C4951004 (BHV3000-406)

BHV3000-406: A Phase 4, Randomized, Double-Blind Placebo-Controlled, Efficacy and Tolerability Trial of Rimegepant for the Acute Treatment of Migraine in Adults Unsuitable for Triptan Use

Statistical Analysis Plan

Version 6

Date: 14-May-2025

SIGNATURE PAGE

Protocol Title:	A Phase 4, Randomized, Double-Blind Placebo-Controlled, Efficacy and Tolerability Trial of Rimegepant for the Acute Treatment of Migraine in Adults Unsuitable for Triptan Use
Document Version:	6
Date:	14-May-2025
Author:	PPD

Signature: PPD

Date:

Approval

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

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

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

PPD

Signature: PPD

Date:_____

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ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AR(1)	First-order autoregressive with homogeneous variances
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
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Technical Criteria for Adverse Events
CTMS	Clinical trial management system
CV	Cardiovascular
DAIDS	Division of Acquired Immune Deficiency Syndrome
DBT	Double-blind Treatment
DCF	Data correction form
eDISH	Evaluation of drug-induced serious hepatotoxicity
EOT	End of Treatment
EQMA	Evaluable qualifying migraine attack
FDA	Food and Drug Administration
IOL=F	Intervening OL Rimegepant = Failure
IP	Investigational Product
LFT	Liver function test
LSLV	Last subject last visit
LSM	Least-squares mean
MBS	Most bothersome symptom
MDRD	Modification of diet in renal disease
MIBS	Migraine Interictal Burden Scale
MQoL	Migraine Quality of Life Questionnaire
MSQ	Migraine-Specific Quality-of-Life Questionnaire
NC=F	Noncompleter = Failure

NC=M	Noncompleter = Missing
NC1=F	Noncompleter With Missing Data at More Than 1 Time Point = Failure
ODT	Oral disintegrating tablets
OLE	Open-Label Extension
PCD	Primary completion date
PT	Preferred term
RM=F	Rescue Medication = Failure
RTSM	Randomization and Trial Supply Management
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

REVISION HISTORY

Version	Description of Change
1	Original version (03-May-2023) based on Protocol Version 3
2	Amended version (24-May-2024) based on Protocol Version 5 Signature page: Changed "Hospital Products" to "Infectious Disease". General: Applied Pfizer Global Style Guide throughout. Changed "eDiary reference date" to "eDiary measurement date" throughout. Changed "BHV3000-406" to "C4951004" throughout. Removed references to Section 7.4.5 throughout. Revision History: Moved after Abbreviations. Abbreviations: Added AR(1), DAIDS, EQMA, LSLV, LSM, PCD, and SE. Removed P-gp and first instance of RTSM (typo). Section 1.2: Specified the timing of the 2 database locks (PCD and LSLV) and their corresponding CSRs. Section 2.4: Specified that SAP Version 2 is based on Protocol Version 5. Specified that the protocol modified the definition of the DBT efficacy analysis set and added 3 exploratory objectives. Section 3.1.3: Added 3 exploratory objectives per protocol. Section 3.2: Added intercurrent events of nonrescue headache medication, prophylactic migraine medication use, and intervening OL rimegepant use, and specified their handling strategies. Specified that the intercurrent event of rescue medication use does not apply to efficacy objectives based on rescue medication use and acute migraine medication days per month. Section 3.2.1: Specified that the intercurrent events of nonrescue headache medication use and prophylactic migraine medication use are handled with a treatment policy strategy. Section 3.2.2.1: Specified that the intercurrent events of nonrescue headache medication use and prophylactic migraine medication use are handled with a treatment policy strategy. In Table 2 for Objective #2, changed "intercurrent event" to "rescue medication". Section 3.2.2.2: In Table 3: for Objective #1, changed "qualifying migraine attack" to "evaluable qualifying migraine attack (EQMA)", specified that the first 5 EQMAs must be ≥23 hours apart, and added the intercurrent event of intervening OL rimegepant use; for Objectives #2 and #3, modified the intercurrent event handling strategy for rescue medication use; for Objective #13, removed "part of"; for all objectives, added intercurrent events of nonrescue headache medication use and prophylactic migraine medication use with handling strategies. Specified the rationale for defining the endpoint for the objective of reliability of rimegepant effect in the OLE Phase differently from the protocol. Section 3.2.3: In Table 4: for Objective #2, changed "qualifying migraine attack" to "EQMA"; for Objective #13, specified that the first 5 qualifying migraine attacks must be ≥23 hours apart; for efficacy objectives during the DBT Phase, added intercurrent event of study drug discontinuation; for all objectives, added intercurrent events of nonrescue headache medication use and prophylactic migraine medication use with handling strategies. Section 4.1: Modified the definition of the DBT efficacy analysis set per protocol. Removed the COVID-19 impacted analysis set. Section 4.3: Removed "Subgroup analyses are performed for the primary efficacy endpoint only." Section 4.3.1: New section "Efficacy Subgroups". Section 4.3.2: New section "Safety Subgroups". Section 5: Specified the Pfizer study numbers.

Section 6.1.1.1: Removed "and pretreatment safety endpoints" and corresponding reference to Section 6.4. Specified the format of subgroup tables.

Section 6.1.1.2: Added the listing of significant protocol deviations.

Section 6.1.1.3: Removed "All listings except administrative listings identify subjects who are impacted by COVID-19.", and "and visits impacted by COVID-19 visit impact". Specified that select listings also display DBT day ≥1 and OL rimegepant day ≥1.

Section 6.2.1: Removed "(excluding COVID-19 impacted)". Changed "all randomization numbers and block numbers, even those not assigned to a subject" to "the full analysis set".

Section 6.2.3: Removed "Premature study termination due to COVID-19 status" from the by-subject listing of subject discontinuation.

Sections 6.2.3.1 and 6.2.3.2: Removed premature termination due to COVID-19.

Section 6.2.3.3: Changed "CSR" to "PCD". Modified the algorithm for the "Did not continue to the OLE Phase" category. Removed premature termination due to COVID-19.

Section 6.2.3.4: Changed "CSR" to "LSLV". Modified the algorithm for the "Did not continue to the Follow-Up Phase" category. Removed premature termination due to COVID-19.

Sections 6.2.3.5 and 6.2.3.6: Removed.

Section 6.2.4.1: Moved text from Section 6.2.4 here. Changed "enrolled" to "full".

Section 6.2.4.2: New section "Significant Protocol Deviations".

Section 6.2.5: Added select tables of baseline characteristics by subgroup level and overall for all efficacy and safety subgroups of interest. Removed the frequency table of randomization stratum.

Section 6.2.5.1: Modified the contents of the table of demographics and other relevant baseline characteristics to (1) exclude RTSM randomization stratum, (2) include "Imputed randomization stratum: history of CV disease (yes, no)", and (3) include "History of documented failure to ≥2 triptans with ≥1 reason due to lack of efficacy (yes, no)". Modified the definition of randomization stratum based on actual data. Changed "United States" to "Unites States of America". Removed "and calculating age at a reference date". Added a frequency cross table of randomization stratum.

Section 6.2.5.2: Modified the definition of documented contraindication to the use of triptans. Modified the contents of the table of triptan-unsuitable criteria to (1) include reasons for contraindication to triptans as subcategories, including not reported, and (2) exclude triptan names.

Section 6.2.5.4: Removed "Screening Phase". Changed "acute migraine triptan" to "triptan". Added 3 tables of previous triptan medications for the DBT efficacy analysis set. Added references to Section 6.2.6.3 and the Core SAP.

Section 6.2.6.1: Modified the contents of the by-subject listing of study drug dosing and accountability. Added tables of OL exposure by subgroup level and overall for all safety subgroups of interest. Removed the administrative listing of investigational drug batch numbers.

Section 6.2.6.2: Modified frequency table of DB study drug compliance by (1) removing "DB study drug taken before using the eDiary resulting in missing MBS before dosing, and (2) modifying criteria for "DB study drug taken without having a qualifying migraine attack". Modified frequency table of OL rimegepant compliance by (1) modifying criteria for "OL rimegepant taken using the eDiary without having a qualifying migraine attack, and (2) adding "OL rimegepant taken without using the eDiary" and "OL rimegepant taken but DB study drug never taken".

Section 6.2.6.3: Specified that the Concomitant Medications CRF collects indications, and links medical history and AE terms respectively to the Medical History and AE CRFs. Defined acute migraine-specific medications. Removed acute nonrescue migraine medications. Modified the definitions of acute migraine, prophylactic migraine, DBT rescue, OLE rescue, and headache medications. Specified that DBT rescue and OLE rescue medications are subset of DBT concomitant and OL rimegepant concomitant medications, respectively.

Section 6.3: Specified that analyses use the imputed randomization stratum and provide the rationale. Changed "assessment" to "measurement" throughout subsections. Modified the definition of RM=F to specify 2 criteria consistent with Section 8.6, and specified the use of criteria 2. Changed "This method applies to all secondary efficacy endpoints analyses, except the key secondary endpoint of rescue medication use within 24 hours postdose." to "The RM=F method applies to analyses of all binary efficacy endpoints, except those based on rescue medication use (see Section 7.5)", and "RM=F is applied only to the other secondary endpoint of the reliability of rimegepant during the OLE Phase" to "use of acute migraine-specific rescue medication is part of the endpoint definition of continuous efficacy endpoints based on migraine days per month".

Section 6.3.2.1: Removed "RTSM" and the last paragraph.

Section 6.3.2.2: Specified that the RM=F method uses both criteria to classify subjects as failures. Changed "m=20" to "n = 30" in the copy from reference multiple imputation analysis.

Sections 6.3.3.6 through 6.3.3.9: Added "only" to the second bullet defining responders.

Sections 6.3.4.1, 6.3.5.4, and 9.2: Added "analysis period" for clarity.

Section 6.3.5.1: Specified that for endpoints defined below, "rescue medication" denotes DBT rescue medication.

Section 6.3.5.2: Added third censoring criterion.

Section 6.3.5.3: Removed the first paragraph. Modified the definitions of relapsers and nonrelpasers. Specified that the RM=F method uses both criteria to classify subjects as failures.

Sections 6.3.5.5: Renamed section as "Rescue Medication Use After Each of the First 5 Qualifying Migraine Attacks During the OLE Phase". Replaced previous text. Moved the definition of qualifying migraine attack from Section 7.4.4 here.

Section 6.3.5.6: Removed.

Section 6.4: Removed "Pretreatment for the safety analysis set by treatment group and overall".

Section 6.4.1: Changed "by intensity" to "by worst intensity" in subsections.

Section 6.4.1.2: Modified the contents of the AE overview table. Added tables by subgroup level and overall for all safety subgroups of interest.

Sections 6.4.1.3 and 6.4.1.8: Removed.

Section 6.4.1.4: Renumbered as Section 6.4.1.3. Added select tables by subgroup level and overall for all safety subgroups of interest. Removed tables of AEs by relationship to study drug and medication-overuse headache AEs.

Section 6.4.1.5: Renumbered as Section 6.4.1.4.

Section 6.4.1.6: Renumbered as Section 6.4.1.5. Added select tables by subgroup level and overall for all safety subgroups of interest. Removed tables of AEs by relationship to study drug, medication-overuse headache AEs, and exposure-adjusted multiple occurrences of unique AEs.

Section 6.4.2: Specified that TLFs display results using both SI and US units, if applicable. In subsections, removed some tables.

Section 6.4.2.1: Specified that separate tables are provided for each toxicity grading scale: CTCAE/DAIDS using SI units; and FDA using US units. Removed "where shifts are based on OL rimegepant baseline". Added select tables by subgroup level and overall for all safety subgroups of interest.

Section 6.4.2.2: Specified that analyses use SI units. Removed "where shifts are based on OL rimegepant baseline". Removed tables of pretreatment LFT elevations, on-treatment exposure-adjusted cumulative LFT elevations, and time to LFT elevations on treatment.

Section 6.4.2.3: Specified that a separate table is provided for each unit system (SI or US).

Sections 6.4.3.2 and 6.4.4.2: Removed "using OL rimegepant baseline".

Section 6.4.6: Changed "AE" to "non-SAE" for AEs leading to study drug discontinuation and AEs of special interest.

Section 6.5.1.1: Defined EQMA and specified that reliability is based on the first 5 EQMAs ≥23 hours apart in the OLE Phase. Modified the definitions of responder and failure. Added a new response subcategory "No intervening OL rimegepant taken before the MQoL Question 16 value at 24 hours postdose". Added a new failure subcategory "Intervening OL rimegepant taken before the MQoL Question 16 value at 24 hours postdose (IOL=F)". Specified that for an EQMA, the percentage is calculated against the number of evaluable subjects, i.e., those defined as responders or failures. Removed ". Results support exploratory objective #12." and "Percentages are also displayed with 2-sided exact Clopper-Pearson 95% CIs.". Specified the use of the RM=F and IOL=F algorithms. Added a table of reliability of rimegepant effect and a frequency table of MQoL overall change in migraine symptoms outcomes for the sensitivity analyses, which uses the first 5 EQMAs ≥47 hours apart in the OLE Phase.

