamine) days per month and acute migraine medication days per month in each month and the entire course of the DBT Phase.

7. To evaluate the mean number of acute migraine-specific medication days per month and acute migraine medication days per month in each month and the entire course of the OLE Phase.

8. To evaluate the mean changes from baseline in MSQoL domain scores, MIDAS scores, and EQ-5D-5L VAS score over time during the DBT and OLE Phases.

3.2 Estimands

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

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

Intercurrent Events

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

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

- For efficacy objectives assessed with a continuous endpoint during the DBT Phase, study drug discontinuation is handled with a "hypothetical strategy," i.e., the hypothetical scenario is that had subjects not discontinued DB study drug, their efficacy would have been similar to the efficacy of subjects from the same treatment group and randomization stratum who did not discontinue DB study drug. All observed values of the endpoint of interest are excluded after DB study drug discontinuation 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 endpoint during the DBT Phase, DB study drug discontinuation is handled with a "composite strategy," i.e., the occurrence of the intercurrent event is integrated as a component of the endpoint. All observed values of the endpoint of interest are excluded after DB study drug discontinuation plus 1 day (see Section 7.2), and subjects with missing data are considered failures.
- For efficacy objectives assessed during the OLE Phase, OL 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. All observed values of the endpoint of interest are used on or before OL study drug discontinuation + 1 day (see Section 7.2).
- For safety objectives, study drug discontinuation is handled with a "while-on-treatment strategy". All observed values of the endpoint of interest are used on or before study drug discontinuation + 7 days (see Section 7.2 and the Core SAP).
- For outcomes research, study drug discontinuation is handled with a "treatment policy strategy", i.e., the occurrence of the intercurrent event is considered irrelevant. All observed values of the endpoint of interest are used regardless of study drug discontinuation.

Non-study prophylactic migraine medication use before the time point of interest defining the endpoint is considered an intercurrent event. For all objectives, this intercurrent event is handled with a treatment policy strategy; all observed values of the endpoint of interest are used.

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, MSQoL domain scores, MIDAS scores, and EQ-5D-5L VAS score are derived from eDiary data from the external source YPrime. Acute migraine-specific medications are triptans and ergotamine. Acute migraine medications are triptans, ergotamine, and other protocol-allowed medications to treat headache (migraine or nonmigraine) or aura taken on migraine days.

AEs are determined from AE CRFs.

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

3.2.1 Primary Objective Estimand

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

Table 1 Primary Objective Estimand

Objective	**Mean reduction from baseline in the number of migraine days per month in the last 4 weeks of the DBT Phase**
Efficacy Endpoint	Mean change from OP in the number of migraine days per month in the last 4 weeks (Weeks 9 to 12) of the DBT Phase
Summary	Change from OP by treatment group using descriptive statistics and linear mixed effects model with repeated measures, and difference between treatment groups from the model for the DBT migraine analysis set
Intercurrent Events	Study drug discontinuation: hypothetical strategy
	Non-study prophylactic migraine medication use: treatment policy strategy
	Nonstudy acute migraine-specific medication use: composite strategy
	Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy

3.2.2 Secondary Objective Estimands

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

Table 2 Secondary Objective Estimands

Objective 1	**Proportion of subjects with ≥ 50% reduction from baseline in the number of moderate to severe migraine days per month in the last 4 weeks of the DBT Phase**
Efficacy Endpoint	Proportion of subjects with ≥ 50% reduction from OP in number of moderate or severe migraine days per month in the last 4 weeks (Weeks 9 to 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 migraine analysis set
Intercurrent Events	Study drug discontinuation: composite strategy Non-study 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 baseline in the number of migraine days per month over the entire course of the DBT Phase**
Efficacy Endpoint	Mean change from OP in the number of migraine days per month over the entire DBT Phase (Weeks 1 to 12)
Summary	Change from OP by treatment group using descriptive statistics and linear mixed effects model with repeated measures, and difference between treatment groups from the model for the DBT migraine analysis set
Intercurrent Events	Study drug discontinuation: hypothetical strategy Non-study 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 baseline in the number of migraine days per month in the first 4 weeks of the DBT Phase**
Efficacy Endpoint	Mean change from OP in the number of migraine days per month in the first 4 weeks (Weeks 1 to 4) of the DBT Phase
Summary	Change from OP by treatment group using descriptive statistics and linear mixed effects model with repeated measures, and difference between treatment groups from the model for the DBT migraine analysis set
Intercurrent Events	Study drug discontinuation: hypothetical strategy Non-study prophylactic migraine medication use: treatment policy strategy Nonstudy acute migraine-specific medication use: composite strategy Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy
Objective 4	**Mean number of acute migraine-specific medication days per month in the last 4 Weeks of the DBT Phase**

Efficacy Endpoint	Mean number of acute-migraine-specific days per month in the last 4 weeks (Weeks 9 to 12) of the DBT Phase
Summary	Value by treatment group using descriptive statistics and linear mixed effects model with repeated measures, and difference between treatment groups from the model for the DBT migraine analysis set
Intercurrent Events	Study drug discontinuation: hypothetical strategy Non-study prophylactic migraine medication use: treatment policy strategy Nonstudy acute migraine-specific medication use: not applicable Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy
Objective 5	**Mean change from baseline in the MSQoL restrictive role function domain score at Week 12 of the DBT Phase**
Outcomes Research Endpoint	Mean change from baseline in the MSQoL restrictive role function domain score at Week 12 of the DBT Phase
Summary	Change from baseline by treatment group using descriptive statistics and linear regression models, and difference between treatment groups from the model for the DBT efficacy analysis set
Intercurrent Events	Study drug discontinuation: treatment policy strategy Non-study 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 MIDAS total score at Week 12 of the DBT Phase**
Outcomes Research Endpoint	Mean change from baseline in the MIDAS total score at Week 12 of the DBT Phase
Summary	Change from baseline by treatment group using descriptive statistics and linear regression models, and difference between treatment groups from the model for the DBT efficacy analysis set
Intercurrent Events	Study drug discontinuation: treatment policy strategy Non-study 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 EQ-5D-5L VAS score at Week 12 of the DBT Phase**
Outcomes Research Endpoint	Mean change from baseline in the EQ-5D-5L VAS score at Week 12 of the DBT Phase
Summary	Change from baseline by treatment group using descriptive statistics and linear regression models, and difference between treatment groups from the model for the DBT efficacy analysis set
Intercurrent Events	Study drug discontinuation: treatment policy strategy Non-study 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	**Safety and tolerability of rimegepant during the DBT and OLE Phases**
Safety Endpoint	Number and percentage of subjects with AEs by intensity, serious adverse events (SAEs), AEs leading to study drug discontinuation, and grade 3 to 4 laboratory test abnormalities on treatment
Summary	Frequency by treatment group for the DB and OL rimegepant safety analysis sets
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy
	Non-study prophylactic migraine medication use: treatment policy strategy
	Nonstudy acute migraine-specific medication use: treatment policy strategy
	Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy
Objective 9	**Frequency of ALT or AST > 3x upper limit of normal (ULN) concurrent with TBL > 2x ULN in subjects treated with rimegepant during the DBT and OLE Phases**
Safety Endpoint	Number and percentage of subjects with AST or ALT elevations > 3x ULN concurrent (i.e., on the same laboratory collection date) with TBL > 2x ULN on treatment
Summary	Frequency by treatment group for the DB and OL rimegepant safety analysis sets with LFT data
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy
	Non-study 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	**Frequencies of hepatic-related AEs and hepatic-related AEs leading to study drug discontinuation in subjects treated with rimegepant during the DBT and OLE Phases**
Safety Endpoint	Number and percentage of subjects with hepatic-related AEs and hepatic-related AEs leading to study drug discontinuation on treatment
Summary	Frequency by treatment group for the DB and OL rimegepant safety analysis sets
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy
	Non-study prophylactic migraine medication use: treatment policy strategy
	Nonstudy acute migraine-specific medication use: treatment policy strategy
	Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy

3.2.3 Exploratory Objective Estimands

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

Table 3 Exploratory Objective Estimands

Objective 1	**Mean reduction from baseline in the number of migraine days per month by intensity (total; moderate or severe) in each month and over the entire course of the DBT Phase**
Efficacy Endpoint	Changes from the OP in the number of migraine days per month in each month and over the entire DBT Phase by pain intensity (total; moderate or severe)
Summary	Changes from the OP by treatment group using descriptive statistics and linear mixed effects model with repeated measures, and difference between treatment groups from the model for the DBT migraine analysis set
Intercurrent Events	Study drug discontinuation: hypothetical strategy Non-study 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	**Proportions of subjects with ≥ 50% reduction, ≥ 75% reduction, and 100% reduction from baseline in the number of migraine days per month by pain intensity (total; moderate or severe) in each month and over the entire course of the DBT Phase**
Efficacy Endpoint	Proportions of subjects with ≥ 50% reduction, ≥75% reduction, and 100% reduction from the OP in the number of migraine days per month in each month and over the entire DBT Phase by pain intensity (total; moderate or severe)
Summary	Percentages by treatment group, and difference in percentages between treatment groups using Mantel-Haenszel risk estimation for the DBT migraine analysis set
Intercurrent Events	Study drug discontinuation: composite strategy Non-study 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 baseline in the number of migraine days per week by pain intensity (total; moderate or severe) in each week of the first 4 weeks of the DBT Phase**
Efficacy Endpoint	Changes from the OP in the number of migraine days per week during DBT in each week of the first 4 weeks by pain intensity (total; moderate or severe)
Summary	Changes from the OP by treatment group using descriptive statistics and linear mixed effects model with repeated measures, and difference between treatment groups from the model for the DBT first month migraine analysis set
Intercurrent Events	Study drug discontinuation: hypothetical strategy Non-study 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 reduction from baseline in the number of migraine days per month by intensity (total; moderate or severe) in each month and over the entire course of the OLE Phase**
Efficacy Endpoint	Mean changes from the OP in the number of migraine days per month in each month and over the entire OLE Phase by pain intensity (total; moderate or severe)
Summary	Changes from the OP by treatment group using descriptive statistics for the OL rimegepant migraine analysis set
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy Non-study 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 5	**Proportions of subjects with ≥ 50% reduction, ≥ 75% reduction, and 100% reduction from baseline in the number of migraine days per month by pain intensity (total; moderate or severe) in each month and over the entire course of the OLE Phase**
Efficacy Endpoint	Proportions of subjects with ≥ 50% reduction, ≥75% reduction, and 100% reduction from the OP in the number of migraine days per month in each month and over the entire OLE Phase by pain intensity (total; moderate or severe)
Summary	Percentages by treatment group for the OL rimegepant migraine analysis set
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy Non-study 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 6	**Mean number of acute migraine-specific medication days per month and acute migraine medication days per month in each month and over the entire course of the DBT Phase**
Efficacy Endpoint	Mean number of acute migraine-specific medication days per month and acute migraine medication days per month in each month and over the entire DBT Phase
Summary	Values by treatment group using descriptive statistics and linear mixed effects model with repeated measures, and difference between treatment groups from the model for the DBT migraine analysis set
Intercurrent Events	Study drug discontinuation: hypothetical strategy Non-study 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 for acute migraine-specific medication day and not applicable for acute migraine medication day
Objective 7	**Mean number of acute migraine-specific medication days per month and acute migraine medication days per month in each month and over the entire course of the OLE Phase**