Section 6.5.1.2: Modified section title as "6.5.1.2 MQoL Scores by EQMA During the DBT and OLE Phases". Specified that the first 5 EQMAs ≥23 hours apart in the OLE Phase are used.

Section 6.5.1.3: New section "MQoL Overall Change in Migraine Symptoms During the OLE Phase Using Model Estimation".

Section 6.6: Removed.

Section 7.1: Modified the derivation of the eDiary measurement date, OLE Phase end date, and last contact date. Removed the COVID-19 visit date. Defined the eDiary finding date/time. Specified that DB study drug date/time and OL rimegepant date/time can be either reported (time is not missing) or manual DCF (time is missing).

Section 7.2: Removed "and to assess pretreatment safety endpoints". Removed the pre-OL rimegepant safety analysis period. Specified that AEs with imputed start date equal to the OL rimegepant start date are NOT part of the on-DBT safety analysis period.

Section 7.3: Defined DBT day and OL rimegepant day. Modified the definition of follow-up day.

Section 7.4: Changed "the migraine" to "headache or aura status". Defined a set of eDiary parameters.

Section 7.4.2: Changed "not rederived" to "determined using the difference between the eDiary reported study medication date/time and the eDiary finding date/time of the postdose measurement".

Section 7.4.4: Moved the definition of qualifying migraine attack to Section 6.3.5.5. Specified that that the eDiary allows subjects to assess multiple MQoLs on the same date.

Section 7.4.5: Removed.

Section 7.5: Changed "assessment" to "measurement". Created separate subsections 7.5.1 and 7.5.2 respectively for the RM=F algorithm during the DBT and OLE Phases for clarity. For the DBT Phase, modified the language for RM=F criteria 1 and 2 for clarity, and specified to use the first DBT rescue medication date/time.

Section 7.7: New section "IOL=F Algorithm During the OLE Phase".

Section 8.1: New section "PCD Final CSR". Specified a list of TLFs that are produced.

Section 8.2: New section "LSLV Final CSR". Specified that all TLFs in the SAP are produced.

	Section 9.1: Changed "more than once and assigned" to "under". Added migraine history issue category and subcategories. For medical history, modified existing criteria, defined "present at screening", and specified the identification of active medical history status. For pretreatment eGFR, modified existing criteria and added new criteria to align with Protocol Version 4 Section 5.3. Modified acetaminophen-related deviation. Changed "RTSM" to "the RTSM system" where applicable. Changed "history of CV" to history of clinically relevant CV". For randomization stratum discrepancies, modified existing criteria. Changed "dosing error" to "dosing issue". Removed "DB study drug taken before using eDiary resulting in missing MBS before dosing". Changed "moderate or strong CYP3A4 inhibitor" to "strong CYP3A4 inhibitor". Removed "Select P-gp inhibitor, strong". Changed "Rescue medication usage error" to "DBT rescue medication usage issue", and "rescue" to "DBT rescue" in its 3 subcategories. Added "OL rimegepant taken but DB study drug never taken" and "OLE rescue medication usage issue" with 2 subcategories. Section 9.2: Removed "or headache day". Sections 9.2.1.1 and 9.2.1.3: Removed. Section 9.2.1.2: Renumbered as Section 9.2.1.1. Changed "acute migraine medications taken" to "headache medications taken". Modified the definition of an acute migraine medication day. Section 9.2.1.4: Renumbered as Section 9.2.1.2. Specified that eDiary data are also used. Modified the definition of an acute migraine-specific medication day. Specified that acute migraine-specific medication days are also a subset of migraine days. Section 9.2.2: Modified the definition of a migraine day. Section 9.2.3: Removed. Section 9.3: New section "Analyses of Reliability of Rimegepant Effect in the OLE Phase".
3	Amended version (06-Sep-2024) based on Protocol Version 6 Section 2.4: Specified that SAP Version 3 is based on Protocol Version 6. Section 6.3.5.1: Changed "longitudinal" to "line". Section 6.4.2.2: Changed "longitudinal LFT" to "LFT line". Section 8.1: Added a table of AEs related to study drug by worst intensity on OL rimegepant. Section 9.1: Removed "medical history" category and "during pretreatment" from "finding out of range" subcategories. Changed "finding out of range" to "finding out of range during pretreatment", "females with a positive pregnancy test on or after informed consent" to "females with a positive pregnancy test", and "dosing error" to "dosing noncompliance" (2 instances).
4	Amended version (24-Oct-2024) based on Protocol Version 6 General: Changed "all safety subgroups" to "all high-level safety subgroups", and "headache medication" to "acute headache medication". Section 2.4: Specified that SAP Version 4 is based on Protocol Version 6. Section 4.3:.2 Specified that medical history of hypertension is a safety subgroup of interest for hypertension-related safety endpoints for the DBT and OL rimegepant safety analysis sets, and referenced the Core SAP. Section 6.2.5.1: Changed "models or" to "models or risk" in footnote. Section 6.2.5.3: Added a frequency table of medical history of hypertension. Section 6.2.6.3: Modified the definition of headache medication. Section 6.3.2.1: Removed results by randomization stratum from the risk estimation table. Section 6.4.1.2: Added hypertension AE and Raynaud's AE to AE overview tables. Section 6.4.1.3 and 6.4.1.5: Added tables of hypertension AEs, overall and for subjects with medical history of hypertension.

	Section 6.4.3.1: Added a table of values and changes from baseline in vital sign parameters for the safety analysis set with medical history of hypertension. Section 6.4.3.2: Added tables of vital sign abnormalities on DBT and on OL rimegepant for subjects with medical history of hypertension. Section 6.4.6: Changed "SAE on DB or OL rimegepant" to "SAE on DB or OL rimegepant or during follow-up". Added hypertension non-SAE and Raynaud's phenomenon non-SAE. Section 9.1: Changed "Paracetamol-containing product taken for a nonacute migraine indication" to "Paracetamol-containing product not taken as acute headache medication", and modified the definition.
5	Amended version (20-Feb-2025) based on Protocol Version 6 Section 2.4: Specified that SAP Version 5 is based on Protocol Version 6. Section 6.2.5.2: Specified the display of results in the frequency table of history of CV events, conditions, procedures, and other risk factors. Defined reason for failure subcategories in the frequency table of triptan-unsuitable criteria. Section 6.2.6.2: Changed "Time in the OLE Phase > 14" to "Time on OL rimegepant ≥ 14" in the "OL Rimegepant Treatment Compliance" subsection. Section 6.2.6.3: Specified that prophylactic migraine medications are displayed by preferred name without therapeutic class. Specified the display of rescue medication date/time in the listing. Section 6.3.2.2: Changed "copy from reference" to "copy reference" (2 instances), and added geographic region as a covariate. Removed "n/N" from the copy reference table. Section 6.4.3: Specified the derivation of BMI. Section 6.4.6: Added PT of drug induced liver injury to select hepatic-related non-SAEs. Section 6.5.1.3: Specified the handling of imputed randomization stratum. Section 7: Specified that conventions may be further modified in dataset specifications documents instead of the SAP as needed. Section 7.1: Modified the definitions of the DB study drug date/time and OL rimegepant date/time. Section 7.2: Removed reference to COVID-19 impact in the definition of follow-up phase. Section 7.4.1.1: Changed "matches an eDiary reported study medication date/time" to "matches an eDiary reported study medication date/time within ± 1 second". Section 9.1: Clarified the definition of DBT rescue medication taken at or before 2 hours postdose. Specified the identification of nonpermitted DBT rescue medication taken.
6	Amended version (14-May-2025) based on Protocol Version 6 Section 2.4: Specified that SAP Version 6 is based on Protocol Version 6. Section 6.2.5.1: Added geographic region to the table of demographics and other relevant baseline characteristics. Section 6.4.1: Changed "AEs of special interest" to "significant AEs". Removed "exposure-adjusted multiple occurrences of unique AEs". Section 6.4.6: Modified text based on the latest version of the C495/C530 Core SAP. Section 9.1: Modified the definition of prophylactic migraine medication started or ended from 3 months before informed consent to randomization.

1 BACKGROUND AND RATIONALE

This document presents the statistical analysis plan (SAP) for Protocol C4951004: A Phase 4, Randomized, Double-Blind Placebo-Controlled, Efficacy and Tolerability Trial of Rimegepant for the Acute Treatment of Migraine in Adults Unsuitable for Triptan Use.

This SAP contains the analysis details and methodology to answer the study objectives, including planned summary tables, by-subject listings, and figures (TLFs), which will 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 acute treatment of migraine in adults who are unsuitable for triptan use because of prior intolerance, lack of efficacy, or contraindication (including a history of clinically relevant cardiovascular disease).

1.2 Schedule of Analyses

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

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

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

No interim analyses are planned.

2 STUDY DESCRIPTION

2.1 Study Design

C4951004 is a multicenter, Phase 4, randomized, double-blind placebo-controlled study, with an Open-Label Extension (OLE) Phase to assess the efficacy and tolerability of rimegepant for the acute treatment of migraine in subjects who are unsuitable for triptan use.

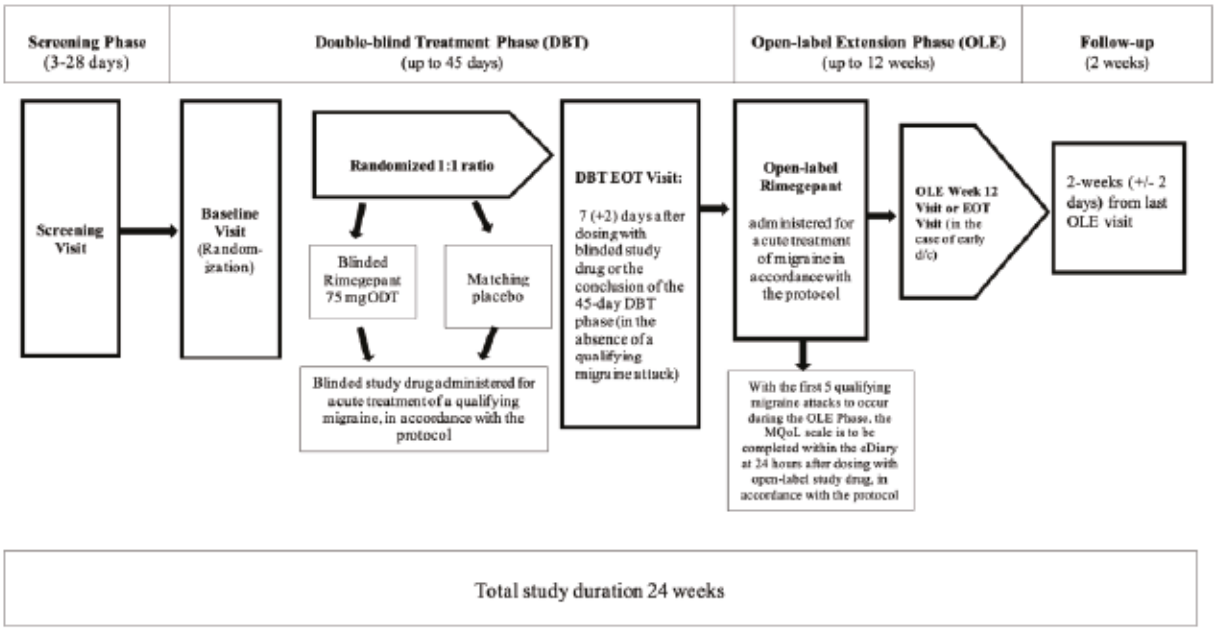
The study has 4 phases:

- Screening Phase: Lasts up to 28 days and includes the Screening Visit.
- DBT Phase:
  - Includes the Baseline Visit at which randomization occurs, and DBT EOT Visit.