Efficacy Endpoint	Mean number of acute migraine-specific medication days per month and acute migraine medication days per month in each month and over the entire OLE Phase
Summary	Values by treatment group using descriptive statistics for the OL rimegepant migraine analysis set
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy Non-study 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 for acute migraine-specific medication day and not applicable for acute migraine medication day
Objective 8	**Mean change from baseline in MSQoL domain scores (restrictive role function, preventive role function, emotional function), MIDAS scores (total, absenteeism, presenteeism), EQ-5D-5L VAS score during the DBT and OLE Phases**
Outcomes Research Endpoint	Mean change from baseline in MSQoL domain scores (restrictive role function, preventive role function, emotional function), MIDAS scores (total, absenteeism, presenteeism), EQ-5D-5L VAS score at Week 12 of the DBT Phase and Week 24 and Week 52 of the OLE Phase
Summary	• DBT Phase: Change from baseline by treatment group using descriptive statistics and linear regression model, and difference between treatment groups from the model for the DBT efficacy analysis set • OLE Phase: Change from baseline by treatment group using descriptive statistics for the OL rimegepant efficacy analysis set
Intercurrent Events	Study drug discontinuation: treatment policy strategy Non-study 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 used for statistical analyses, as applicable:

- Enrolled: subjects who signed informed consent and were assigned a subject identification number by the interactive web response system (IWRS), 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 were assigned a randomized treatment group by IWRS, i.e., nonmissing IWRS randomization date. This analysis set is used mainly to assess study population.
- Safety: subjects in the enrolled analysis set who take ≥ 1 dose of study drug (DB or OL), i.e., nonmissing study drug start date. This analysis set is used to assess study population, exposure, and on-treatment safety, 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 (1) are randomized only once, and (2) take ≥ 1 dose of DB study drug. This analysis set is used mainly to assess outcomes research endpoints during the DBT Phase.
  - DBT migraine: subjects in the DBT efficacy analysis set with ≥ 14 days of eDiary data (not necessarily consecutive) in both the OP and ≥ 1 month (4-week interval) during the DBT Phase (see Section 6.3.1.1). This analysis set is used to assess migraine days, headache days, acute migraine-specific medication days, and acute migraine medication days during the DBT Phase.
  - DBT 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 6.3.3.1). This analysis set is used to assess migraine and headache days per week during the DBT Phase.
- OL rimegepant efficacy: subjects in the DBT efficacy analysis set who take ≥ 1 dose of OL rimegepant. This analysis set is used to assess outcomes research endpoints during the OLE Phase.
  - OL rimegepant migraine: subjects in both the DBT migraine and OL rimegepant efficacy analysis sets with ≥ 14 days of eDiary efficacy data (not necessarily consecutive) in ≥ 1 month (4-week interval) in the OLE Phase. This analysis set is used to assess migraine days, headache days, acute migraine-specific medication days, and acute migraine medication days during the OLE 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 ODT and placebo ODT. The safety analysis sets are assessed by as-treated treatment group (i.e., actual treatment received), the full, DBT efficacy, and migraine analysis sets are assessed by as-randomized treatment group, and the enrolled analysis set is assessed overall.

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

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

4.3 Subgroups

Subgroup tables present results by subgroup level for subjects with nonmissing subgroup level data, unless otherwise specified. Subgroup levels may be redefined or combined based on the availability of data.

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

- Randomization stratum: stable prophylactic migraine medication use through randomization (yes or no; see Section 6.2.5.4). Note that randomization strata are based on the actual data, not those assigned by IWRS. Results for efficacy endpoints by randomization stratum are shown as described in Section 6.3.
- Historical chronic migraine according to ICHD 3rd edition (yes or no). This is from the Migraine History CRF.

5 SAMPLE SIZE, POWER, AND TYPE I ERROR

The study randomizes approximately 245 subjects per treatment arm to obtain roughly 225 evaluable subjects per treatment arm.

With a sample size of roughly 490 subjects randomized, and 245 subjects per group, we expect roughly 225 evaluable subjects per group in the efficacy data set. Assuming rimegepant provides roughly a 1 day advantage over placebo on the primary endpoint, a common standard deviation of 3.75 days, and a 2-sided alpha level of 0.05, then the study will have roughly 80% power on the primary endpoint. The estimates for the change in migraine days per month and the standard deviation are consistent with publicly available information from another investigational oral CGRP antagonist for this indication.

Type I error will be controlled by using a hierarchical gate keeping procedure. If the primary endpoint is significant at the 2-sided alpha level of 0.05, then secondary efficacy or outcomes research endpoints are tested hierarchically, each at a 2-sided alpha level of 0.05, in the order in which they appear in Section 3.2.2. Thus, a secondary efficacy or outcomes research endpoint is tested only if the preceding secondary endpoint in the hierarchy is determined to be significant (i.e., p-value ≤ 0.05). 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. Note that secondary safety endpoints are not tested.

For exploratory endpoints, no attempt is made to adjust for multiplicity. Any exploratory endpoints for which p-values are produced are evaluated at an unadjusted, 2-sided alpha level of 0.05 and presented only for descriptive purposes.

6 STATISTICAL ANALYSES

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

6.1 General

6.1.1 Programmed Output

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

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

6.1.1.1 Tables

Treatment Group Presentation

Treatment group presentation in tables by analysis set is shown in Table 4. Exceptions are specified in subsequent sections as needed.

Table 4 Treatment Group Presentation in Tables by Analysis Set

Analysis Set	Number of Columns	Abbreviated Treatment Group
Enrolled	1	Overall
Full, DBT efficacy, DBT migraine, safety, DBT safety, interim safety by treatment group and {overall}	2 to 3	Rimegepant Placebo {Overall}
OL rimegepant efficacy, OL rimegepant migraine, OL rimegepant safety, DB or OL rimegepant safety by treatment group/OL rimegepant and overall	3	DB Rimegepant/OL Rimegepant DB Placebo/OL Rimegepant Overall
Follow-up safety by treatment group/OL rimegepant status and overall	5	DB Rimegepant/OL Rimegepant DB Placebo/OL Rimegepant DB Placebo to OL Rimegepant DB Placebo No OL Rimegepant Overall

"DB Placebo to OL rimegepant" denotes as-treated DB placebo subjects in the OL rimegepant safety analysis set, and "DB Placebo No OL Rimegepant" denotes as-treated DB placebo

subjects not in the OL rimegepant safety analysis set; note that these 2 placebo groups add to the "DB Placebo/OL Rimegepant" group.

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

6.1.1.2 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 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); 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).

Refer to the Core SAP for additional details about listings.

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 Handling of Missing Data

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

6.2 Study Population

Refer to the Core SAP for TLF contents.

6.2.1 Analysis Sets

The frequency table of analysis sets described in Section 4.1 displays results by treatment group (as-randomized for the full and efficacy 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 site is provided for the enrolled analysis set, and 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 displays a separate record for each study phase (i.e., Screening, DBT, OLE and Follow-up) that is discontinued (i.e., completed or not completed) corresponding to each type of subject status CRF. The listing includes the following:

- Relevant reference dates: i.e., last contact date*, IWRS randomization date
- Study phase: Screening, DBT, OLE, or Follow-up. For each study phase:
  - Last visit date. Derived from visit dates from the Visit Date and Unscheduled Visit Checklist CRFs as follows:
    - Screening Phase: latest visit date before the IWRS randomization date
    - DBT Phase: latest visit date on or after the IWRS randomization date and through the on-DBT safety analysis period
    - OLE Phase: latest visit date in the OL rimegepant safety analysis period
    - Follow-up Phase: latest visit date in the follow-up safety analysis period
  - Phase completion status:
    - Screening Phase: “randomized”; or “not randomized” concatenated with the reason for screen failure (see Section 6.2.3.1)
    - DBT, OLE, or Follow-up Phase: “completed”; or “not completed” concatenated with the reason for non-completion (see Sections 6.2.3.2, 6.2.3.4, 6.2.3.5, and 6.2.3.5)
  - Next phase continuation status: “continued” concatenated with the name of the next phase (OLE or Follow-up); or “not continued” concatenated with the reason for non-continuation (see Sections 6.2.3.3 and 6.2.3.4). This applies only to the DBT and OLE Phase.

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

6.2.3.1 Subject Disposition from Enrollment to Randomization

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

- Randomized (identified as subjects with nonmissing randomization date)

- Not randomized (identified as subjects with missing randomization date)
    - Reasons for screen failure, including not reported. For subjects whose reason is "subject did not meet inclusion/exclusion criteria", the inclusion/exclusion criteria 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 nonmissing study drug start date)
    - Reasons for not treated (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 DBT Phase, including not reported
- Continued to the next phase. These are identified as subjects with "yes" response to the question "Will the subject continue into the next phase of the study?". Results are also shown by subcategories "Completed the DBT phase" and "Did not complete the DBT 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 "Will the subject continue into the next phase of the study?". Subjects with missing response to this question after the PCD database lock are also included. Results are also shown by subcategories "Completed the DBT phase" and "Did not complete the DBT phase".
    - Reasons for not continuing to the next phase, including not reported.

6.2.3.4 Subject Disposition during the OLE Phase

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

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

6.2.3.5 Subject Disposition during the Follow-up Phase

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

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

  A footnote explains that these are subjects with data in the follow-up safety analysis period who did not continue to the Follow-up Phase as per DB or OLE Subject Status CRF.
- Ongoing in the Follow-up Phase. These are identified as subjects with missing response to the question "Did the subject complete the Follow-up Phase?" and who are not already categorized as "Did not formally enter the Follow-up Phase".

This category only exists before the LSLV database lock. After the LSLV database lock, these subjects are categorized as "Did not complete the Follow-up Phase".

- Completed the Follow-up Phase. These are identified as subjects with "yes" response to the question "Did the subject complete the Follow-up Phase?")
- Did not complete the Follow-up Phase. These are identified as subjects with "no" response to the question "Did the subject complete the Follow-up Phase?".
  - Reasons for not completing the Follow-up Phase, including not reported

6.2.4 Protocol Deviations

6.2.4.1 Relevant Protocol Deviations

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

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

6.2.4.2 Significant Protocol Deviations

The by-subject listing of significant protocol deviations is provided for the full analysis set, and is based on the protocol deviation external file provided by the data management vendor. This includes occurrence date, category, subcategory, and non-compliance summary, which are additional sorting variables. 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.".

6.2.5 Baseline Characteristics

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

Baseline characteristics are provided for each of the following analysis sets as follows:

- DBT 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 OL rimegepant 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 DB or OL rimegepant baseline characteristics by treatment group/OL rimegepant and overall to support DB or OL rimegepant safety.

The frequency cross table of randomization stratum (i.e., prior prophylactic migraine medication use [yes, no]) from IWRS and actual data (Sections 4.3 and 6.2.5.4) is provided for the full analysis set by treatment group and overall.

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

By-subject listings are provided for the enrolled analysis set for the following: demographics and other relevant baseline characteristics; medical history; and migraine history. Refer to the Core SAP for additional details.

6.2.5.1 Demographics and Other Relevant Baseline Characteristics

Refer to the Core SAP for the table of demographics and other relevant baseline characteristics, and calculating age at a reference date. Other relevant characteristics also include randomization stratum based on actual data, i.e., use of non-study stable prophylactic migraine medication through randomization (yes, no; see Section 6.2.5.4). Note that race and ethnicity are not summarized.

6.2.5.2 Baseline Disease Characteristics

Migraine History

Refer to the Core SAP for the table of migraine history. The table also displays the following categorical variables:

- Experienced migraines for ≥ 1 year prior to screening (yes, no)
- Prophylactic migraine medications taken (yes, no).

Efficacy during the OP

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

- Migraine days per month by pain intensity (total; moderate or severe). Categories are < 6, ≥ 6, < 8, ≥ 8, < 12, ≥ 12, < 15, ≥ 15.
- 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.
- Acute migraine medication days per month. Categories are the same as for acute migraine-specific medication days per month above.

The table of efficacy endpoints per week during the OP is provided only for the DBT first month migraine analysis set, and summarizes the following efficacy parameters descriptively as continuous or categorical variables during the OP analysis period:

- Migraine days per week by 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 Sections 6.3.1 for migraine days per month, Section 6.3.2.2 for acute migraine-specific medication days per month, Section 6.3.3.3 for migraine days per week, Section 6.3.3.4 for acute migraine medication days per month, and Section 7.2 for the OP analysis period.

6.2.5.3 Medical History

Medical history is provided by system organ class (SOC) and preferred term (PT), and displayed in descending order of overall frequency within SOC and PT. Refer to the Core SAP for more details.

6.2.5.4 Non-study Prior Medications

Frequency tables of the following non-study medications are provided by therapeutic class and preferred name:

- Current medications: all; prophylactic migraine
- Stable prophylactic migraine medications through randomization.

Medications are displayed in descending order of overall frequency within therapeutic class and preferred name. See also Section 6.2.6.3.

Stable medications through randomization are defined as those taken > 12 weeks before informed consent and through randomization, i.e., (1) informed consent date – imputed medication start date > 84 days, and (2) IWRS randomization date ≤ imputed medication end date.

Refer to the Core SAP for the definition of non-study current medication type.

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 rimegepant or matching placebo depending on the randomization. During the OLE Phase, each wallet contains only rimegepant. The Investigational Product (IP) Administration – DB and OL CRFs collect the dosing date, number of tablets taken, and dosing day type (scheduled or non-scheduled), and wallet number (see Section 9.4).

The wallet type identifier associated with a wallet number is DB rimegepant, DB placebo, or OL rimegepant, and is obtained by merging the IP Administration CRF data with the external DB study drug wallet list file data and OL rimegepant wallet list file data by wallet number (i.e., kit number).

The by-subject listing of study drug is provided for the safety analysis set, and presents dosing date, study day derived from the dosing date, number of tablets taken, dosing day type (scheduled, non-scheduled) wallet number, and wallet type identifier. Records with number of tablets taken ≥ 0 are displayed for scheduled dosing days to account for missed doses. Records with number of tablets taken > 0 are displayed for non-scheduled dosing days. The listing also displays rimegepant exposure parameters (time on DBT, time on OL rimegepant, time on DB or OL rimegepant, DB study drug start end dates, and OL rimegepant start and end dates), and identifies invalid wallet numbers. Valid DB wallet numbers are those in the DB study drug wallet list file. Valid OL wallet numbers are those in the OL rimegepant wallet list file. The listing is sorted by site-subject ID, dosing date, day type, and wallet number.

DB Study Drug Exposure

DB study drug exposure is summarized descriptively by treatment group, and includes the following parameters:

- Time on DBT (weeks), derived as (DBT end date – DBT start date + 1)/7
- Time on study drug categories: < 2, ≥ 2 to < 4, ≥ 4 to < 8, ≥ 8 to < 12, ≥ 12 weeks
- Cumulative DB exposure (tablets), derived by summing the number of tablets across records with complete dosing date and valid DB wallet number
- Average DB exposure (tablets per month), derived as (1) cumulative DB exposure if time on DB study drug < 14 days, or (2) 4 × cumulative DB exposure/time on DB study drug if time on DB study drug if time on DB study drug ≥ 14 days
- Total DB exposure (tablets) summed across all subjects, derived by summing cumulative DB exposure across all subjects
- Total DB exposure (patient-years), derived by summing (DBT end date – DBT start date + 1)/365.25 across all subjects.

OL Rimegepant Exposure

OL rimegepant exposure is provided descriptively by treatment group/OL rimegepant and overall for the OL rimegepant safety analysis set, and includes the following parameters:

- Time on OL rimegepant (weeks), derived as (OL rimegepant end date – OL rimegepant start date + 1)/7
- Time on OL rimegepant (weeks) categories: ≤ 12, ≤ 24, > 24
- Time on OL rimegepant milestone categories:
  - ≥ 3 months, defined as ≥ 11 weeks
  - ≥ 6 months, defined as ≥ 23 weeks
- Cumulative OL rimegepant exposure (tablets), derived by summing the number of tablets 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 if time on OL rimegepant < 14 days, or (2) 4 × cumulative OL rimegepant exposure/time on OL rimegepant if time on OL rimegepant ≥ 14 days
- Total OL rimegepant exposure (tablets) summed across all subjects, derived by summing cumulative OL 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

DB or OL rimegepant exposure is provided descriptively by treatment group/OL rimegepant and overall for the DB or OL rimegepant safety analysis set, and includes the following parameters:

- Time on DB or OL rimegepant (weeks), derived as (DB or OL rimegepant end date – DB or OL rimegepant start date + 1)/7
- Time on DB or OL rimegepant (weeks) categories: ≤ 12, ≤ 24, > 24
- Time on DB or OL rimegepant milestone categories:
  - ≥ 3 months, defined as ≥ 11 weeks
  - ≥ 6 months, defined as ≥ 23 weeks
  - ≥ 1 year, defined as ≥ 51 weeks.
- Cumulative DB or OL rimegepant exposure (tablets), derived by summing the number of tablets across records with complete dosing date and valid DB rimegepant or OL rimegepant wallet number
- Average DB or OL rimegepant exposure (tablets per month), derived as (1) cumulative DB or OL rimegepant exposure if time on DB or OL rimegepant < 14 days, or (2) 4 × cumulative DB or OL rimegepant exposure/time on DB or OL rimegepant if time on DB or OL rimegepant ≥ 14 days

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

DB Treatment Compliance

The by-subject listing of DB treatment compliance is provided for the safety analysis set, and displays results for DB treatment compliance parameters in separate columns: average DB exposure (tablets per month; see Section 6.2.6.1); percentage for DB tablet count compliance and odd study drug dosing day compliance; flags for the other parameters ("Y" or missing).

The frequency table of DB treatment compliance is provided by treatment group for the 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 DB exposure/required cumulative DB exposure, where
  - Cumulative DB exposure is defined in Section 6.2.6.1.
  - Required cumulative DB exposure is derived as follows:
    - Let n = DB maxdate – DB study drug start date + 1.
      - DB maxdate is defined as the latest of the (1) Week 2, 4, 8, and 12 visit dates from the Visit Date – DB CRFs, (2) Week 52/EOT visit date from the Visit Date – OL CRF, if it is in the DBT safety analysis period (see Section 7.2), and (3) DB study drug end date.
      - If DB maxdate ≥ OL rimegepant start date, then DB maxdate is set to OL rimegepant start date – 1 day.
    - If n is even, then the required cumulative DB exposure is n/2.
    - If n is odd, then the required cumulative DB exposure is n/2 + 1.
- 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 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 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 6.3.1.1 for months). For example, suppose a subject takes 20 tablets through 4 weeks, 10 tablets after 4 weeks to 8 weeks, and 25 tablets after 8 weeks to 12 weeks. Thus, this subject is not considered to have taken ≥ 14 tablets (more than EOD frequency) per month for 3 consecutive months.
- > 1 DB tablet taken on any 1 day
- ≥ 1 non-scheduled DB study drug dosing day (see Section 9.4)
- Incorrect DB study drug taken
  - All the time. Defined as as-treated treatment group not equal to as-randomized treatment group, i.e., any of the following:
    - Subjects randomized to rimegepant who took (1) ≥ 1 tablet from a DB placebo wallet, and (2) no tablets from a DB rimegepant wallet
    - Subjects 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:
    - Subjects randomized to rimegpant who took ≥ 1 tablet from a DB placebo wallet
    - Subjects randomized to placebo who took ≥ 1 tablet from a DB rimegepant wallet.
- Time on study drug > 14 weeks.

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

OL Rimegepant Treatment Compliance

The by-subject listing of OL rimegepant treatment compliance is provided for the safety analysis set, and displays results for OL rimegepant treatment compliance parameters in separate columns: average DB exposure (tablets per month; see Section 6.2.6.1); percentage for OL rimegepant tablet count compliance; flags for the other parameters ("Y" or missing).