        - Subjects are randomized 1:1 to rimegepant orally dissolving tablet (ODT) 75 mg or matching placebo.
        - Randomization is stratified using a Randomization and Trial Supply Management (RTSM) system by history of clinically relevant cardiovascular (CV) disease (yes or no). See Section 2.2.
    - After randomization, 1 tablet of study medication is dispensed to subjects to take home for up to 45 days.
    - Subjects are instructed by an electronic diary (eDiary) to take 1 tablet of study drug after a migraine attack of moderate or severe headache pain intensity.
    - Subjects return to the study site for the DBT EOT Visit either (1) within 7 (± 2) days after taking study drug, or (2) within 45 days after randomization otherwise.
- OLE Phase:
    - Subjects who complete the DBT Phase and continue to meet all inclusion/exclusion criteria may enter the OLE Phase, pending review of laboratory test results at the DBT EOT Visit.
    - Subjects may take up to 1 tablet of open-label ODT rimegepant 75 mg per calendar day as needed for acute treatment of migraine for a maximum of 18 doses per month (month is 28 days).
    - Lasts up to 12 weeks, and includes the Week 2, Week 4, Week 8, Week 12, and OLE EOT Visits.
    - All subjects who discontinue early from the OLE Phase should complete the OLE EOT Visit. Otherwise, subjects should complete the Week 12 Visit.
- Follow-Up Phase
    - Lasts up to 2 weeks, and includes the Follow-Up Week 2 Visit primarily for safety assessments. This visit should occur approximately 2 weeks after the Week 12 or OLE EOT Visit.
    - All subjects who enter the OLE Phase should complete the Follow-Up Week 2 Visit (regardless of completing the OLE Phase), except those who discontinue early from the OLE Phase due to withdrawal by subject or lost to follow-up.

The study design is shown in Figure 1. Approximately 900 subjects are screened in order to randomize approximately 600 subjects. It is estimated that approximately 510 subjects will be entered into the OLE Phase.

Figure 1 Study Schematic



2.2 Treatment Assignment

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

The RTSM system randomizes eligible subjects to treatment groups (see Section 2.1) using permuted blocks of size 4 within each of the 2 randomization strata at the Baseline Visit. Randomization is stratified by history of clinically relevant CV disease (yes or no). The RTSM also assigns specific container numbers for all study drug to be dispensed.

2.3 Blinding and Unblinding

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

2.4 Protocol and Protocol Amendments

C4951004 SAP Version 1 is based on C4951004 Protocol Version 3 (06-Apr-2023).

C4951004 SAP Version 2 is based on C4951004 Protocol Version 5 (06-Feb-2024). Protocol changes that affected statistical analyses were the following: changing the sponsorship to Pfizer; adding 3 exploratory objectives; modifying the definition of the DBT efficacy analysis set; stating that there are 2 planned database locks and 2 final CSRs; and modifying exclusion criteria, which affects relevant protocol deviations.

C4951004 SAP Versions 3, 4, 5, and 6 are based on C4951004 Protocol Version 6 (29-Aug-2024).

3 STUDY OBJECTIVES AND ESTIMANDS

3.1 Objectives

3.1.1 Primary Objectives

To compare the efficacy of rimegepant with placebo in the acute treatment of migraine, as measured by migraine headache pain relief at 2 hours postdose during the DBT Phase.

3.1.2 Secondary Objectives

3.1.2.1 Key Secondary Objectives

1. To compare rimegepant with placebo for migraine headache pain freedom at 2 hours postdose during the DBT Phase.
2. To compare rimegepant with placebo for rescue medication use within 24 hours postdose during the DBT Phase.
3. To compare rimegepant with placebo for return to normal function, as measured by the functional disability scale, at 2 hours postdose during the DBT Phase.
4. To compare rimegepant with placebo for sustained return to normal function, as measured by the functional disability scale, from 2 to 24 hours postdose during the DBT Phase.
5. To compare rimegepant with placebo for sustained return to normal function, as measured by the functional disability scale, from 2 to 48 hours postdose during the DBT Phase.
6. To compare rimegepant with placebo for sustained migraine headache pain relief from 2 to 24 hours postdose during the DBT Phase.
7. To compare rimegepant with placebo on sustained migraine headache pain relief from 2 to 48 hours postdose during the DBT Phase.
8. To compare rimegepant with placebo for sustained migraine headache pain freedom from 2 to 24 hours postdose during the DBT Phase.
9. To compare rimegepant with placebo for sustained migraine headache pain freedom from 2 to 48 hours postdose during the DBT Phase.
10. To compare rimegepant with placebo for freedom from the most bothersome symptom (MBS) associated with migraine at 2 hours postdose during the DBT Phase.

3.1.2.2 Other Secondary Objectives

1. To evaluate reliability of rimegepant effect in the OLE Phase, as measured by Migraine Quality of Life Questionnaire (MQoL) Question 16 (overall change in migraine symptoms since taking study medication) at 24 hours postdose in the DBT Phase and after each of the first 5 qualifying migraine attacks in the OLE Phase.

2. To evaluate the mean change from historical baseline in the number of migraine days per month by headache pain intensity (total; moderate or severe) in each month and over the entire OLE Phase.

3. To evaluate the proportions of subjects with ≥50% reduction from historical baseline in the number of migraine days per month by headache pain intensity (total; moderate or severe) in each month and over the entire OLE Phase.

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

5. To evaluate the mean change from baseline in the Migraine Interictal Burden Scale (MIBS) score over time during the OLE Phase.

3.1.3 Exploratory Objectives

1. To evaluate the Migraine Quality of Life Questionnaire (MQoL) at 24 hours postdose during the DBT Phase.

2. To evaluate the Migraine Quality of Life Questionnaire (MQoL) at 24 hours postdose after each of the first 5 qualifying migraine attacks during the OLE Phase.

3. To evaluate migraine headache pain relief at all scheduled time points postdose during the DBT Phase.

4. To evaluate migraine headache pain freedom at all scheduled time points postdose during the DBT Phase.

5. To evaluate MBS freedom at all scheduled time points postdose during the DBT Phase.

6. To evaluate return to normal function, as measured by the functional disability scale, at all scheduled time points postdose during the DBT Phase.

7. To evaluate photophobia freedom at all scheduled time points postdose during the DBT Phase.

8. To evaluate phonophobia freedom at all scheduled time points postdose during the DBT Phase.

9. To evaluate nausea freedom at all scheduled time points postdose during the DBT Phase.

10. To evaluate pain relapse from 2 to 48 hours postdose during the DBT Phase.

11. To evaluate time to migraine headache pain relief through 48 hours postdose during the DBT Phase.

12. To evaluate the mean number of acute migraine medication (rescue or non-rescue) days per month in each month and over the entire OLE Phase.

13. To evaluate the proportion of subjects who use rescue medication after each of the first 5 qualifying migraine attacks during the OLE Phase.

14. 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.

15. To evaluate the mean changes from baseline in the Migraine-Specific Quality-of-Life Questionnaire v2.1 (MSQ) domain scores at Week 12 of the OLE Phase.

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

17. To evaluate primary and key secondary endpoints during the DBT Phase and high-level safety endpoints during the DBT and OLE Phases by history of clinically relevant CV disease (yes or no).

18. To evaluate primary and key secondary endpoints during the DBT Phase by history of documented failure to ≥2 triptans with ≥1 reason due to lack of efficacy (yes or no).

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.

Population 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.

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

Intercurrent Events

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

Rescue medication taken at or before a data assessment at the time point of interest defining the endpoint is considered an intercurrent event, except for the efficacy objectives based on rescue medication use and acute migraine medication days per month.

- For select objectives, rescue medication use is handled with a composite strategy, i.e., the occurrence of the intercurrent event is integrated as a component of the endpoint. See Section 6.3 for additional details.
- For select objectives, rescue medication use is handled with a "treatment policy strategy", i.e., the occurrence of the intercurrent event is considered irrelevant, such that all observed values of the endpoint of interest are used, regardless of rescue medication use.

Nonrescue acute headache medication use before the time point of interest defining the endpoint is also considered an intercurrent event for all objectives, except for the efficacy objective based on acute migraine medication days per month. For efficacy objectives based on migraine days per month, this intercurrent event is handled with a composite strategy if it is acute migraine-specific medication. Otherwise, this intercurrent event is handled with a treatment policy strategy.

Prophylactic migraine medication use before the time point of interest defining the endpoint is also considered an intercurrent event. For all objectives, this intercurrent event is handled with a treatment policy strategy.

Intervening OL rimegepant use at or before a 24-hour MQoL is also considered an intercurrent event only for the outcomes research objective of reliability of rimegepant effect during the OLE Phase, and is handled with a composite strategy (see Section 6.5.1.1). Intervening OL rimegepant use is not an intercurrent event for any other objective.

During the OLE Phase, study drug discontinuation before the time point of interest defining the endpoint is considered an intercurrent event.

- For select objectives, study drug discontinuation is handled with a "while-on-treatment strategy," i.e., response to treatment prior to the occurrence of the intercurrent event of interest, such that all observed values of the endpoint of interest are used prior to study drug discontinuation (plus 9 days for safety; see Section 7.2).
- For select objectives, study drug discontinuation is handled with a "treatment policy strategy", i.e., the occurrence of the intercurrent event is considered irrelevant, such that all observed values of the endpoint of interest are used, regardless of study drug discontinuation.

See Section 6.2.6.3 for the definitions of nonstudy medications.

Data Sources for Endpoints

The following are from the eDiary: migraine characteristics (i.e., pain, MBS, nausea, phonophobia, photophobia, and functional disability); study medication; and MQoL.

Rescue medication use is determined from the Rescue Medication case report form (CRF).

AEs are determined from AE/SAE 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.

MSQ domain scores, MIBS scores, and Columbia-Suicide Severity Rating Scale (C-SSRS) parameters are derived from their respective CRFs.

3.2.1 Primary Objective Estimand

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

The intercurrent events of rescue medication use is handled with a composite strategy (see Section 6.3), while the intercurrent events of nonrescue acute headache medication use and prophylactic migraine medication use are handled with a treatment policy strategy.

Table 1 Primary Objective Estimand

Objective	**Pain relief at 2 hours postdose during the DBT Phase**
Efficacy Endpoint	Percentage of subjects with a headache pain intensity of none or mild at 2 hours postdose in the DBT Phase. Migraine headache pain intensity is measured on a 4-point numeric rating scale (0=none, 1=mild, 2=moderate, 3=severe).
Summary	Percentage of subjects achieving the endpoint response criteria by treatment group and difference in percentages between treatment groups (rimegepant – placebo) using Mantel-Haenszel risk estimation for the DBT efficacy analysis set

3.2.2 Secondary Objective Estimands

3.2.2.1 Key Secondary Objective Estimands

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

For each objective, the summary is the percentage of subjects achieving the endpoint response criteria by treatment group and difference in the percentages between the rimegepant and placebo treatment groups (rimegepant – placebo) using Mantel-Haenszel risk estimation for the DBT efficacy analysis set.

For each objective (excluding objective #2 rescue medication use within 24 hours postdose), the intercurrent events of rescue medication use is handled with a composite strategy (see Section 6.3), while the intercurrent events of nonrescue acute headache medication use and prophylactic migraine medication use are handled with a treatment policy strategy.

Table 2 Key Secondary Objective Estimands

Objective 1	**Pain freedom at 2 hours postdose during the DBT Phase**
Efficacy Endpoint	Percentage of subjects with a headache pain intensity of none at 2 hours postdose during the DBT Phase
Objective 2	**Rescue medication use within 24 hours postdose during the DBT Phase**
Efficacy Endpoint	Percentage of subjects taking rescue medication within 24 hours postdose for the DBT efficacy analysis set during the DBT Phase
Intercurrent Events	Not applicable (rescue medication is the endpoint)
Objective 3	**Return to normal function at 2 hours postdose during the DBT Phase**
Efficacy Endpoint	Percentage of subjects with a functional disability level of normal at 2 hours postdose in the DBT Phase; evaluated for the subset with functional disability at the time of dosing. Functional disability level is measured on a 4-point numeric rating scale (0=normal, 1=mildly impaired, 2=severely impaired, 3=requires bedrest), and functional disability are defined as mildly impaired, severely impaired, or requires bedrest
Objectives 4 and 5	**Sustained return to normal function from 2 to 24 hours postdose, and from 2 to 48 hours postdose during the DBT Phase**
Efficacy Endpoint	Percentage of subjects with a functional disability level of normal at all time points from the start to the end of the time period of interest in the DBT Phase; evaluated for the subset with functional disability at the time of dosing
Objectives 6 and 7	**Sustained pain relief from 2 to 24 hours postdose, and 2 to 48 hours postdose**
Efficacy Endpoint	Percentage of subjects with headache pain intensities of none or mild at all time points from the start to the end of the time period of interest during the DBT phase
Objectives 8 and 9	**Sustained headache pain freedom from 2 to 24 hours postdose, and from 2 to 48 hours postdose during the DBT Phase**
Efficacy Endpoint	Percentage of subjects with headache pain intensities of none at all time points from the start to the end of the time period of interest during the DBT Phase
Objective 10	**MBS freedom at 2 hours postdose during the DBT Phase**
Efficacy Endpoint	Percentage of subjects with MBS reported on study before dosing that is absent at 2 hours postdose during the DBT Phase. The MBS before dosing is reported as nausea, phonophobia, or photophobia. Symptom status is reported postdose as present or absent for each symptom (nausea, phonophobia, and photophobia)