The frequency table of OL rimegepant treatment compliance is provided by treatment group for the 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 OL rimegepant exposure/required cumulative OL rimegepant exposure, where
  - Cumulative OL rimegepant exposure is defined in Section 6.2.6.1.
  - Required cumulative OL rimegepant exposure is derived as follows:

  - Let n = OL maxdate – OL rimegepant start date + 1.
    - OL maxdate is defined as the latest of the (1) Week 14, 16, 20, 24, 28, 32, 36, 40, 44, and 48 visit dates from the Visit Date – OL CRFs, (2) Week 52/EOT visit date from the Visit Date – OL CRF, if it is in the OL rimegepant safety analysis period (see Section 7.2), and (3) OL rimegepant end date.
  - If n is even, then the required exposure is n/2.
  - If n is odd, then the required exposure is n/2 + 1.
- Average OL rimegepant exposure (tablets per month) categories: ≤ 14, > 14 to ≤ 16, > 16, ≤ 17, > 17, > 18, > 19, > 20, > 22, > 24, > 26. Categories with 0 counts overall are not displayed. Average OL rimegepant exposure is defined in Section 6.2.6.1.
- > 1 OL rimegepant tablet taken on any 1 day
- Time on OL rimegepant > 44 weeks
- OL rimegepant start on or before DB study drug end. Defined as nonmissing OL rimegepant start date on or before DB study drug end date.
- OL rimegepant taken but DB study drug never taken. Defined as nonmissing OL rimegepant start date and missing DB study drug start date.

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

eDiary Usage Compliance

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:

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

eDiary DBT usage compliance is summarized as a continuous variable, and as the number and percentage of subjects 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 provided; see Section 7.2 for the 28-day OP analysis period and Section 9.2.2 for eDiary efficacy data days.

eDiary Usage Compliance during the OLE Phase

The table of eDiary usage compliance during the OLE Phase is provided by treatment group/OL rimegepant and overall for the OL rimegepant safety analysis set.

eDiary OLE usage compliance is derived as follows:

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

eDiary OLE usage compliance is summarized as a continuous variable, and as the number and percentage of subjects in the following categories: ≥ 90% compliance; ≥ 80% compliance.

6.2.6.3 Non-study Concomitant Medications

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

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

The following conventions apply to non-study medications:

- Non-study medications are identified from those reported on the Concomitant Medication CRF. The Concomitant Medication CRF links medical history and AE terms respectively to the Medical History and AE CRFs.
- Prophylactic migraine medications are defined as those with "yes" response to the "Is this a prophylactic migraine medication?" question.
- Acute migraine medications are defined as those with "yes" response to the "Is this a rescue drug to treat a migraine?" question.
- Migraine standard of care medications are defined as acute migraine or prophylactic migraine medications.

Non-study DBT Concomitant Medications

Frequency tables of the following non-study DBT concomitant medications are provided by treatment group for the DBT safety analysis set: all; migraine standard of care; prophylactic migraine. Medications are displayed in descending order of rimegepant frequency within therapeutic class and preferred name.

Non-study OL Rimegepant Concomitant Medications

Frequency tables of the following non-study OL rimegepant concomitant medications are provided by treatment group and overall for the OL rimegepant safety analysis set: all; migraine standard of care; prophylactic 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 by prior prophylactic migraine medication use (i.e., randomization stratum; yes or no). Hence, treatment group comparisons of continuous efficacy endpoints are *adjusted* by the randomization stratum, whereas treatment group comparisons of binary efficacy endpoints are *stratified* by the randomization stratum. If there is sparse data within a stratum, then results may be presented unstratified. Randomization is stratified using IWRS, but the randomization stratum used in analyses is based on actual data (i.e., stable prophylactic migraine medication use through randomization; see Sections 4.3 and 6.2.5.4). The rationale for using the actual data in analyses is that sites may erroneously report the wrong stratum in IWRS. Note that the phrase "randomization stratum" refers to the randomization stratum based on actual data, not IWRS, throughout this section.

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

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

The by-subject listing of primary and secondary efficacy endpoints is provided for the full analysis set, and includes the reason for exclusion from the DBT migraine analysis set (see Sections 6.3.1 and 6.3.2): 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 efficacy data (not necessarily consecutive) in the month defining the endpoint are flagged for endpoints based on a single month.

6.3.1 Reduction in Migraine Days per Month

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

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.

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

The number of migraine days per month in the DBT phase is examined relative to the number of migraine days per month in the OP for the DBT migraine analysis set, i.e., subjects with ≥ 14 days of eDiary efficacy data (not necessarily consecutive) in both the OP analysis period and ≥ 1 month (i.e., 4-week interval) in the on-DBT efficacy analysis period.

Months in the DBT phase are defined as follows:

- Month 1 (≤ 4 weeks; study days 1 to 28)
- Month 2 (> 4 to ≤ 8 weeks; study days 29 to 56)
- Month 3 (> 8 to ≤ 12 weeks; study days 57 to 84).

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

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

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

Missing Efficacy Data

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

- Included in the DBT migraine analysis set: ≥ 14 days of eDiary efficacy data (not necessarily consecutive) 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 DBT migraine analysis set
  - < 14 days of eDiary efficacy data in the OP
  - < 14 days of eDiary efficacy data in all 3 months of the DBT Phase.

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

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 DBT migraine analysis set, and summarizes parameters descriptively as continuous variables (including 2-sided normal 95% CIs for mean change) by treatment group and by pain intensity in each month of the DBT Phase and overall DBT. Pain intensity categories are (1) total (mild, moderate, severe, none, or not reported) and (2) moderate or severe. The table also presents 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 to 28 days) of appropriate migraine severity in the OP analysis period to be included.

Treatment Group Comparisons

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

Main Analysis: DBT Migraine Analysis Set

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

- Variables: change from the OP in number of total migraine days per month as the dependent variable; number of total migraine days per month in the OP as a covariate; treatment group, randomization stratum, 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 robust "sandwich" (refer to the Core SAP).

The table displays the following model estimates:

- Least-squares mean (LSM) change from OP, standard error (SE), and 95% CI by month and overall DBT for each treatment group
- Difference in LSM changes from OP between rimegepant and placebo, SE, 95% CI, and p-value at each month and overall DBT. Results in the last month support the primary objective, results in the overall DBT support secondary objective #2, results in the first

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

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

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

The line plot displays the LSM change from OP in the number of total migraine days from OP per month on the y-axis versus month of the DBT Phase on the x-axis by treatment group. Error bars denote 95% CIs.

J2R Imputation Sensitivity Analysis: DBT Efficacy Analysis Set

A sensitivity analysis of the primary endpoint uses the same linear mixed effects 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.[1, 2]
   a) Subjects with < 14 days of eDiary efficacy data in a specified month in the on-DBT efficacy analysis period have missing data imputed in that month.
   b) Data imputation is applied to each treatment group.
   c) The imputation model uses the following variables: number of total migraine days per month in the OP, age, sex, randomization stratum, and treatment group.
   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 Ndraws and thin parameters may be modified as needed (e.g., to decrease MCMC 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, and only if the p-value ≤ 0.05 for the treatment group comparison for the main analysis of the last 4 weeks of the DBT Phase.

The analysis is performed using the following steps:

1) A shift parameter of δ = 0 is selected.
   a) Data are imputed under the missing not at random (MNAR) assumption for the rimegepant 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. [1, 2]
      i) Subjects with < 14 days of eDiary efficacy data in a specified month in the on-DBT efficacy analysis period have missing data imputed in that month.
      ii) Data imputation is applied to each treatment group.
      iii) The fully conditional specification (FCS) method is used with regression to impute data at Months 1 to 3.
      iv) The imputation model specifies variables in the following order: changes from OP in the number of total migraine days per month at Months 1 to 3, number of total migraine days per month in the OP, age, sex, randomization stratum, and treatment group.
      v) A shift of δ is applied to imputed data only for subjects in the rimegepant 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 last 4 weeks of the DBT Phase 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 last 4 weeks of the DBT Phase. Results across all shift parameters are displayed together in the same table.

Subgroup Analyses

Subgroup analyses of the primary endpoint will use the same linear mixed effects model specified for the main analysis of the primary endpoint. The following model estimates will be reported by subgroup of historical chronic migraine according to ICHD 3rd edition (yes or no) (Section 4.3). P-values are presented only for descriptive purpose.

- LSM change from OP, SE, 95% CI by month in the DBT Phase and overall DBT for each treatment group
- Difference in LSM changes from OP between treatment groups (rimegepant - placebo), SE, 95% CI, and p-value at each month and overall DBT.

6.3.1.2 Reduction in Migraine Days per Month in the OLE Phase

The number of migraine days per month in the OLE Phase is examined relative to the number of migraine days per month in the OP for the OL rimegepant migraine analysis set, i.e., subjects with ≥ 14 days of eDiary efficacy data (not necessarily consecutive) in the OP analysis period, ≥ 1 month (i.e., 4-week interval) in the on-DBT efficacy analysis period, and ≥ 1 month in the on-OL rimegepant efficacy analysis period.

Months in the OLE Phase are defined as:

- Month 1 (> 12 to ≤ 16 weeks; study days 85 to 112)
- Month 2 (> 16 to ≤ 20 weeks; study days 113 to 140)
- Month 3 (> 20 to ≤ 24 weeks; study days 141 to 168)
- Month 4 (> 24 to ≤ 28 weeks; study days 169 to 196)
- Month 5 (> 28 to ≤ 32 weeks; study days 197 to 224)
- Month 6 (> 32 to ≤ 36 weeks; study days 225 to 252)
- Month 7 (> 36 to ≤ 40 weeks; study days 253 to 280)
- Month 8 (> 40 to ≤ 44 weeks; study days 281 to 308)
- Month 9 (> 44 to ≤ 48 weeks; study days 309 to 336)
- Month 10 (> 48 to ≤ 52 weeks; study days 337 to 364).

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

The number of migraine days per month are to 28 days, and derived as follows:

- OP: See Section 6.3.1.1.
- Month (i.e., 4-week interval) in the on-OL rimegepant efficacy analysis period: 28 × (total number of migraine days in the month)/(total number of 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 OL rimegepant: 28 × (total number of migraine days through Month 10 in the on-OL rimegepant efficacy analysis period)/(total number of efficacy data days through Month 10 in the on-OL rimegepant efficacy analysis period).