3.2.2.2 *Other Secondary Objective Estimands*

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

Table 3 Other Secondary Objective Estimands

Objective 1	**Reliability of rimegepant effect in the OLE Phase**
Outcome Research Endpoint	Percentages of subjects achieving response after (1) the single evaluable qualifying migraine attack (EQMA) in the DBT Phase for those randomized to rimegepant, and (2) each of the first 5 EQMAs ≥23 hours apart in the OLE Phase. • Reliability of rimegepant effect during the OLE Phase is defined as proportions for ≥4 of the first 5 EQMAs ≥23 hours apart in the OLE Phase being no more than 7% less than the proportion in the DBT Phase. • Response is defined as a category of "moderately better" or "very much better" for MQoL Question 16 (overall change in migraine symptoms since taking study medication) at 24 hours postdose. • EQMAs are defined in Section 6.5.1.1.
Summary	Percentages of subjects achieving response after (1) the single EQMA in the DBT Phase for the DBT efficacy analysis set randomized to rimegepant, and (2) each of the first 5 EQMAs ≥23 hours apart in the OLE Phase in the OLE efficacy analysis set
Intercurrent Event	Rescue medication use: composite strategy Intervening OL rimegepant use: composite strategy Nonrescue acute headache medication use: treatment policy strategy Prophylactic migraine medication use: treatment policy strategy Study drug discontinuation: treatment policy strategy
Objective 2	**Mean change from historical baseline in the number of migraine days per month by headache pain intensity (total; moderate or severe) in each month and over the entire OLE Phase**
Efficacy Endpoint	Mean change from historical baseline in the number of migraine days per month by headache pain intensity (total; moderate or severe) in each month (defined as 4-week interval), and over the entire OLE Phase (Weeks 1 to 12)
Summary	Change from historical baseline using descriptive statistics by treatment group and overall for the OLE migraine analysis set
Intercurrent Events	Rescue medication use: composite strategy if acute migraine-specific medication; treatment policy strategy if not acute migraine-specific medication Nonrescue acute headache medication use: composite strategy if acute migraine-specific medication; treatment policy strategy if not acute migraine-specific medication Prophylactic migraine medication use: treatment policy strategy Study drug discontinuation: treatment policy strategy
Objective 3	**Percentages of subjects with ≥50% reduction from historical baseline in the number of migraine days per month by headache pain intensity (total; moderate or severe) in each month and over the entire OLE Phase**

Efficacy Endpoint	Percentages of subjects with ≥50% reduction from historical baseline in the number of migraine days per month by headache pain intensity (total; moderate or severe) in each month (defined as 4-week period) and over the entire OLE Phase (Weeks 1 to 12)
Summary	Percentage of subjects with ≥50% reduction by treatment group and overall for the OLE migraine analysis set
Intercurrent Events	Rescue medication use: composite strategy if acute migraine-specific medication; treatment policy strategy if not acute migraine-specific medication
	Nonrescue acute headache medication use: composite strategy if acute migraine-specific medication; treatment policy strategy if not acute migraine-specific medication
	Prophylactic migraine medication use: treatment policy strategy
	Study drug discontinuation: treatment policy strategy
Objective 4	**Frequencies of AEs by intensity, SAEs, AEs leading to study drug discontinuation, and grade 3 to 4 laboratory test abnormalities during the DBT and OLE Phases**
Efficacy Endpoint	Number and percentage of subjects with AEs by intensity (mild, moderate, severe, total), SAEs, AEs leading to study drug discontinuation, and grade 3 to 4 laboratory test abnormalities on treatment during the DBT and OLE Phases
Summary	Frequency by (1) treatment group on DBT for the DBT safety analysis set, and (2) treatment group and overall on OL rimegepant for the OL rimegepant safety analysis set
Intercurrent Events	Rescue medication use: treatment policy strategy
	Nonrescue acute headache medication use: treatment policy strategy
	Prophylactic migraine medication use: treatment policy strategy
	Study drug discontinuation: while-on-treatment strategy
Objective 5	**Mean changes from baseline in the MIBS score over time during the OLE Phase**
Outcome research Endpoint	Mean changes from baseline in the MIBS score at Weeks 4, 8, and 12 of the OLE Phase
Summary	Change from baseline by treatment group and overall using descriptive statistics at Weeks 4, 8, and 12 of the OLE Phase for the OLE efficacy analysis set
Intercurrent Events	Rescue medication use: treatment policy strategy
	Nonrescue acute headache medication use: treatment policy strategy
	Prophylactic migraine medication use: treatment policy strategy
	Study drug discontinuation: treatment policy strategy

Note that the endpoint for the objective of reliability of rimegepant effect in the OLE Phase is defined differently from the protocol. In order to reduce the amount of missing MQoL data at 24 hours postdose, the definition has been modified to use EQMAs instead of qualifying migraine attacks. Given that the protocol specifies that subjects should not take >1 tablet of rimegepant in 24 hours, the definition has been further modified to use EQMAs ≥23 hours apart, where 23 hours is the lower bound of the 24-hour postdose analysis visit window.

3.2.3 *Exploratory Objective Estimands*

Table 4 Exploratory Objective Estimands

Objective 1	**MQoL at 24 hours postdose during the DBT Phase**
Outcome Research Endpoint	Mean total and domain scores at 24 hours postdose during the DBT Phase
Summary	Values using descriptive statistics at 24 hours postdose by treatment group during the DBT Phase for the DBT efficacy analysis set
Intercurrent Events	Rescue medication use: treatment policy strategy Nonrescue acute headache medication use: treatment policy strategy Prophylactic migraine medication use: treatment policy strategy Study drug discontinuation: treatment policy strategy
Objective 2	**MQoL at 24 hours postdose after each of the first 5 qualifying migraine attacks during the OLE Phase**
Outcome Research Endpoint	Mean total and domain scores at 24 hours postdose for each of the first 5 EQMAs ≥23 hours apart, reported separately, in the OLE Phase
Summary	Values using descriptive statistics at 24 hours postdose after each of the first 5 EQMAs ≥23 hours apart in the OLE Phase by treatment group and overall for the OLE efficacy analysis set
Intercurrent Events	Rescue medication use: treatment policy strategy Nonrescue acute headache medication use: treatment policy strategy Prophylactic migraine medication use: treatment policy strategy Study drug discontinuation: treatment policy strategy
Objective 3	**Migraine headache pain relief at all scheduled time points postdose during the DBT Phase**
Efficacy Endpoint	Percentage of subjects with migraine headache pain intensity of none or mild at each time point postdose (15, 30, 45, 60, 90 min and 2, 3, 4, 6, 8, 24, 48 hours) during the DBT Phase. Migraine headache pain intensity is measured on a 4-point numeric rating scale (0=none, 1=mild, 2=moderate, 3=severe)
Summary	Percentage of subjects achieving the endpoint response criteria by treatment group and difference in percentages between treatment groups using Mantel-Haenszel risk estimation for the DBT efficacy analysis set
Intercurrent Events	Rescue medication use: composite strategy Nonrescue acute headache medication use: treatment policy strategy Prophylactic migraine medication use: treatment policy strategy Study drug discontinuation: not applicable (single dose)
Objective 4	**Migraine headache pain freedom at all scheduled time points postdose during the DBT Phase**
Efficacy Endpoint	Percentage of subjects with migraine headache pain intensity of none at each time point postdose (15, 30, 45, 60, 90 min and 2, 3, 4, 6, 8, 24, 48 hours) during the DBT Phase. Migraine headache pain intensity is measured on a 4-point numeric rating scale (0=none, 1=mild, 2=moderate, 3=severe)

Summary	Percentage of subjects achieving the endpoint response criteria by treatment group and difference in percentages between treatment groups using Mantel-Haenszel risk estimation for the DBT efficacy analysis set
Intercurrent Events	Rescue medication use: composite strategy Nonrescue acute headache medication use: treatment policy strategy Prophylactic migraine medication use: treatment policy strategy Study drug discontinuation: not applicable (single dose)
Objective 5	**MBS freedom at all scheduled time points postdose during the DBT Phase**
Efficacy Endpoint	Percentage of subjects with MBS reported on study before dosing but absent at each time point postdose (15, 30, 45, 60, 90 min and 2, 3, 4, 6, 8, 24, 48 hours) during the DBT Phase
Summary	Percentage of subjects achieving the endpoint response criteria by treatment group and difference in percentages between treatment groups using Mantel-Haenszel risk estimation for the DBT efficacy analysis set
Intercurrent event	Rescue medication use: composite strategy Nonrescue acute headache medication use: treatment policy strategy Prophylactic migraine medication use: treatment policy strategy Study drug discontinuation: not applicable (single dose)
Objective 6	**Return to normal function at all scheduled time points postdose during the DBT Phase**
Efficacy Endpoint	Percentage of subjects with a functional disability level of normal at each time point postdose (15, 30, 45, 60, 90 min and 2, 3, 4, 6, 8, 24, 48 hours) during the DBT Phase; evaluated for the subset with functional disability at the time of dosing. Functional disability level is measured on a 4-point numeric rating scale (0=normal, 1=mildly impaired, 2=severely impaired, 3=requires bedrest), and functional disability are defined as mildly impaired, severely impaired, or requires bedrest
Summary	Percentage of subjects achieving the endpoint response criteria by treatment group and difference in percentages between treatment groups using Mantel-Haenszel risk estimation for the DBT efficacy analysis set with functional disability at the time of DB study drug dosing
Intercurrent event	Rescue medication use: composite strategy Nonrescue acute headache medication use: treatment policy strategy Prophylactic migraine medication use: treatment policy strategy Study drug discontinuation: not applicable (single dose)
Objective 7	**Photophobia freedom at all scheduled time points postdose during the DBT Phase**
Efficacy objective	Percentage of subjects with photophobia absent at each time point postdose (15, 30, 45, 60, 90 min and 2, 3, 4, 6, 8, 24, 48 hours during the DBT Phase; evaluated for the subset with photophobia present at the time of dosing
Summary	Percentage of subjects achieving the endpoint response criteria by treatment group, and difference in percentages between treatment groups using Mantel-Haenszel risk estimation for the DBT efficacy analysis set with photophobia present at the time of DB study drug dosing
Intercurrent Events	Rescue medication use: composite strategy Nonrescue acute headache medication use: treatment policy strategy

	Prophylactic migraine medication use: treatment policy strategy Study drug discontinuation: not applicable (single dose)
Objective 8	**Phonophobia freedom at all scheduled time points postdose during the DBT Phase**
Efficacy Endpoint	Percentage of subjects with phonophobia absent at each time point postdose (15, 30, 45, 60, 90 min and 2, 3, 4, 6, 8, 24, 48 hours) during the DBT Phase; evaluated for the subset with phonophobia present at the time of dosing
Summary	Percentage of subjects achieving the endpoint response criteria by treatment group and difference in percentages between treatment groups using Mantel-Haenszel risk estimation for the DBT efficacy analysis set with phonophobia present at the time of DB study drug dosing
Intercurrent Events	Rescue medication use: composite strategy Nonrescue acute headache medication use: treatment policy strategy Prophylactic migraine medication use: treatment policy strategy Study drug discontinuation: not applicable (single dose)
Objective 9	**Nausea freedom at all scheduled time points postdose during the DBT Phase**
Efficacy Endpoint	Percentage of subjects with nausea absent at each time point postdose (15, 30, 45, 60, 90 min and 2, 3, 4, 6, 8, 24, 48 hours) during the DBT Phase; evaluated for the subset with nausea present at the time of dosing
Summary	Percentage of subjects achieving the endpoint response criteria by treatment group and difference in percentages between treatment groups using Mantel-Haenszel risk estimation for the DBT efficacy analysis set with nausea present at the time of DB study drug dosing
Intercurrent Events	Rescue medication use: composite strategy Nonrescue acute headache medication use: treatment policy strategy Prophylactic migraine medication use: treatment policy strategy Study drug discontinuation: not applicable (single dose)
Objective 10	**Pain relapse from 2 to 48 hours post dose during the DBT Phase**
Efficacy Endpoint	Percentage of subjects with migraine headache pain intensity of mild, moderate, or severe at any time point after 2 hours postdose during the DBT Phase; evaluated for the subset with pain freedom at 2 hours postdose during the DBT Phase
Summary	Percentage of subjects achieving the endpoint failure criteria by treatment group and difference in percentages between treatment groups using Mantel-Haenszel risk estimation for the DBT efficacy analysis set with pain freedom at 2 hours postdose during the DBT Phase
Intercurrent Events	Rescue medication use: composite strategy Nonrescue acute headache medication use: treatment policy strategy Prophylactic migraine medication use: treatment policy strategy Study drug discontinuation: not applicable (single dose)
Objective 11	**Time to migraine headache pain relief through 48 hours postdose during the DBT Phase**
Efficacy Endpoint	Time to first migraine headache pain relief (defined as headache pain intensity of none or mild) through 48 hours postdose during the DBT phase