Missing Efficacy Data

The frequency table of missing efficacy data in the OP and OLE Phase is provided for the OL rimegepant efficacy analysis set by treatment group/OL rimegepant and overall, and displays the following categories:

- Included in the OL rimegepant migraine analysis set: ≥ 14 days of eDiary efficacy data (not necessarily consecutive) in the OP, ≥ 1 month (i.e., 4-week interval) of the DBT Phase, and ≥ 1 month of the OLE Phase
  - Month 1: > 12 to ≤ 16 weeks *
  - Additional months defined previously
  - Month 10: > 48 to ≤ 52 weeks *
- Excluded from the OL rimegepant migraine analysis set
  - < 14 days of eDiary efficacy data in the OP
  - < 14 days of eDiary efficacy data in all 3 months of the DBT Phase (see Section 6.3.1.1)
  - < 14 days of eDiary efficacy data in all 10 months of the OLE Phase.

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

Descriptive Analyses

Analyses are based on the OL rimegepant migraine analysis set, unless otherwise specified.

The table of values and changes (both absolute and percent) from the OP in the number of migraine days per month in the OLE Phase is provided, and summarizes parameters descriptively as continuous variables (including 2-sided 95% CIs for mean change) by treatment group/OL rimegepant and overall and by pain intensity (total; moderate or severe) in each month of the OLE Phase and overall OL rimegepant. Results support exploratory objective #4.

A line plot displays the mean change from OP in the number of total migraine days per month on the y-axis versus month (Month 1 to 10) of the OLE Phase on the x-axis by treatment group/OL rimegepant. Another line plot displays the mean change from OP in the number of total migraine days per month on the y-axis versus month (Month 1 to 13) of the DBT and OLE Phases on the x-axis for the DBT migraine analysis set by (1) treatment group during the DBT Phase and (2) overall for the OLE Phase. Error bars denote 95% CIs.

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

6.3.2 Secondary Efficacy Endpoints

6.3.2.1 Percentages of Subjects with Reduction in Number of Migraine Days per Month

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

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

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

Analyses are based on the DBT migraine analysis set with eDiary efficacy dates in the OP and on-DBT efficacy analysis periods (see Section 6.3.1.1).

Treatment Group Comparisons

For each pain intensity (total; moderate or severe) and select percentage reductions (≥ 50%, ≥ 75%, and 100%), the percentages of subjects with reductions are compared between treatment groups using Mantel-Haenszel risk estimation with stratification by randomization stratum (yes, no). This may be accomplished using SAS proc stdrate with the following options: method=mh, stat=risk, and effect=diff. Percentages are calculated against the number of subjects in the DBT migraine analysis set.

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

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

Results for ≥ 50% reduction of moderate or severe migraine severity in the last 4 weeks (i.e., Month 3) support secondary objective #1. All other results support exploratory objective #2.

Subgroup analyses

Proportion of subjects with ≥ 50% reduction from baseline in the number of moderate to severe migraine days will also be compared between treatment groups using a Mantel-Haenszel risk estimation with stratification by randomization stratum (yes, no) by subgroup of historical chronic migraine according to ICHD 3rd edition (yes or no) (Section 4.3). P-values are presented only for descriptive purpose.

The following statistics will be presented for each month in the DBT Phase and overall DBT mean by subgroup of historical chronic migraine according to ICHD 3rd edition (yes or no):

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

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

Analyses are based on the OL rimegepant migraine analysis set with eDiary efficacy dates in the OP and on-OL rimegepant efficacy analysis periods.

The frequency table of reductions from the OP in the number of migraine days per month in the OLE Phase is provided by treatment group/OL rimegepant and overall and by pain intensity (total; moderate or severe) in each month of the OLE Phase and overall OLE (see Section 6.3.1.2 for months), and displays the number and percentage of evaluable subjects in the following reduction categories: ≥ 50%, ≥ 75%, and 100%. Percentages are calculated against the number of evaluable subjects in the OL rimegepant migraine analysis set:

- In analyses by month, evaluable subjects are those with ≥ 1 migraine day of appropriate pain intensity in the OP and ≥ 14 days of eDiary efficacy data in the specified month.
- In analyses of the overall OLE, evaluable subjects are those with ≥ 1 migraine day of appropriate pain intensity in the OP.

Results support exploratory objective #5.

6.3.2.2 Acute Migraine-specific Medication Days per Month

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

Acute migraine-specific medication days per month are assessed as "acute migraine-specific medication days per 4 weeks" to correspond with the 4-week visit schedule. Acute migraine-specific medication days per month are based on 4-week interval, and are prorated to account for missing migraine reports. See Section 9.2.4 for the definition of acute migraine-specific medication day.

Acute Migraine-specific Medication Days per Month in the DBT Phase

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

The number of acute migraine-specific medication days per month in the DBT phase is prorated to 28 days and derived as follows:

- Month (i.e., 4-week interval) in the on-DBT efficacy analysis period: 28 × (total number of acute migraine-specific medication days in the month)/(total number of efficacy data days in the month). Subjects must have ≥ 14 days of efficacy data (not necessarily consecutive) in the specified month to be evaluable.
- Overall DBT: 28 × (total number of acute migraine-specific medication days through Month 3 in the on DBT efficacy analysis period)/(total number of efficacy data days through Month 3 in the on DBT efficacy analysis period).

Descriptive Analyses

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

Treatment Group Comparisons

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

- Variables: number of acute migraine-specific medication days per month as the dependent variable; treatment group, randomization stratum, month (i.e., Months 1 to 3 of the DBT Phase), and the month-by-treatment group interaction as fixed effects
- Covariance structure for repeated measures accounting for within-subject correlated errors: See Section 6.3.1.1.
- SE estimation method: See Section 6.3.1.1.

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 treatment groups (rimegepant – placebo), SE, 95% CI, and p-value at each month and overall DBT. Results in the last 4 weeks support secondary objective #4, whereas results at other time points support exploratory objective #6.

Model estimates by randomization stratum (yes, no) are presented in the same table, using additional models that exclude randomization stratum as a fixed effect.

Subgroup Analyses

Subgroup analyses of the acute migraine-specific medication days will use the same linear mixed effects model specified above. The following model estimates will be reported by subgroup of historical chronic migraine according to ICHD 3rd edition (yes or no) (Section 4.3). P-values are presented only for descriptive purpose.

- LSM, SE, and 95% CI by month in the DBT Phase and overall DBT for each treatment group

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

Acute Migraine-specific Medication Days per Month in the OLE Phase

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

The number of acute migraine-specific medication days per month in the OLE Phase is prorated to 28 days and derived as follows:

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

- Overall OL rimegepant: 28 × (total number of acute migraine-specific medication days through Month 10 in the on-OL rimegepant efficacy analysis period)/(total number of efficacy data days through Month 10 in the on-OL rimegepant efficacy analysis period).

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

Results support exploratory objective #7.

6.3.2.3 Overall Summary of Primary and Secondary Endpoints in Hierarchical Testing

The overall summary table of treatment comparisons of all primary and 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), overall LSM change and 95% CI for each treatment group
  - Difference in overall LSM changes between treatment groups (rimegepant – placebo), 95% CI, and p-value.

  This applies to the primary endpoint and the following secondary efficacy and outcomes endpoints: mean change in the number of migraine days per month in the overall DBT Phase (see main analysis in Section 6.3.1.1); mean change in the number of migraine days per month in the first month of the DBT Phase (see main analysis in Section 6.3.1.1); MSQoL restrictive role domain score change from baseline at Week 12 (see Section 6.5.1); MIDAS total score change from baseline at Week 12 (see Section 6.5.2); and EQ-5D-5L VAS score change from baseline at Week 12 (see Section 6.5.3).
- Continuous endpoints not involving change from OP or baseline

  - n, overall LSM and 95% CI for each treatment group
  - Difference in overall LSMs between treatment groups (rimegepant – placebo), 95% CI, and p-value.

  This applies to the secondary efficacy endpoint of the mean number of acute migraine-specific medication days per month in the last month of the DBT Phase (see Section 6.3.2.2).

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

  This applies to the secondary efficacy endpoint of the percentage of subjects with ≥ 50% reduction in the mean 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. P-values that are determined to be significant based on the testing hierarchy are flagged.

If the primary endpoint is significant, then the 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. Thus, a secondary efficacy or outcomes research endpoint is tested only if the preceding secondary endpoint in the hierarchy is determined to be significant (i.e., p-value ≤ 0.05). 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 a given treatment 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 comparison of a binary endpoint, the hypotheses are based on percentages instead of mean changes.

6.3.3 Exploratory Efficacy Endpoints

For exploratory efficacy endpoints, no attempt is made to adjust for multiplicity. Any exploratory endpoints for which p-values are produced are evaluated at an unadjusted, 2-sided alpha level of 0.05 and presented only for descriptive purposes.

This section also includes analyses of endpoints based on headache days that are typically included for migraine prevention studies. These are not formally prespecified in Section 3.2.3.

6.3.3.1 Reduction in Number of Headache Days per Month in the DBT Phase

The number of headache days per month is prorated to 28 days and defined analogously to

migraine days per month (see Section 6.3.1).
A headache day is defined in Section 9.2.6.
Analyses are analogous to those described in Sections 6.3.1.1 and 6.3.1.2 for the reduction in migraine days per month during the DBT and OLE Phases, respectively.

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.

Reduction in Headache Days per Month in the DBT Phase

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

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 6.3.1.1.

Treatment Group Comparisons

Treatment groups are compared using a linear mixed effects model with repeated measures 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 6.3.1.1.

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.

Reduction in Headache Days per Month in the OLE Phase

Analyses are based on the OL rimegepant migraine analysis set with eDiary efficacy dates in the OP and on-OL rimegepant efficacy analysis periods.

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

6.3.3.2 Percentages of Subjects with Reduction in Number of Headache Days per Month in the DBT Phase

The percentages of subjects with reduction in the number of headache days during the DBT and OLE Phases are defined and assessed analogously to the percentages of subjects with reduction in the number of migraine days during the DBT and OLE Phases (see in Section 6.3.2.1).

Percentages of Subjects with Reduction in Headache Days per Month in the DBT Phase

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

For each pain intensity and select percentage reduction, the percentages of subjects with reductions from the OP in the number of headache days per month in the DBT Phase are compared between treatment groups using Mantel-Haenszel risk estimation with stratification by randomization stratum (yes, no). The table has the same format as the one described in Section 6.3.2.1.

Percentages of Subjects with Reduction Headache Days per Month in the OLE Phase

Analyses are based on the OL rimegepant migraine analysis set with eDiary efficacy dates in the OP and on-OL rimegepant efficacy analysis periods.

The frequency table of reductions from the OP in the number of headache days per month in the OLE Phase is provided, and has the same format as the one described in Section 6.3.2.1.

6.3.3.3 *Reduction in the Number of Migraine Days per Week and Headache Days per Week in the First Month of the DBT Phase*

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 DBT 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 DBT first month migraine analysis set using eDiary efficacy 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 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.

Treatment Group Comparisons

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

- Variables: change from the OP in number of total migraine days per week as the dependent variable; number of total migraine days per week in the OP as a covariate; treatment group, randomization stratum, week (i.e., Weeks 1 to 4 of the DBT Phase), and the week-by-treatment group interaction as fixed effects.
- Covariance structure for repeated measures accounting for within-subject correlated errors: See Section 6.3.1.1.
- SE estimation method: See Section 6.3.1.1.

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 treatment groups (rimegepant – placebo), SE, 95% CI, and p-value for each week.

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

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

Results support exploratory objective #3.

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

6.3.3.4 Acute Migraine Medication days per Month

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.

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

Acute Migraine Medication Days per Month in the DBT Phase

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

Descriptive Analyses

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

Treatment Group Comparisons

Treatment groups are compared using a linear mixed effects model with repeated measures with the same properties as the model specified in Section 6.3.2.2, except that the number of acute migraine medication days per month is the dependent variable.

Results support exploratory objective #6.

Acute Migraine Medication Days per Month in the OLE Phase

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

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

Results support exploratory objective #7.

6.3.3.5 Medication Days per Month on Planned OL Rimegepant Dosing Days

This section includes analyses which are not formally prespecified in Section 3.2.3, but are typically included for migraine prevention studies with an OLE Phase.

Planned OL rimegepant dosing days are defined in Section 9.4. Medications are OL rimegepant and acute migraine medication.

For a given medication, the medication days per month on planned scheduled OL rimegepant dosing days through Month 10 is calculated as: 14 × (total number of medication days on the same days as planned scheduled OL rimegepant dosing days through Month 10 in the on-OL rimegepant efficacy analysis period)/(total number of planned scheduled OL rimegepant dosing days through Month 10 in the on-OL rimegepant efficacy analysis period).

For a given medication, the medication days per month on planned non-scheduled OL rimegepant dosing days through Month 10 is calculated as: 14 × (total number of medication days on the same days as planned non-scheduled OL rimegepant dosing days through Month 10 in the on-OL rimegepant efficacy analysis period)/(total number of planned non-scheduled OL rimegepant dosing days through Month 10 in the on-OL rimegepant efficacy analysis period).

The table of medication days per month on planned scheduled OL rimegepant dosing days through Month 10 is provided, and summarizes parameters descriptively as continuous variables for the OL rimegepant migraine analysis set by treatment group/OL rimegepant and overall for the following medications:

- Any medication: rimegepant or acute migraine medication (triptan, ergotamine, or other)
- Rimegepant or acute migraine-specific medication (triptan or ergotamine)
- Rimegepant and acute migraine medication
- Rimegepant and acute migraine-specific medication
- Rimegepant only (i.e., no acute migraine medication)
- Acute migraine medication
- Acute migraine medication only (i.e., no rimegepant)
- Acute migraine-specific medication
- Acute migraine-specific medication only (i.e., no rimegepant or other medication)
- Other medication
- Other medication only (i.e., no rimegepant or acute migraine-specific medication).

The table of medication days per month on planned non-scheduled OL rimegepant dosing days through Month 10 is also provided, and summarizes parameters analogously.

6.4 Safety

Safety analyses are provided according to 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.

Treatment group is as-treated treatment group according to Section 4.2.

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

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

1) Measurements are slotted into the pretreatment, on-treatment safety, and follow-up safety analysis periods.
2) Measurements are slotted into analysis visits in the analysis periods listed in the previous step (see Table 5).
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; rules for counting and rounding in frequency tables; definition of AEs of special interest, and exposure-adjusted multiple occurrences of unique AEs; and TLF contents. An AE is considered to be related to study drug if the relationship to study drug is unlikely related, possibly related, or related.

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 the question “Did the AE result in death?”; complete or partially complete death date
- Screening Status CRF: death as reason for screen failure
- DB Subject Status CRF with any of the following: death as reason for DBT Phase non-completion, or death as reason for not continuing to the next phase
- 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.
- Follow-up Subject Status CRF: death as reason for Follow-up Phase non-completion.

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; mild AE; moderate AE; severe 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; and suicidality AE.

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

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

6.4.1.3 On-DBT AEs

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

- AEs by worst intensity (secondary objective #8)
- AEs related to study drug by worst intensity
- AEs by relationship to study drug (related, possibly related, unlikely related, not related, not reported)
- SAEs (secondary objective #8)
- AEs leading to study drug discontinuation (secondary objective #8)
- Hepatic-related AEs (secondary objective #9)
- Hepatic-related AEs leading to study drug discontinuation (secondary objective #9)
- Potential drug abuse AEs, displayed in alphabetical order by worst intensity and PT without SOC
- Cardiovascular AEs
- Suicidality AEs

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

- AEs by worst intensity (secondary objective #8)
- AEs related to study drug by worst intensity
- AEs by relationship to study drug (related, possibly related, unlikely related, not related, not reported)
- SAEs (secondary objective #8)
- AEs leading to study drug discontinuation (secondary objective #8).
- Hepatic-related AEs (secondary objective #9)
- Hepatic-related AEs leading to study drug discontinuation (secondary objective #9)
- Potential drug abuse AEs, displayed in alphabetical order by worst intensity and PT without SOC
- Cardiovascular AEs
- Suicidality AEs

6.4.1.5 On-DB or OL Rimegepant AEs

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

- AEs by worst intensity (secondary objective #8)
- SAEs (secondary objective #8)
- Exposure-adjusted multiple occurrences of unique AEs.

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

6.4.1.6 Follow-up AEs

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

- AEs by worst intensity

- SAEs.

6.4.2 Laboratory Tests

Results are based on (1) external data from the central laboratory which reports both laboratory collection date and time, and (2) local data reported on Urine Pregnancy Test CRFs which capture only collection date. TLFs display results in Systeme Internationale (SI) units, if applicable.

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

- Hematology: Screening; Baseline; Weeks 4, 8, 12, 24, and 52/EOT
- Serum chemistry: Screening; Baseline; Weeks 4, 8, 12, 24, and 52/EOT. Exceptions are for the following:
  - LFTs (ALT, AST, ALP, TBL, direct bilirubin, indirect bilirubin): All visits
  - Lipids (total cholesterol, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, triglycerides): Baseline; Weeks 24 and 52/EOT
- Urinalysis: Baseline; Week 52/EOT.

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

- Laboratory test results (SI units). The listing displays all test results over time for subjects with select findings (grade 3 to 4 laboratory test abnormalities or positive pregnancy tests) at any time point. A positive pregnancy test result is defined as serum or urine pregnancy test with either (1) "positive" character value, or (2) numeric value > ULN.
- LFT values and ratios to ULN (i.e., ALT, AST, TBL and ALP) for 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.

Refer to the protocol for laboratory tests of clinical interest, Refer to the Core SAP for toxicity grades and TLF contents. Laboratory test values are graded according to numeric laboratory test criteria using below toxicity grading scales:

- Common Terminology Criteria for Adverse Events (CTCAE) if available; otherwise according to Division of Acquired Immune Deficiency Syndrome (DAIDS) Table for Grading the Intensity of Adult and Pediatric Adverse Events. These are based on SI units.

6.4.2.1 Laboratory Test Worst Abnormalities

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

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

Grade 3 to 4 results support secondary objective #8.

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

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

6.4.2.2 LFT Elevations

LFT Elevations

Frequency tables of LFT elevations 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.

Results support exploratory objective #9.

LFT Shifts from Baseline to Worst Elevation

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

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

Exposure-adjusted Cumulative LFT Elevations

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

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

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

Time to First LFT Elevation

Frequency tables of time to first LFT elevation are provided for subjects with select LFT elevations (ALT > 3x ULN; AST > 3x ULN; ALT or AST > 3x ULN) 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 to ≤ 28, > 28 to ≤ 32, > 32 to ≤ 36, > 36 to ≤ 40, and > 40 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 longitudinal LFT 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 dosing days and OL rimegepant dosing days using symbols along the x-axis (see Section 9.4), and denotes additional study milestones (e.g., start of the on-DBT safety analysis period, start of the on-OL rimegepant safety analysis period, and start of the follow-up safety analysis period) using vertical lines with their corresponding descriptions in footnotes.

6.4.2.3 Laboratory Test Changes from Baseline over Time

The table of values and changes from baseline in all hematology and serum chemistry laboratory tests is provided by treatment group and overall for the safety analysis set at the following time points: baseline; each scheduled visit through Week 12 and EOT in the on-DBT safety analysis period; each scheduled visit after Week 12 through Week 52 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 in the on-OL rimegepant and follow-up safety analysis periods.

Note that scheduled visits vary according to laboratory test.

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 Measurement

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 with a date at the following visits: Screening; Baseline; Weeks 4,

8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52/EOT; and Follow-up Week 2. Height is measured at the Screening Visit only.

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 52 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.

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.

6.4.4 Electrocardiograms

ECG parameters include QRS, PR, QT, QTcB, QTcF, and ventricular heart rate. ECGs are measured with assessment date on ECG CRFs at the following visits: Screening; Baseline; Weeks 4, 16, 24, and 52/EOT; and Follow-up Week 2.

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; each scheduled visit after Week 12 through Week 52 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 in the on-OL rimegepant and follow-up safety analysis periods.

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 DB or 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 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 early termination and all visits except Pre-randomization. At the Screening Visit, the recall period for completing is 12 months for suicidal ideation and 10 years for suicidal behavior; at all other visits, the recall period for completing the C-SSRS is since the last visit.

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

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

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

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

6.4.6 Safety Narrative Subject Identifiers

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

- Death in any analysis period for the enrolled analysis set
- SAE on DB or OL rimegepant or during follow-up for the DB or OL rimegepant safety analysis set
- AE leading to study drug discontinuation in any analysis period for the DB or OL rimegepant safety analysis set

- Event of special interest on DB or OL rimegepant for the DB or OL rimegepant safety analysis set:
  - ALT or AST > 3x ULN
  - ALT or AST ≥ 3x ULN and ≥ 2x baseline
  - ALT or AST > 3x ULN concurrent with TBL > 2x ULN
  - TBL > 2x ULN
  - Select hepatic-related AE, i.e., PT containing cirrhosis, hepatic failure, hepatitis, jaundice, or liver failure
  - Suicidality AE.

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 sets.