Summary	Descriptive statistics by treatment group, and by randomization stratum within treatment group: (1) estimated median (hours) with measures of variance; and (2) Kaplan-Meier estimated cumulative probabilities through 48 hours
Intercurrent Events	Rescue medication use: composite strategy Nonrescue acute headache medication use: treatment policy strategy Prophylactic migraine medication use: treatment policy strategy Study drug discontinuation: not applicable (single dose)
Objective 12	**Mean number of acute migraine medication days per months in each month and over the entire OLE Phase**
Efficacy Endpoint	Mean number of acute migraine medication days per month in each month (defined as 4-week interval), and over the entire OLE Phase (Weeks 1 to 12)
Summary	Values by treatment group and overall using descriptive statistics for the OLE migraine analysis set
Intercurrent Events	Rescue medication use: not applicable (rescue medication is part of the endpoint) Nonrescue acute headache medication use: not applicable (nonrescue acute headache medication is part of the endpoint) Prophylactic migraine medication use: treatment policy strategy Study drug discontinuation: treatment policy strategy
Objective 13	**Proportion of subjects who use rescue medication after each of the first 5 qualifying migraine attacks during the OLE Phase**
Efficacy Endpoint	Percentage of subjects who use rescue medication after each of the first 5 qualifying migraine attacks ≥23 hours apart in the OLE Phase
Summary	Percentage of subjects who have the event after each of the first 5 qualifying migraine attacks ≥23 hours apart in the OLE Phase by treatment group and overall for the OLE migraine analysis set
Intercurrent Events	Rescue medication use: not applicable (rescue medication is the endpoint) Nonrescue acute headache medication use: treatment policy strategy Prophylactic migraine medication use: treatment policy strategy Study drug discontinuation: treatment policy strategy
Objective 14	**Frequencies of hepatic-related AEs and hepatic-related AEs leading to study drug discontinuation in subjects treated with rimegepant during the DBT and the OLE Phase**
Safety Endpoint	Number and percentage of subjects with hepatic-related AEs and hepatic-related AEs leading to study drug discontinuation on treatment during the DBT Phase, and the OLE
Summary	Frequency (1) by treatment group on DBT for the DBT safety analysis set, and (2) treatment group and overall on OL rimegepant for the OL rimegepant safety analysis set
Intercurrent Events	Rescue medication use: treatment policy strategy Nonrescue acute headache medication use: treatment policy strategy Prophylactic migraine medication use: treatment policy strategy Study drug discontinuation: while-on-treatment strategy

Objective 15	**Mean change from baseline in the MSQ restrictive role function domain score at Week 12 of the OLE Phase**
Outcome Research Endpoint	Mean change from baseline in the MSQ restrictive role function domain score at Week 12 of the OLE Phase
Summary	Change from baseline using descriptive statistics by treatment group and overall for the OLE efficacy analysis set
Intercurrent Events	Rescue medication use: treatment policy strategy Nonrescue acute headache medication use: treatment policy strategy Prophylactic migraine medication use: treatment policy strategy Study drug discontinuation: treatment policy strategy
Objective 16	**Frequency of LFT elevations based on fold changes above ULN in subjects treated with rimegepant during the DBT and OLE Phases**
Safety Endpoint	Number and percentage of subjects with LFT elevations (ALT, AST, or TBL) based on fold changes above ULN on treatment during the DBT and OLE Phases
Summary	Frequency (1) by treatment group on DBT for the DBT safety analysis set with LFT data, and (2) treatment group and overall on OL rimegepant for the OL rimegepant safety analysis set with LFT data
Intercurrent Events	Rescue medication use: treatment policy strategy Nonrescue acute headache medication use: treatment policy strategy Prophylactic migraine medication use: treatment policy strategy Study drug discontinuation: while-on-treatment strategy
Objective 17	**Primary and key secondary efficacy endpoints during the DBT Phase and high-level safety endpoints during the DBT and OLE Phases by history of clinically relevant CV disease (yes, no)**
Efficacy and Safety Endpoints	• Efficacy endpoints: see Table 1 and Table 2 • Safety endpoints: see Table 3 Objective 4; also the number and percentage of subjects with AEs related to study drug by intensity on treatment during the DBT and OLE Phases
Summary	• Efficacy endpoints: see Table 1 and Table 2 • Safety endpoints: see Table 3 Objective 4
Intercurrent Events	• Efficacy endpoints: see Table 1 and Table 2 • Safety endpoints: see Table 3 Objective 4
Objective 18	**Primary and key secondary efficacy endpoints during the DBT Phase by history of documented failure to ≥2 triptan medications with ≥1 failure due to lack of efficacy (yes, no)**
Efficacy Endpoints	See Table 1 and Table 2.
Summary	See Table 1 and Table 2.
Intercurrent Events	See Table 1 and Table 2.

4 ANALYSIS SETS, TREATMENT GROUPS, AND SUBGROUPS

4.1 Analysis Sets

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

- Enrolled: subjects who sign an informed consent form and are assigned a subject identification number, i.e., nonmissing informed consent date. This analysis set is used mainly to assess study population and in by-subject listings.
- Full: subjects in the enrolled analysis set who receive a randomized treatment group assignment (rimegepant or placebo) from RTSM, i.e., nonmissing RTSM randomization date. This analysis set is used mainly to assess study population.
  - DBT efficacy: subjects in the full analysis set who meet all the following criteria:
    (1) Randomized only once
    (2) Take double-blind (DB) study drug, i.e., nonmissing DB study drug date/time
    (3) Have a qualifying migraine attack at the time of DB study drug dosing (see Section 6.3.5.5)
    (4) Have DB postdose efficacy data. Defined as nonmissing efficacy data (i.e., nonmissing migraine headache pain intensity, phonophobia status, photophobia status, nausea status, or functional disability level) with eDiary measurement date in the DBT Phase analysis period at ≥1 planned time point postdose (i.e., 15 minutes through 48 hours).

    This analysis set is used mainly to assess efficacy endpoints and MQoL in the DBT Phase.
    - OLE efficacy: subjects in the DBT efficacy analysis set who take ≥1 dose of OL rimegepant, i.e., nonmissing OL rimegepant start date. This analysis set is used to assess outcomes research endpoints during the OLE Phase.
      - OLE migraine: subjects in the OLE efficacy analysis set with time in the OLE Phase ≥14 days. This analysis set is used to assess efficacy days in the OLE Phase.
- Safety: subjects in the enrolled analysis set who take ≥1 dose of study drug (DB rimegepant, DB placebo, or OL rimegepant). This analysis set is used to assess study population, exposure, and on-treatment safety.
  - DBT safety: subjects in the safety analysis set who take DB study drug. 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 date > 9 days. This analysis set is used to assess post-DBT pre-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.
- 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 only to produce safety narrative subject identifiers.

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

4.2 Treatment Groups

The 2 treatment groups are rimegepant and placebo. The safety analysis sets are assessed by as-treated treatment group (i.e., actual treatment received), the full and efficacy analysis sets are assessed by as-randomized treatment group, and the enrolled analysis set is assessed overall.

If a subject receives ≥1 dose of the planned randomized study drug, then that subject is considered to have as-treated treatment group equal to as-randomized treatment group.

If there are non-randomized subjects who receive 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 and overall for subjects with nonmissing subgroup level data.

4.3.1 Efficacy Subgroups

The following efficacy subgroups are of interest for primary and key secondary efficacy endpoints and supportive endpoints for the DBT efficacy analysis set:

- Imputed randomization stratum: history of clinically relevant CV disease (yes or no; see Section 6.2.5.1)
- History of documented failure to ≥2 triptans with ≥1 reason due to lack of efficacy (yes or no; see Section 6.2.5.1).

4.3.2 Safety Subgroups

The following safety subgroups are of interest for high-level safety and supportive endpoints for the DBT and OL rimegepant safety analysis sets:

- Imputed randomization stratum: history of clinically relevant CV disease (yes or no; see Section 6.2.5.1).

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

5 SAMPLE SIZE, POWER, AND TYPE I ERROR

It is anticipated that about 90% of the 300 subjects randomized to each treatment group will have a migraine in the allotted time period of the DBT Phase, resulting in approximately 270 subjects evaluable for efficacy in each treatment group.

The sample size calculation is based on pooled results from Phase 3 single-dose migraine studies C4951054 (BHV3000-301), C4951055 (BHV3000-302), and C4951056 (BHV3000-303). Pooled response rates for migraine headache pain relief at 2 hours postdose were 57.9% for rimegepant 75 mg and 43.9% for placebo in these studies.

A total sample size of 540 evaluable subjects (270 per treatment group) will provide approximately 90% power for the primary endpoint of migraine headache pain relief at 2 hours postdose in the DBT Phase. This is based on a chi-square test with a 2-sided alpha level of 0.05, and assumes that the true response rates in the subjects unsuitable for triptan use is equivalent to the overall pooled response rates above.

Type 1 error is controlled using a 2-sided alpha level of 0.05 and hierarchical testing. First, the significance of the primary endpoint is evaluated at the 2-sided alpha level of 0.05 for rimegepant versus placebo. If the primary endpoint is not significant (i.e., p-value > 0.05), then any further tests on key secondary endpoints will have p-values presented only for descriptive purposes. If the primary endpoint is significant (i.e., p-value ≤ 0.05), then the key secondary endpoints are tested hierarchically, each at a 2-sided alpha level of 0.05, in the order specified in Section 3.2.2.1. Thus, a key secondary endpoint is tested only if the preceding key secondary endpoint in the hierarchy is determined to be significant (i.e., p-value ≤ 0.05). If a test in the hierarchy is not significant, then any further tests on endpoints in the sequence have p-values presented only for descriptive purposes, and no conclusions are drawn from those results.

For testing of other secondary or exploratory endpoints, no attempt is made to adjust for multiplicity. P-values 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 5. Exceptions are specified in subsequent sections as needed.

Table 5 Treatment Group Presentation in Tables by Analysis Set

Analysis Set	Number of Columns	Abbreviated Treatment Group
Enrolled	1	Overall
Full, DBT efficacy, DBT safety, interim safety by treatment group and {overall}	2 to 3	Rimegepant Placebo {Overall}
OLE efficacy, OLE migraine, OL rimegepant safety by treatment group and {overall}	2 to 3	DB Rimegepant/OL Rimegepant DB Placebo/OL Rimegepant {Overall}
Follow-up safety by treatment group and overall	3	DB Rimegepant/OL Rimegepant DB Placebo/OL Rimegepant Overall

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

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

Subgroup tables of non-efficacy endpoints have the same format as the main non-efficacy tables, but display each subgroup level and overall in separate columns under 1 spanning column header for each DB treatment group (rimegepant, placebo). The spanning header is not displayed for OL rimegepant safety endpoints. A separate table is produced for each subgroup of interest.

Time-to-Event Tables

Time-to-event endpoints are summarized with Kaplan-Meier tables. Refer to the Core SAP for additional details.

Time-to-event distributions of endpoints are tabulated with the following descriptive statistics: number and percentage of subjects with events; number and percentage of subjects censored in or before the last time interval; number and percentage of subjects censored in the last time interval; time-to-event median with 95% CI, first quartile, and third quartile. The 95% CI for the median is estimated using the method of Brookmeyer and Crowley.

6.1.1.2 Figures

Refer to the Core SAP for additional details.

6.1.1.3 Listings

Unless otherwise specified, by-subject listings are sorted by randomization status (randomized, not randomized), site-subject ID, and additional variables such as time points, as applicable. Listings display as-randomized treatment group abbreviated as "RMG" for rimegepant, and "PBO" for placebo 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, DBT day ≥1 derived from the measurement date, OLE day ≥1 derived from the measurement date, and OL rimegepant day ≥1 derived from the measurement date (see Section 7.3).

Refer to Core SAP for additional details about listings.

6.1.2 Statistical Methods

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

6.1.3 Handling of Missing Data

For all binary efficacy endpoints, main analyses impute missing data as failure using methods described in Section 6.3. Sensitivity analyses of the primary endpoint impute missing data using different methods (see Section 6.3.2.2). Otherwise, all analyses are based on observed data without using imputation.

6.2 Study Population

Refer to the Core SAP for TLF contents.

6.2.1 Analysis Sets

The number of subjects in each analysis set described in Section 4.1 is tabulated 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 country and site is provided for the enrolled analysis set. The table also displays results for the full and safety analysis sets.

6.2.3 Subject Disposition

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

- Reference dates: last contact date* and RTSM randomization date
- Study phase: DBT or OLE. For each study phase:
  - Last visit date, derived from visit dates from the Visit Date and Unscheduled Visit CRFs
    - DBT Phase: latest visit date in the Screening or DBT Phase analysis period
    - OLE Phase: latest visit date in the OLE Phase analysis period
  - Phase completion status: "completed"; or "not completed" concatenated with the reason for noncompletion (see Sections 6.2.3.1, 6.2.3.2, 6.2.3.3, and 6.2.3.4)
  - Next phase continuation status: "continued" concatenated with the name of the next phase (OLE or Follow-up); or "not continued" concatenated with the reason for noncontinuation (see Sections 6.2.3.2, 6.2.3.3 and 6.2.3.4).

A footnote describes the derivation of the last contact date as "* Derived as the death date (if it exists); otherwise, the maximum date collected across study population, efficacy, safety, and outcomes research parameters".

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

6.2.3.1 Subject Disposition From Enrollment to Randomization

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

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

6.2.3.2 Subject Disposition From Randomization to Treatment

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

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

6.2.3.3 Subject Disposition During the DBT Phase

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

- Ongoing in the DBT Phase. These are identified as subjects with missing response to the question "Did the subject complete the DBT Phase?". 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 "yes" response to the question "Did the subject complete the DBT Phase?".
- Did not complete the DBT Phase. These are identified as subjects with "no" response to the question "Did the subject complete the DBT Phase?".
  - Reasons for not completing the DBT Phase, including not reported
- Continued to the OLE Phase. These are identified as subjects with "yes" response to the question "Is the subject continuing to the OLE Phase?".
- Did not continue to the OLE Phase. These are identified as subjects with "no" response to the question "Is the subject continuing to the OLE Phase?". Subjects with missing response to this question after the PCD database lock are also included.
  - Reasons for not continuing to the OLE Phase, including not reported.

6.2.3.4 Subject Disposition During the OLE Phase

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

- Ongoing in the OLE Phase. These are identified as subjects with missing response to the question "Did the subject complete the OLE Phase?". This category only exists before the LSLV database lock; otherwise, subjects with missing response are categorized as "Did not complete the OLE Phase".
- Completed the OLE Phase. These are identified as subjects with "yes" response to the question "Did the subject complete the OLE Phase?"
- Did not complete the OLE Phase. These are identified as subjects with "no" response to the question "Did the subject complete the OLE Phase?".
  - Reasons for not completing the OLE Phase, including not reported

- Continued to the Follow-Up Phase. These are identified as subjects with "yes" response to the question "Is the subject continuing to the Follow-Up Phase?".
- Did not continue to the Follow-Up Phase. These are identified as subjects with "no" response to the question "Is the subject continuing to the Follow-Up Phase?". Subjects with missing response to this question after the LSLV database lock are also included.
    - Reasons for not continuing to the next phase, including not reported.

6.2.4 Protocol Deviations

6.2.4.1 Relevant Protocol Deviations

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

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

6.2.4.2 Significant Protocol Deviations

The by-subject listing of significant protocol deviations is provided for the full analysis set, and is based on a protocol deviation external file provided by the data management vendor from a clinical trial management system. This includes deviation date, category, subcategory, and description, which are additional sorting variables. Significant protocol deviations are defined as those reported with major severity. A footnote describes the raw data source and how significant protocol deviations are identified, e.g., "Significant protocol deviations are those reported with major severity by the data management vendor in the clinical trial management system.".

6.2.5 Baseline Characteristics

Baseline characteristics include (1) demographics and other relevant baseline characteristics, (2) baseline disease characteristics (i.e., migraine history; history of CV events, conditions, procedures, and other risk factors; triptan-unsuitable criteria; and migraine characteristics at the time of DB study drug dosing), (3) medical history, and (4) nonstudy prior medications. These are detailed in Sections 6.2.5.1 through 6.2.5.4, respectively.

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

- DBT efficacy analysis set:
    - Baseline characteristics (1) and (2) by as-randomized treatment group and overall to support efficacy. Baseline characteristics (1) and (2) by subgroup level and overall for all efficacy subgroups of interest (except randomization stratum) described in Sections 4.3.1 for each treatment group. Results support exploratory objectives #17 and #18.

- DBT safety analysis set:
  - Baseline characteristics (1) through (4) by as-treated treatment group and overall to support safety.
  - Baseline characteristics (1) and (2) by subgroup level and overall for all high-level safety subgroups of interest described in Section 4.3.2 for each treatment group. Results support exploratory objective #17.
- OL rimegepant safety analysis set: Demographics and other relevant baseline characteristics by treatment group/OL rimegepant and overall to support OL rimegepant safety.

Baseline for a parameter (e.g., weight) is defined according to analysis set; refer to the Core SAP for details, including handling of ties on the same measurement date.

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

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. Other relevant characteristics also include the following categorical variables:

- Geographic region: Australia/Europe, North America
  - North America is defined as Canada, Mexico, or United States of America.
- Previous study participation (e.g., any study, BHV3000-301, BHV3000-302, BHV3000-303, etc.)
- Randomization stratum based on actual data: history of clinically relevant CV disease (yes, no)
  - Subjects are categorized as "yes" if they have history of CV event, condition, or procedure (i.e., are in category 1, 2, or 3 in Section 6.2.5.2 "History of CV Events, Conditions, Procedures, and Other Risk Factors").
  - Otherwise, subjects are categorized as missing if they have "no" or missing response to the question "Was a Cardiovascular History assessed?" on the History of CV Events, Conditions, Procedures, and Other Risk Factors CRF.
  - Otherwise, subjects are categorized as "no".
- Imputed randomization stratum #: history of clinically relevant CV disease (yes, no). This is an efficacy and safety subgroup of interest (see Sections 4.3.1 and 4.3.2).
  - If the randomization stratum value based on actual data is missing, then it is imputed with the randomization stratum value from the RTSM system. Otherwise, the imputed randomization stratum value is equal to the randomization stratum value based on actual data.
  - A footnote specifies that "# Missing randomization stratum based on actual data is imputed with the randomization stratum from the RTSM system. Used in subgroup

analyses and efficacy/outcomes research analyses that use randomization stratum as a variable in models or risk stratification.".

- History of documented failure to ≥2 triptans with ≥1 reason due to lack of efficacy. This is an efficacy subgroup of interest (see Section 4.3.1).
  - Subjects are categorized as "yes" if they meet the applicable criteria defined in Section 6.2.5.2 "Triptan-Unsuitable Criteria", i.e., they are in the "History of documented failure to ≥2 triptans" category and "lack of efficacy" subcategory.
  - Otherwise, subjects are categorized as missing if they have "no" or missing response to the question "Was a Cardiovascular History assessed?" on the History of CV Events, Conditions, Procedures, and Other Risk Factors CRF.
  - Otherwise, subjects are categorized as "no".

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

The frequency cross table of randomization stratum (history of clinically relevant CV disease) from the RTSM system versus actual data is provided for the full analysis set by as-randomized treatment group and overall. Categories are:

- RTSM value of "yes" and CRF value of "yes"
- RTSM value of "yes" and CRF value of "no" or missing
- RTSM value of "no" and CRF value of "no"
- RTSM value of "no" and CRF value of "yes" or missing.

6.2.5.2 Baseline Disease Characteristics

Migraine History

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

History of CV Events, Conditions, Procedures, and Other Risk Factors

Results are based on the History of CV Events, Conditions, Procedures, and Other Risk Factors CRF.

The frequency table of history of CV events, conditions, procedures, and other risk factors displays the number and percentage of subjects in the following categories and subcategories based on "yes" responses to CRF questions:

- History of CV disease (event, condition, or procedure) or risk factor. Defined as any of the 4 categories listed below.
- (1) History of CV event. Defined as any of the following:
  - Cardiac arrest

  - Cerebrovascular accident
  - Myocardial infarction
  - Transient ischemic attack
- (2) History of CV condition. Defined as any of the following:
  - Angina pectoris (myocardial ischemia)
  - Cardiac conduction disorder
  - Coronary artery vasospasm (Prinzmetal's angina)
  - Ischemic coronary artery disease
  - Ischemic bowel disease
  - Peripheral artery disease (including claudication)
- (3) History of CV procedure. Defined as any of the following:
  - Angioplasty (with or without stent placement)
  - Carotid endarterectomy
  - Coronary artery bypass grafting
- (4) Other CV disease or risk factor. Defined as any of the following:
  - Other significant underlying CV disease
  - Uncontrolled hypertension
  - Known hypersensitivity to triptan
  - Treatment for hypertension
  - Diabetes
  - Current smoker
  - Treatment with a statin
  - Family history of coronary artery disease.

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

Triptan-Unsuitable Criteria

Results are based on the Triptan-Unsuitable Criteria CRF.

The frequency table of triptan-unsuitable criteria displays the number and percentage of subjects in the following categories:

- History of documented failure to ≥2 triptan medications or documented contraindication to the use of triptans. These 2 categories are defined below. The number of failure reasons are the following mutually exclusive subcategories:

  - All 3 reasons: lack of efficacy, prior intolerance, and documented contraindication to the use of triptans
  - Only 2 reasons
  - Only 1 reason.
- History of documented failure to ≥2 triptan medications
  - History of documented failure to a triptan is defined as a triptan meeting all the following criteria:
    - Nonstudy medication type of previous; refer to the Core SAP for the definition.
    - "Lack of efficacy" or "prior intolerance" as a reason for failure.
  - Triptan medications are identified from 7 distinct triptan names, i.e., almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, or zolmitriptan.
  - The following reasons for failure are subcategories:
    - Lack of efficacy. Defined as ≥1 reason due to lack of efficacy.
    - Prior intolerance. Defined as ≥1 reason due to prior intolerance.
    - Lack of efficacy and prior intolerance. Defined as ≥1 reason due to lack of efficacy and ≥1 reason due to prior intolerance.
- Documented contraindication to the use of triptans. Defined as "yes" response to (1) the question "Does the subject have documented contraindication to the use of triptans?" or (2) any of the 4 CRF questions about reasons for contraindication. Reasons are the following subcategories:
  - Specified CV event, condition, or procedure *
  - Documented hypersensitivity to triptans *
  - Uncontrolled hypertension *
  - Other aspects *
  - Not reported.

Categories marked with "*" are based on "yes" responses to CRF questions.

The listing of triptan-unsuitable criteria is provided for the enrolled analysis set. The listing displays the following parameters in columns: history of documented failure to ≥2 triptan medications status ("Y" or missing), as defined above; documented contraindication to the use of triptans ("Y" or missing), as defined above; response (yes, no) to each contraindication reason category marked with "*"; and triptan medication names and reason(s) for failure (lack of efficacy, prior intolerance). Additional triptan medication parameters (e.g., start and end dates) are presented in the by-subject listing of nonstudy medications (see Section 6.2.6.3).

Migraine Characteristics at the Time of DB Study Drug Dosing

Migraine characteristics at the time of DB study drug dosing include the following parameters from the eDiary:

- Migraine headache pain intensity (none, mild, moderate, severe)
- MBS before DB study drug dosing (nausea, phonophobia, photophobia)
- Nausea status (present, absent)
- Nausea intensity (none, mild, moderate, severe)
- Phonophobia status (present, absent)
- Phonophobia intensity (none, mild, moderate, severe)
- Photophobia status (present, absent)
- Photophobia intensity (none, mild, moderate, severe)
- Functional disability level (normal, mildly impaired, severely impaired, requires bedrest)
- Aura status preceding or accompanying headache (yes, no).

An intensity of none for a symptom (nausea, photophobia, or phonophobia) is defined as a symptom status of absent.

See Section 7.4.2 for additional details.

6.2.5.3 Medical History

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

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

6.2.5.4 Nonstudy Prior Medications

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

- Previous triptan medications for the DBT efficacy analysis set
- Previous triptan medications for the DBT efficacy analysis set with documented contraindication to the use of triptans (see Section 6.2.5.2)
- Previous triptan medications failed due to lack of efficacy or prior intolerance for the DBT efficacy analysis set with history of documented failure to ≥2 triptan medications (see Section 6.2.5.2)
- Previous triptan medications failed due to lack of efficacy for the DBT efficacy analysis set with history of documented failure to ≥2 triptan medications with ≥1 reason due to lack of efficacy (see Section 6.2.5.2)

- Current medications for the DBT safety analysis set: all; acute migraine; prophylactic migraine.

Medications are displayed in descending order of overall frequency within therapeutic class and preferred name. See Section 6.2.6.3 for the definition of acute migraine and prophylactic migraine medications. Refer to the Core SAP for the definitions of previous, current, and triptan medications.

6.2.6 Exposure

See Section 7.1 for derived dates.