Outcomes research questionnaires MSQoL, MIDAS, and EQ-5D-5L are assessed using the eDiary at Baseline, Week 12, Week 24, and Week 52.

Measurements are slotted into analysis periods and analysis visits using the eDiary finding date and 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 analysis visits in the analysis periods listed in the previous step (see Table 5).

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.

By-subject listings of outcomes research questionnaires (i.e., MSQoL, MIDAS, and EQ-5D-5L) are provided for the enrolled analysis set. The listing displays values and changes from baseline for the following: MSQoL domain scores; MIDAS total, absenteeism, and presenteeism scores; EQ-5D-5L VAS score.

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

6.5.1 MSQoL

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

Descriptive Analyses

The table of values and changes from baseline in scores is provided by treatment group and overall for each domain for the DBT efficacy analysis set at the following time points: baseline; Week 12 of the DBT outcomes research analysis period; Week 24 and Week 52 in the OL rimegepant outcomes research analysis period. Results for overall are displayed only at baseline and time points in the OL rimegepant outcomes research analysis period. Results support exploratory objective #8.

The frequency table of MSQoL domain score reduction from baseline categories is provided by treatment group and overall for the DBT efficacy analysis set at the following time points: Week 12 of the DBT outcomes research analysis period; Week 24 and Week 52 in the OL rimegepant outcomes research analysis period. Results for overall are displayed only at time points in the OL rimegepant outcomes research analysis period.

Treatment Group Comparisons

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

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

- Variables: Week 12 change from baseline in the score as the dependent variable; baseline score as a covariate; treatment group and randomization stratum as fixed effects.
- SE estimation method: See Section 6.3.1.1..

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

- LSM change from baseline at Week 12, SE, and 95% CI for each treatment group
- Difference in LSM changes from baseline at Week 12 between each rimegepant treatment group and placebo (rimegepant – placebo), SE, 95% CI, and p-value.

Results for the restrictive role function support secondary objective #5, whereas results for the other domains support exploratory objective #8.

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

6.5.2 MIDAS

The MIDAS is a retrospective, patient-administered, 5-item questionnaire that measures headache-related disability as lost time due to headache from paid work or school, household work, and non-work activities.

Descriptive Analyses

The table of values and changes from baseline in total, absenteeism, presenteeism, and item scores is provided, and has a similar format as the one described in Section 6.5.1.

Results support exploratory objective #8.

Treatment Group Comparisons

Analyses of each score (total, absenteeism, presenteeism) are based on the DBT efficacy analysis set with scores at both baseline and Week 12 of the DBT outcomes research analysis period.

For each score, treatment groups are compared using a linear regression model with the same attributes as the one described in Section 6.5.1. The table has the same format.

Results for the total score support secondary objective #6, whereas results for the other scores support exploratory objective #8.

6.5.3 EQ-5D-5L

The EQ-5D-5L is a 2-part assessment questionnaire of the subject's current health. In the first part, subjects rate their current level of function in 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. In the second part, subjects rate their health on a VAS scale from 0 (worst imaginable health) to 100 (best imaginable health).

Descriptive Analyses

The table of values and changes from baseline in the VAS and utility index scores is provided, and has a similar format as the one described in Section 6.5.1. The utility index score is calculated from the official Japanese tariff based on time trade-off data.[3]

The frequency table of EQ-5D-5L dimension function level is provided by treatment group and overall for the DBT efficacy analysis set at the following time points: baseline; Week 12 of the DBT outcomes research analysis period; Week 24 and Week 52 of the OL rimegepant outcomes research analysis period. Results for overall are displayed only at baseline and time points in the OL rimegepant outcomes research analysis period.

Results support exploratory objective #8.

Treatment Group Comparisons

Analyses are based on the DBT efficacy analysis set with VAS scores at both baseline and Week 12 of the DBT outcomes research analysis period.

Treatment groups are compared using a linear regression model with the same attributes as the one described in Section 6.5.1. The table has the same format.

Results support secondary objective #7.

7 CONVENTIONS

7.1 Derived Dates

Derived dates are defined as follows:

- Screening visit date: visit date from the Visit Date – SS CRF with folder name "Screening Visit"
- eDiary efficacy date: complete datepart{eDiary finding date/time} – 1 day from the eDiary headache report
- Study drug start date: earliest complete dose date from IP Administration – DB or OL CRF with number of tablets taken > 0. This is an analysis period reference date.
- Study drug end date: latest complete dose date from IP Administration – DB or OL CRF with number of tablets taken > 0
- Study drug last date:
  - Before the final database lock: study drug end date derived only for subjects who have either (1) or (2):
    - (1) "Yes" or "no" response to the phase completion question on the DB Subject Status CRF, and {either (1a) "no" response to the continuing to the next phase question on the DB Subject Status CRF, or (1b) "Follow-up" specified as the next phase on the DB Subject Status CRF}, and missing OL rimegepant start date
    - (2) "Yes" or "no" response to the phase completion question on the OLE Subject Status or Follow-up Subject Status CRF
  - Final database lock: study drug end date

  This is an analysis period reference date.
- DB study drug start date: earliest complete dose date from IP Administration – DB or OL CRF records with number of tablets taken > 0 and valid DB wallet number. This is an analysis period reference date.
- DB study drug end date: latest complete dose date from IP Administration – DB or OL CRF records with number of tablets taken > 0 and valid DB wallet number
- DB study drug last date:
  - Before the first 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, OLE Subject Status, or Follow-up Subject Status CRF
  - First database lock or after: DB study drug end date

  This is an analysis period reference date.
- OL rimegepant start date: earliest complete dose date from IP Administration – DB or OL CRF records with number of tablets taken > 0 and valid OL wallet number. This is an analysis period reference date.

- OL rimegepant end date: latest complete dose date from IP Administration – DB or OL CRF records with number of tablets taken > 0 and valid OL wallet number
- OL rimegepant last date:
  - Before the final database lock: OL rimegepant end date derived only for subjects with "yes" or "no" response to the phase completion question on the OLE Subject Status or Follow-up Subject Status CRF
  - Final 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 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; informed consent; dose; IWRS randomization; laboratory test collection; non-study 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 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 date on or after the OP start date through the earlier of {OP start date + 27 days; OP end date}. Note that this is a subset of the OP analysis period, and is used only to assess efficacy data issues during the OP as relevant protocol deviations.
  - On-DBT efficacy:
    - If the DB study drug last date or OL rimegepant start date is not missing: eDiary efficacy date on or after the DB study drug start date through the earlier of {DB study drug last date + 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 date on or after the DB study drug start date

    This period is used to assess efficacy during the DBT Phase.
  - On-OL rimegepant efficacy:
    - If the OL rimegepant last date is not missing: eDiary efficacy date on or after the OL rimegepant start date through the OL rimegepant last date + 1 day
    - If the OL rimegepant last date is missing: eDiary efficacy date on or after the OL rimegepant start date
- 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 define analysis visit windows.
- Follow-up safety: This period is used to assess safety endpoints during follow-up for the follow-up safety analysis set.

- Outcomes research endpoints (MSQoL, MIDAS, EQ-5D-5L) *
  - DBT outcomes research: This period is used to assess outcomes research endpoints during the DBT Phase for the DBT efficacy analysis set.
  - OL rimegepant outcomes research: This period is used to assess outcomes research endpoints during the OLE Phase for the OL rimegepant efficacy analysis set.

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

7.3 Analysis Visit Windows

Refer to C4951021 Protocol Section 4.3 (Tables 1 and 2) for the schedule of assessments.

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

Analysis visit windows are shown in Table 5.

Table 5 Analysis Visit Windows

Analysis Period **Analysis Visit**	**Abbreviation in Listings**	**Analysis Day** **Analysis Visit Window**	**Target Day**
Pretreatment	**PRETRT**	**Randomization Day**	
Screening *		≤ -7	
Pre-randomization *	Prerand	-6 to -1	
Baseline *		1	
Post-randomization @	Postrand	≥ 2	
Outcomes Research /On-treatment Safety	**Outcomes Research: DBT or OLRMG/ Safety: DBT, INT, or OLRMG**	**Study Day**	
Week 2		2 to 21	14
Week 4		22 to 42	28
Week 8		43 to 70	56
Week 12		71 to 91	84
Week 14		92 to 105	98
Week 16		106 to 126	112
Week 20		127 to 154	140

Analysis Period **Analysis Visit**	**Abbreviation in Listings**	**Analysis Day** **Analysis Visit Window**	**Target Day**
Week 24		155 to 182	168
Week 28		183 to 210	196
Week 32		211 to 238	224
Week 36		239 to 266	252
Week 40		267 to 294	280
Week 44		295 to 322	308
Week 48		323 to 350	336
Week 52		351 to 378	364
Extension @		≥ 379	
Follow-up Safety	**FU**	**Follow-up Day**	
Follow-up Week 2	FU Week 2	8 to 35	14
Follow-up Extension @	FU Ext	≥ 36	

* For subjects in the enrolled analysis set excluded from the full analysis set, the visit label is used for slotting.
@ Denotes an extended visit in the analysis period and is displayed only in listings

Study days are used to define analysis visit windows in all analysis periods. Follow-up days are used to define analysis visit windows in the follow-up safety analysis period.

8 CONTENT 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: listing; tables and figures of endpoints during the DBT Phase
- Section 6.4 Safety:
  - All listings
  - 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 6.5 Outcomes Research: all tables and listings.

8.2 Week 24 Final CSR

The following TLFs are produced for the Week 24 final CSR, if requested by a regulatory agency, which focuses on efficacy, safety, and outcomes research endpoints during the OLE Phase:

- Section 6.2 Study Population:
  - All listings
  - Sections 6.2.1, 6.2.3.2, 6.2.3.3, 6.2.3.4, 6.2.3.5, and 6.2.4: all tables
  - Sections 6.2.5, 6.2.6.1, and 6.2.6.2: tables for the OL rimegepant safety and DB or OL rimegepant safety analysis sets
  - Section 6.2.6.3: all tables
- Section 6.3 Efficacy: tables, figures and listings of endpoints during the OLE Phase; line plot of migraine day reduction across the DBT and OLE Phases combined
- Section 6.4 Safety:
  - All listings
  - On-DBT and post-DBT pre-OL rimegepant safety analysis periods: all tables and figures
  - On-OL rimegepant safety analysis period: all tables and figures
  - On-DB or OL rimegepant safety analysis period: all tables
  - Follow-up safety analysis period: all tables.
- Section 6.5 Outcomes Research: listing; all tables except those of treatment comparisons.