6.2.6.1 Study Therapy

The by-subject listing of study drug dosing and accountability is produced for the safety analysis set and displays OL rimegepant start and end date/times, time in the OLE Phase (weeks), cumulative OL rimegepant exposure (tablets), average OL rimegepant exposure (tablets per month), kit dispensed date, kit returned date, study drug date/time (see Section 7.1), eDiary source (reported prospective, reported retrospective, manual data correction form [DCF]; see Section 7.4.1), wallet ID, and study drug type (DB rimegepant, DB placebo, OL rimegepant). The listing is sorted by site-subject ID, kit dispensed date, study drug date/time, and eDiary source. Invalid wallet IDs are identified.

Wallet IDs are collected on the Drug Accountability CRF with yes/no questions about wallet dispensed or returned status, and corresponding wallet dispensed and returned dates. Wallet IDs are compared to the study drug wallet list file to determine wallet type (DB rimegepant, DB placebo, or OL rimegepant). Valid wallet IDs are those in the study drug wallet list file.

OL Rimegepant Exposure

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

- Time on OL rimegepant (weeks), derived as (OL rimegepant end date – OL rimegepant start date + 1)/7
- Time on OL rimegepant (weeks) categories: <2, ≥2 to <4, ≥4 to <6, ≥6 to <8, ≥8 to <10, ≥10 to <12, ≥12 to <14, and ≥14
- Time in the OLE Phase (weeks), derived as (OLE Phase end date – OLE Phase start date + 1)/7
- Time in the OLE Phase (weeks) categories: <2, ≥2 to <4, ≥4 to <6, ≥6 to <8, ≥8 to <10, ≥10 to <12, ≥12 to <14, and ≥14
- Cumulative OL rimegepant exposure (tablets), derived by summing number of tablets across records with complete OL rimegepant study drug date

- Average rimegepant exposure (tablets per month), derived as (1) cumulative OL rimegepant exposure (tablets) if time in the OLE Phase <2 weeks, or (2) 4 × cumulative OL rimegepant exposure/{time in the OLE Phase}, if time in the OLE Phase ≥2 weeks
- Total OL rimegepant exposure (tablets) summed across all subjects, derived by summing cumulative OL rimegepant 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.

See Section 7.4.1 for tablet counts.

Tables of OL rimegepant exposure are also provided by subgroup level and overall for all high-level safety subgroups of interest described in Section 4.3.2.

6.2.6.2 Measurements of Treatment Compliance

The by-subject listing of treatment compliance is provided for the safety analysis set, and displays results for DB and OL rimegepant treatment compliance parameters in separate columns as flags ("Y" or missing).

DB Treatment Compliance

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

- DB study drug taken but not randomized. Defined as nonmissing DB study drug date and missing RTSM randomization date.
- DB study drug taken without having a qualifying migraine attack. Defined as nonmissing DB study drug date and no qualifying migraine attack at the time of DB study drug dosing (see Section 9.3.1).
- DB study drug actually received different from randomized treatment assignment (i.e., as-treated treatment group not equal to as-randomized treatment group). Defined as either of the following using the Drug Accountability CRF:
  - Randomized to rimegepant but the first wallet dispensed is DB placebo
  - Randomized to placebo but the first wallet dispensed is DB rimegepant.

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

OL Rimegepant Treatment Compliance

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

- >1 OL rimegepant tablet taken on any 1 day
- OL rimegepant taken before OLE Phase eligibility contact. Defined as OL rimegepant start date before the contact date from the OLE Phase Eligibility CRF.

- OL rimegepant taken without having a qualifying migraine attack. Defined as nonmissing OL rimegepant date and no qualifying migraine attack at the time of OL rimegepant dosing (see Section 9.3.1)
- Time on OL rimegepant ≥14 weeks (see Section 6.2.6.1)
- OL rimegepant taken but DB study drug never taken. Defined as missing DB study drug date/time.

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

6.2.6.3 Nonstudy Concomitant Medications

Frequency tables of the following nonstudy medications are provided by treatment group:

- DBT concomitant for the DBT safety analysis set: all; prophylactic migraine
- DBT rescue medications for the DBT efficacy analysis set.

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

The frequency table of nonstudy post-DBT pre-OL rimegepant medications is provided by treatment group and overall for the interim safety analysis set. Medications are displayed in descending order of overall frequency within therapeutic class and preferred name.

Frequency tables of the following nonstudy medications are provided by treatment group/OL rimegepant and overall:

- OL rimegepant concomitant for the OL rimegepant safety analysis set: all; acute migraine; prophylactic migraine
- OLE rescue medications for the OLE migraine analysis set.

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

Prophylactic migraine medications are displayed by preferred name without therapeutic class.

The by-subject listing of nonstudy medications is provided by therapeutic class and preferred name for the enrolled analysis set. Acute migraine, prophylactic migraine, and rescue medications are identified. For rescue medications, the medication date/time is displayed instead of the medication start and end dates. The listing also displays abbreviated medication types comma-concatenated in the following order: previous ("P"); current ("C"); DBT concomitant ("D"); post-DBT pre-OL rimegepant ("I"); OL rimegepant concomitant ("O"); follow-up ("F"). A medication may be classified into multiple medication types. See Section 7.6 for the definition of the last 4 medication types.

Refer to the Core SAP for the following: counting rules in nonstudy medication frequency tables; non-study medication start and end date imputation; and definition of previous and current medication types.

Note that medications on the Rescue Medication CRF are collected with both medication date and time (where time may be missing), but not start and end dates. Imputed start and end dates for Rescue Medication CRF data are used only to derive nonstudy medication type.

Nonstudy Medications

Nonstudy medications are identified from the (1) Triptan-Unsuitable Criteria CRF, (2) Concomitant Medications CRF, or (3) Rescue Medications CRF. The Concomitant Medications CRF collects indications, and links medical history and AE terms respectively to the Medical History and AE CRFs.

Migraine Standard of Care Medications

Acute migraine-specific medications are defined as nonstudy medications with preferred name containing triptan, ergotamine, lasmiditan, or ubrogepant.

Acute migraine medications are defined as any of the following nonstudy medications:

- Acute migraine-specific medication
- Those with an indication of "acute migraine medication" from the Concomitant Medications CRF
- Those from the Rescue Medications CRF.

Prophylactic migraine medications are defined as nonstudy medications with an indication of "prophylactic migraine medication" from the Concomitant Medications CRF.

Migraine standard of care medications are defined as acute migraine or prophylactic migraine medications.

DBT Rescue Medications

DBT rescue medications are defined as DBT concomitant medications from the Rescue Medications CRF that meet any of the following criteria:

- DB study drug date/time < medication date/time < DB study drug date/time + 49 hours + 1 minute (upper bound of the 48-hour postdose analysis window; see Table 7), if {DB study drug date and time are both nonmissing} and {medication date is complete and time is nonmissing}
- DB study drug date ≤ medication date ≤ DB study drug date + 2 days, if {DB study drug date is nonmissing but time is missing} or {medication date is complete but time is missing}.

Thus, DBT rescue medications are a subset of DBT concomitant medications.

OLE Rescue Medications

OLE rescue medications are defined as OL rimegepant concomitant medications from the Rescue Medications CRF that meet any of the following criteria:

- OL rimegepant date/time < medication date/time < OL rimegepant date/time + 25 hours + 1 minute (upper bound of the 24-hour postdose analysis window; see Table 7), if {OL rimegepant date and time are both nonmissing} and {medication date is complete and time is nonmissing}
- OL rimegepant date ≤ medication date ≤ OL rimegepant date + 1 day, if {OL rimegepant date is nonmissing but time is missing} or {medication date is complete but time is missing}.

Thus, OLE rescue medications are a subset of OL rimegepant concomitant medications.

Note that subjects may have multiple OL rimegepant date/times. Each medication date/time is compared to each distinct OL rimegepant date/time to determine whether it is OLE rescue medication.

Acute Headache Medications

Acute headache medications are defined as any of the following nonstudy medications:

- Acute migraine medication (which includes rescue medication)
- Those with medical history term, primary AE term, additional AE term, or other specify term (1) containing "headache" or "migraine" and (2) not containing "prevent" or "prophyl" from the Concomitant Medications CRF.

Thus, acute headache medications include both rescue medications and nonrescue acute headache medications.

6.3 Efficacy

Efficacy endpoints are assessed by as-randomized treatment group.

Randomization is stratified using the RTSM system, but analyses use the imputed randomization stratum, which is based primarily on the actual data (i.e., history of clinically relevant CV disease; see Section 6.2.5.1). The rationale for using the actual data in analyses is that sites may erroneously report the wrong stratum in the RTSM system. Hence, treatment group comparisons of binary efficacy endpoints are stratified by the imputed randomization stratum except within subgroups. If there are sparse data within a stratum, then results may be presented unstratified. Note that the phrase "randomization stratum" refers to the imputed randomization stratum throughout this section.

For binary efficacy endpoints, CIs are based on a normal approximation to the binomial distribution using asymptotic standard error (ASE). For continuous efficacy endpoints, CIs are based on the normal distribution. All CIs are 2-sided.

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

Efficacy Endpoints During the DBT Phase

During the DBT Phase, select endpoints are assessed over time at all scheduled time points postdose: 15, 30, 45, 60, and 90 minutes; 2, 3, 4, 6, 8, 24, and 48 hours.

Analyses are based on the DBT efficacy analysis set with eDiary measurement dates in the DBT Phase analysis period at planned time points of 15 minutes through 48 hours from the eDiary Migraine question category (see Section 7.4.2).

Efficacy Endpoints During the OLE Phase

Analyses are based on the OLE migraine analysis set with eDiary measurement dates in the OLE Phase analysis period from the eDiary Migraine question category (see Section 7.4.2).

Methods of Handling Missing Data

Methods of handling missing data in analyses of binary efficacy endpoints during the DBT Phase are defined as follows:

- Noncompleter = Failure (NC=F): Subjects with missing data at a single time point are classified as failures. This missing data imputation method is applied to endpoints based on data from a single time point (e.g., primary endpoint) as the main analysis method.
- Noncompleter Missing Data at More Than 1 Time Point = Failure (NC1=F): Subjects with missing data at >1 time point postdose in a specified time period are classified as failures. This missing data imputation method is applied to endpoints that are based on data from multiple time points (e.g., key secondary endpoint of sustained headache pain freedom from 2 to 24 hours postdose) as the main analysis method.
- Multiple imputation (see Section 6.3.2.2). This missing data exclusion method is applied only to the primary endpoint as a sensitivity analysis.
- Varying response rate imputation (see Section 6.3.2.2). This missing data exclusion method is applied only to the primary endpoint as a sensitivity analysis.

Intercurrent Event of Rescue Medication Use

During the DBT Phase, the intercurrent event of DBT rescue medication use is handled using Rescue Medication = Failure (RM=F), which has 2 criteria:

1) Subjects who take DBT rescue medication at or before a nonmissing efficacy measurement at a postdose time point are classified as failures at that time point, for a given qualifying migraine attack.
2) Subjects who take DBT rescue medication at or before a postdose time point with a missing efficacy measurement are classified as failures at that time point, for a given qualifying migraine attack. This criterion is used only in sensitivity analyses based on data imputation (see Section 6.3.2.2), or analyses that present the rate of rescue medication use for a specific endpoint (e.g., pain relapse) in the DBT Phase.

The RM=F method applies to analyses of all binary efficacy endpoints, except those based on rescue medication use (see Section 7.5).

During the OLE Phase, use of acute migraine-specific rescue medication is part of the endpoint definition of continuous efficacy endpoints based on migraine days per month.

6.3.1 Overall Efficacy

6.3.1.1 Overall Summary of Primary and Key Secondary Efficacy Endpoints During the DBT Phase

Overall Summary Table of Primary and Key Secondary Efficacy Endpoints During the DBT Phase

The overall summary table of treatment comparisons of all primary and key secondary efficacy endpoints during the DBT Phase tested hierarchically is provided for the DBT efficacy analysis set, and presents the following statistics:

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

Analyses are based on main methods described in Section 6.3.2.1. Key secondary efficacy endpoints are displayed in the order presented in Section 3.2.2.1. P-values that are determined to be significant based on the testing hierarchy are identified.

If the main analysis of the primary endpoint is significant (p-value ≤ 0.05; see Section 6.3.2.1), then the key secondary endpoints are tested hierarchically, each at a 2-sided alpha level of 0.05, in the order specified in Section 3.2.2.1. Thus, a key secondary endpoint is tested only if the preceding key secondary endpoint in the hierarchy is determined to be significant (i.e., p-value ≤ 0.05). If a test in the hierarchy is not significant, then any further tests on endpoints in the sequence have p-values presented only for descriptive purposes, and no conclusions are drawn from those results.

If the main analysis of the primary endpoint is not significant (i.e., p-value > 0.05), then any further tests of key secondary endpoints will have p-values presented only for descriptive purposes, and no conclusions are drawn from those results.