8.3 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:

- Randomized or treated with study drug under > 1 subject identifier. These are identified from the external Microsoft Excel file of protocol deviations from the data management vendor.
- Migraine history issue, defined as any of the following subcategories:
  - Experienced migraines for < 1 year prior to screening. Defined as “no” response to the question about experiencing migraines for ≥ 1 year prior to screening.

- ≤ 3 or ≥ 19 moderate or severe migraine attacks per month in the 3 months prior to screening

These are based on the Migraine History CRF.

- Medical history, defined as any of the following subcategories:
  - Type of migraine: basilar; hemiplegic; or retinal, if consented to Protocol Version 4 or higher
  - Active chronic pain syndrome or other pain syndromes other than migraine present at screening
  - Dementia or significant neurological disorder other than migraine present at screening
  - Major depressive disorder with atypical antipsychotics taken as non-study prior medications, schizophrenia, bipolar disorder, or borderline personality disorder present at screening. PTs must contain any of the following: major depress; schizophrenia; bipolar disorder; borderline personality disorder. Refer to the Core SAP for atypical antipsychotics and non-study prior medication type.
  - Active hepatic or biliary disorder present at screening
  - Gastric or small intestinal surgery.

  For each subcategory, PTs are displayed alphabetically as additional subcategories. Unless otherwise specified, PTs are identified by the sponsor medical lead or designee from reviewing a list of unique medical history SOC and PTs. Active medical history status is also identified by the sponsor medical lead or designee from reviewing by-subject listings of medical history and AEs.

  Present at screening is defined as medical history end date of ongoing (refer to the Core SAP) or on or after the informed consent date.

- Finding out of range, defined any as any of the following subcategories:
  - Females with a positive pregnancy test on or after informed consent
  - Estimated glomerular filtration rate (eGFR) ≤ 40 mL/min/1.73m^2 during pretreatment *
  - BMI ≥ 33 kg/m^2 during pretreatment, if consented to Protocol Version 3 or lower *
  - BMI > 35 kg/m^2 during pretreatment, if consented to Protocol Version 4 or higher *
  - C-SSRS suicidal ideation with active intent or plan to act, or suicidal behavior present during pretreatment. Defined as having a "yes" response to any of the following C-SSRS questions 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).

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

- Efficacy data issue during the first 28 days of the OP for the full analysis set, defined as any of the following subcategories:
  - ≤ 3 migraine days
  - ≥ 19 headache days
  - ≤ 23 days of eDiary efficacy data (see Section 9.2.2).

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

Relevant subject management protocol deviations include the following categories:

- Stable prophylactic migraine medication use through randomization discrepant between IWRS and CRF data, defined as any of the following subcategories:
  - IWRS randomization stratum of yes, but no stable prophylactic migraine medication taken through randomization
  - IWRS randomization stratum of no, but stable prophylactic migraine medication taken through randomization.

  See Section 6.2.5.4 for the definition of non-study stable medication through randomization.
- Prophylactic migraine medication usage issue, defined as any of the following subcategories:
  - Prophylactic migraine medication started or stopped from 12 weeks before informed consent to randomization. Defined as informed consent date – 84 days ≤ imputed non-study medication start or end date ≤ IWRS randomization date.
  - > 1 prophylactic migraine medication taken on or after informed consent. "> 1" is defined as > 1 unique preferred name.
- DB study drug dosing issue, defined as any of the following subcategories (see Section 6.2.6.2):
  - DB study drug taken but not randomized
  - > 1 DB tablet taken on any 1 day
  - 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
  - Incorrect DB study drug taken
- OL rimegepant dosing issue, defined as any of the following subcategories (see Section 6.2.6.2)
  - OL rimegepant tablet count compliance < 80% from OL rimegepant start to later of last scheduled OLE Phase visit or OL rimegepant end
  - > 1 OL rimegepant tablet taken on any 1 day
  - OL rimegepant start on or before DB study drug end

  - OL rimegepant taken but DB study drug never taken.
- eDiary usage compliance < 80% from DB study drug start to later of last scheduled DBT Phase visit or DB study drug end (see Section 6.2.6.2)
- eDiary usage compliance < 80% from OL rimegepant start to later of last scheduled OLE Phase visit or OL rimegepant end (see Section 6.2.6.2)
- Prohibited non-study medications, defined as any of the following subcategories:
  - Atypical antipsychotics taken on or after informed consent #
  - Botulinum toxin type A taken on or after informed consent
  - Butterbur root or extract taken up to 14 days before randomization or afterward
  - Calcitonin gene-related peptide (CGRP) antagonist monoclonal antibody or small molecule taken on or after informed consent #
  - Ergotamine taken on or after informed consent
  - Lamotrigine taken on or after informed consent
  - Lasmiditan taken up to 14 days before randomization or afterward
  - Narcotic (barbiturate or opioid) taken up to 2 days before randomization or afterward #
  - Select moderate or strong cytochrome P450 3A4 (CYP3A4) inducer taken on or after informed consent #
  - Select strong CYP3A4 inhibitor taken on or after informed consent #
  - Traditional Chinese medicine taken up to 14 days before randomization or afterward#. These are identified by the sponsor medical lead or designee from reviewing a list of unique therapeutic class and preferred names.
  - Triptan as non-study OL rimegepant concomitant medication (see Section 6.2.6.3) #.

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 non-study medications, except for CYP3A4 inducers and inhibitors which are defined below.

Medication Group	Preferred Name
CYP3A4 inducer, select moderate	Preferred name in column A of worksheet "CYP3A4 Inducer Moderate" of CYP3A4 and P-gp Inducers and Inhibitors.xlsx (latest version)
CYP3A4 inducer, select strong	Preferred name in column A of worksheet "CYP3A4 Inducer Strong" of CYP3A4 and P-gp Inducers and Inhibitors.xlsx (latest version)
CYP3A4 inhibitor, select strong	Preferred name in column A of worksheet "CYP3A4 Inhibitor Strong" of CYP3A4 and P-gp Inducers and Inhibitors.xlsx (latest version)

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

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

9.2 eDiary Efficacy

9.2.1 Efficacy Parameters

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

- Headache (yes, no)
- If the response to headache is "yes", then responses to the following pain features and associated symptoms are collected:
  - Lasts at least 30 minutes (yes, no)
  - Pain severity (mild, moderate, severe)
  - Unilateral (yes, no)
  - Pulsating (yes, no)
  - Worsen or avoid physical activity (yes, no)
  - Nausea (yes, no)
  - Vomiting (yes, no)
  - Photophobia (yes, no)
  - Phonophobia (yes, no)
- Aura (yes, no)
- If the response to headache or aura is "yes", then the responses to the following parameters about taking medications to treat headache or aura are collected:
  - Triptan (yes, no)
  - Ergotamine (yes, no)
  - Other medication (yes, no).

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

9.2.2 eDiary Efficacy Data Day

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

9.2.3 Acute Migraine Medication Day

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

1. Acute migraine-specific medication day (Section 9.2.4)
2. Migraine day (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 (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 either of the 2 questions about taking triptan or ergotamine to treat headache or aura.

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

9.2.5 Migraine Day

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

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)

3) Non-scheduled OL rimegepant dosing day (see Section 9.4).

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.

9.2.6 Headache Day

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

1) Migraine day (see Section 9.2.5)

2) Headache that lasts ≥ 30 minutes: "Yes" response to the question about lasting ≥ 30 minutes

3) Headache of any duration for which acute headache treatment is administered: Meeting both of the following criteria (a and b):

   a) "Yes" response to the question about having a headache

   b) "Yes" response to any of the 3 questions about taking medications to treat headache or aura (i.e., triptan, ergotamine, or other medications).

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

9.3 SAS Code

9.3.1 Linear Mixed Effects Model with Repeated Measures

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

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

Then the SAS code is as follows:

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

9.3.2 Linear Regression Model

Consider the following variables used to evaluate any of the last 3 secondary outcomes research endpoints using a linear regression model:

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

Then the SAS code is as follows:

```
proc mixed data = xxx empirical;
class usubjid rndstr trt;
model scorechg = scorebl rndstr trt;
repeated / subject = usubjid;
lsmeans trt / alpha = 0.05 cl diff;
run;
```

9.4 Study Drug Dosing Day

The sites report the start date for administration of the IP in the phase in the IP Administration – DB and OL CRFs. Based on the start date, the data management vendor autopopulates records with dosing dates from the start date through 12 weeks on the IP Administration – DB CRF and though 40 weeks on the IP Administration – OL CRF. Sites can report additional dose dates beyond the autopopulated records if needed. On each dose date, sites also report the number of tablets taken and dosing day type (scheduled or non-scheduled). During either the DBT or OLE Phase, is expected that sites report number of tablets taken ≥ 0 on scheduled dosing days, where "0" denotes a missed dose. During the OLE Phase, is expected that sites report number of tablets taken > 0 on non-scheduled dosing days only when subjects dosed PRN.

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

drug dosing days are classified as scheduled if the dosing day type is "scheduled" on that day. Otherwise, DB study drug dosing days are classified as non-scheduled.

An OL rimegepant dosing day is defined as a day with nonmissing dose date on which ≥ 1 tablet of OL rimegepant study drug was taken, which is determined using valid OL wallet numbers. OL rimegepant dosing days are classified as scheduled or non-scheduled analogously.

Non-study drug dosing days are days on which no study drug was taken (i.e., number of tablets taken is 0 or missing).

All days in the OL rimegepant efficacy analysis period are classified as either planned scheduled or planned non-scheduled OL rimegepant dosing days. A planned scheduled OL rimegepant dosing day is defined as any of the following:

- Scheduled OL rimegepant dosing day
- Non-study drug dosing day that is (1) an even number of days after a scheduled OL rimegepant dosing day and (2) before the next OL rimegepant dosing day, if it exists
- Non-study drug dosing day that is (1) an odd number of days after a non-scheduled OL rimegepant dosing day and (2) before the next OL rimegepant dosing day, if it exists.

All other days in the OL rimegepant efficacy analysis period are classified as planned non-scheduled OL rimegepant dosing days.

For example, suppose days 1, 3, 5, 8, and 10 are scheduled OL rimegepant dosing days and days 6 and 14 are non-scheduled OL rimegepant dosing days. Then:

- Days 1, 3, 5, 7, 8, 10, 12, and 15 are planned scheduled OL rimegepant dosing days.
- Days 2, 4, 6, 9, 11, 13, and 14 are planned non-scheduled OL rimegepant dosing days.

10 REFERENCES

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