For each comparison, the null hypothesis of interest H_0 is that the percentage of responders observed on rimegepant (denoted $p_{rimegepantl}$) is equal to the percentage observed on placebo (denoted $p_{placebo}$), i.e., H_0: $p_{rimegepantl} = p_{placebo}$. The alternative 2-sided hypothesis of interest H_1 is that the rates of responders observed on rimegepant and placebo differ, i.e., H_1: $p_{rimegepantl} \neq p_{placebo}$.

The overall summary table of treatment comparisons of all primary and key secondary efficacy endpoints during the DBT Phase is also produced by subgroup level for all efficacy subgroups of interest described in Section 4.3.1. Separate tables are provided for each subgroup. Analyses are performed unstratified, and p-values are presented only for descriptive purposes. Results support exploratory objectives #17 and #18.

Forest Plot of Primary and Key Secondary Efficacy Endpoints During the DBT Phase

The forest plot of treatment comparisons of all primary and key secondary efficacy endpoints during the DBT Phase is provided for the DBT efficacy analysis set, and is based on the overall summary. The plot displays the following statistics:

- Response rate (i.e., "n/N" and percentage) by treatment group
- Stratified percentage difference between treatment groups (rimegepant – placebo) and 95%CI.

Percentage differences with p-values that are determined to be significant based on the testing hierarchy are identified. Note that the plot displays results for no rescue medication use within 24 hours postdose so that positive percentage differences favor rimegepant for these key secondary endpoints.

By-Subject Listing of Primary and Key Secondary Efficacy Endpoints During the DBT Phase

The by-subject listing of primary and key secondary efficacy endpoints during the DBT Phase is provided for the full analysis set that includes first DBT rescue medication date/time (see Section 7.1), time to first DBT rescue medication use in hours (see Section 6.3.3.2), migraine headache pain intensity at the time of DB study drug dosing, MBS before DB study drug dosing, and reason(s) for exclusion from the DBT efficacy analysis set (randomized more than once; not treated with DB study drug; treated with DB study drug but no qualifying migraine attack at the time of DB study drug dosing; qualifying migraine attack at the time of DB study drug dosing but no postdose efficacy data in the DBT Phase); note that the last 3 reasons are mutually exclusive.

Results for each binary endpoint are based on the NC=F and RM=F analysis methods, except for key secondary endpoint #2. Results for each endpoint are abbreviated as follows: "R" for responder; "F" for failure; "N/A" for not applicable for key secondary endpoints #3, 4, and 5 for the DBT analysis set with functional disability level of normal at the time of DB study drug dosing; and missing (blank) for subjects excluded from the DBT efficacy analysis set.

6.3.1.2 Missing Efficacy Data During the DBT Phase

Missing efficacy data during the DBT Phase are tabulated by treatment group as the number and percentage of subjects in the DBT efficacy analysis set in the following categories:

- Missing headache pain intensity at each time point from 15 minutes through 48 hours postdose. These categories are not mutually exclusive because subjects may have missing headache pain intensity at multiple time points.
- Number of time points with missing migraine headache pain intensity from 2 hours to 48 hours postdose: 0 (i.e., no missing migraine headache pain intensity), 1, 2, 3, 4, 5, 6, 7. These categories are mutually exclusive.

- Missing data for the following efficacy parameters at 2, 24, and 48 hours postdose: migraine headache pain intensity, nausea status, phonophobia status, photophobia status, and functional disability level.

6.3.2 Primary Efficacy Endpoint: Pain Relief at 2 Hours Postdose During the DBT Phase

The primary efficacy endpoint is evaluated for the DBT efficacy analysis set.

Pain relief at a single time point postdose is defined as having a headache pain intensity of none or mild at that time point.

6.3.2.1 Primary Efficacy Endpoint: Main Analysis

The percentage of subjects with pain relief at 2 hours postdose during the DBT Phase is compared between treatment groups using Mantel-Haenszel risk estimation (e.g., SAS proc stdrate) with stratification by history of clinically relevant CV disease randomization stratum (yes or no). In these analyses, the NC=F and RM=F methods are applied (see Section 6.3.5.1). The following statistics are presented:

- 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.

These results are presented together in the same table as those for pain relief over time during the DBT Phase (see Section 6.3.5.1).

6.3.2.2 Primary Efficacy Endpoint: Sensitivity Analyses

Sensitivity analyses of the primary efficacy endpoint (i.e., pain relief at 2 hours postdose during the DBT Phase) are provided in separate tables.

The RM=F method uses both criteria to classify subjects as failures (see Section 7.5).

Copy Reference Multiple Imputation

The main analysis is repeated using the copy reference multiple imputation approach with n = 30 imputations to impute missing headache pain intensity at 2 hours postdose. The fully conditional specification (FCS) method is used with a generalized logit distribution. Covariates may include history of clinically relevant CV disease randomization stratum (yes or no), sex, migraine headache pain intensity at the time of DB study drug dosing (moderate or severe), historical number of moderate to severe migraine attacks per month (< median, ≥ median), MBS before DB study drug dosing (nausea, phonophobia, or photophobia), and geographic region (Australia/Europe or North America). First, the RM=F method of handling rescue medication use is applied. Next, missing response status (responder versus failure) in the 2-hour postdose analysis window is imputed for subjects who are not missing any of the covariates (subjects

missing any of the covariates are considered failures). The same statistics as the main analysis are presented, except "n/N".

Varying Response Rate Imputation

The main analysis is repeated by imputing missing headache pain intensity at 2 hours postdose in each treatment group with varying response rates over the range of 0%, 10%, 20% and 30%. First, the RM=F method of handling rescue medication use is applied. Next, missing response status (responder versus failure) in the 2-hour postdose analysis window is imputed. The following statistics are presented: stratified percentage difference between treatment groups (rimegepant – placebo), ASE, 95% CI, and p-value.

6.3.3 Key Secondary Efficacy Endpoints

Key secondary efficacy endpoints are assessed using the DBT efficacy analysis set, unless specified otherwise. Results in Sections 6.3.3.1 though 6.3.3.10 support key secondary efficacy endpoints #1 through #10, respectively.

6.3.3.1 Pain Freedom at 2 Hours Postdose During the DBT Phase

Pain freedom at a single time point post dose is defined as having a migraine headache pain intensity of none at that time point.

The percentage of subjects with pain freedom at 2 hours postdose is compared between treatment groups using analogous methods as the main analysis of the primary endpoint with NC=F and RM=F (see Section 6.3.2.1). These results are presented together in the same table as those for pain freedom over time during the DBT Phase (see Section 6.3.5.1).

6.3.3.2 Rescue Medication Use Within 24 Hours Postdose During the DBT Phase

Analyses are based on the evaluable DBT efficacy analysis set, i.e., subjects in the DBT efficacy analysis set with first DBT rescue medication date ≤ DB study drug date + 1 day and missing first DBT rescue medication time are excluded.

Time to first DBT rescue medication use is defined as (first DBT rescue medication date/time – DB study drug date/time) in hours (see Section 7.1). Rescue medication use within 24 hours postdose during the DBT Phase is defined as time to first DBT rescue medication use ≤ 24 hours.

Treatment Group Comparisons

The percentage of subjects with rescue medication use within 24 hours postdose is compared between treatment groups using analogous methods as the main analysis of the primary endpoint, except that the NC=F and RM=F methods are not applied because they are not applicable to this endpoint (see Section 6.3.2.1).

Time to Rescue Medication Use Through 24 Hours Postdose

Time to rescue medication use through 24 hours postdose is assessed by treatment group as follows:

- Kaplan-Meier plot and table using 2-hour time intervals (i.e., 0 to ≤2, >2 to ≤4, ... , >24). The Kaplan-Meier plot displays the percentage of subjects taking rescue medication within 24 hours postdose on the y-axis versus time in hours on the x-axis.
- Time-to-event distribution table (hours).

See Section 6.1.1.1 for time-to-event plot and table attributes. Rescue medication use through 24 hours postdose is considered as an event in these time-to-event analyses. Subjects who do not take rescue medication within 24 hours postdose are censored at 24 hours and 1 minute (i.e., 1441 minutes).

6.3.3.3 Return to Normal Function at 2 Hours Postdose During the DBT Phase

Return to normal function at a single time point postdose is defined as a functional disability level of normal at that time point for the subset of subjects with functional disability at the time of dosing. Functional disability is defined as a functional disability level of mildly impaired, severely impaired, or requires bedrest. Thus, all analyses of return to normal function during the DBT Phase are based on the DBT efficacy analysis set with functional disability at the time of DB study drug dosing (see Section 7.5.2).

The percentage of subjects with return to normal function at 2 hours postdose during the DBT Phase is compared between treatment groups using analogous methods as the main analysis of the primary endpoint with NC=F and RM=F (see Section 6.3.2.1). These results are presented together in the same table as those for return to normal function over time during the DBT Phase (see Section 6.3.5.1).

6.3.3.4 Sustained Return to Normal Function From 2 to 24 Hours Postdose During the DBT Phase

Analyses are based on the DBT efficacy analysis set with functional disability at the time of DB study drug dosing.

Sustained return to normal function from 2 to 24 hours postdose is defined as a functional disability level of normal at all time points from 2 to 24 hours postdose.

Subjects who meet all the following criteria are classified as responders:

- Functional disability level of normal at all time points from 2 to 24 hours postdose, i.e., in the 2 to 24-hour postdose analysis windows
- Missing functional disability level at ≤1 time point from 3 to 8 hours postdose, i.e., in the 3, 4, 6, or 8-hour postdose analysis window
- No rescue medication taken at or before the functional disability level measurement in the 24-hour postdose analysis window (see Section 7.5).

Subjects who are not responders are classified as failures. Failure criteria include any of the following:

- Rescue medication taken at or before 24 hours postdose (RM=F; see Section 7.5)
- Functional disability level of mildly impaired, severely impaired, or requires bedrest at any time point from 2 to 24 hours postdose, i.e., in the 2, 3, 4, 6, 8 or 24-hour postdose analysis window
- Missing functional disability measurement at 2 or 24 hours postdose (NC=F), i.e., in the 2 or 24-hour postdose analysis window
- Missing functional disability measurement at >1 time point from 3 to 8 hours postdose (NC1=F), i.e., in the 3, 4, 6, or 8-hour postdose analysis window.

The percentage of subjects with sustained return to normal function from 2 to 24 hours postdose during the DBT Phase is compared between treatment groups using analogous methods as the main analysis of the primary endpoint with NC=F, NC1=F, and RM=F (see Section 6.3.2.1). These results are presented together in the same table as those for sustained return to normal function from 2 to 48 hours postdose during the DBT Phase (see Section 6.3.3.5).

6.3.3.5 Sustained Return to Normal Function From 2 to 48 Hours Postdose During the DBT Phase

Analyses are based on the DBT efficacy analysis set with functional disability at the time of DB study drug dosing.

Sustained return to normal function from 2 to 48 hours postdose is defined as a functional disability level of normal at all time points from 2 to 48 hours postdose.

Subjects who meet all the following criteria are classified as responders:

- Functional disability level of normal at all time points from 2 to 48 hours postdose, i.e., in the 2 to 48-hour postdose analysis windows
- Missing functional disability level at ≤1 time point only from 3 to 8 hours postdose, i.e., in the 3, 4, 6, or 8-hour postdose analysis window
- No rescue medication taken at or before the functional disability level measurement in the 48-hour postdose analysis window (see Section 7.5).

Subjects who are not responders are classified as failures. Failure criteria include any of the following:

- Rescue medication taken at or before 48 hours postdose (RM=F; see Section 7.5)
- Functional disability level of mildly impaired, severely impaired, or requires bedrest at any time point from 2 to 48 hours postdose, i.e., in the 2, 3, 4, 6, 8, 24, or 48-hour postdose analysis window
- Missing functional disability measurement at 2, 24, or 48 hours postdose (NC=F), i.e., in the 2, 24, or 48-hour postdose analysis window

- Missing functional disability measurement >1 time point from 3 to 8 hours postdose (NC1=F), i.e., in the 3, 4, 6, or 8-hour postdose analysis window.

The percentage of subjects with sustained return to normal function from 2 to 48 hours postdose during the DBT Phase is compared between treatment groups using analogous methods as the main analysis of the primary endpoint with NC=F, NC1=F, and RM=F (see Section 6.3.2.1). These results are presented together in the same table as those for sustained return to normal function from 2 to 24 hours postdose during the DBT Phase (see Section 6.3.3.4).

6.3.3.6 Sustained Pain Relief From 2 to 24 Hours Postdose During the DBT Phase

Sustained pain relief from 2 to 24 hours postdose is defined as migraine headache pain intensity of none or mild at all time points from 2 to 24 hours postdose.

Subjects who meet all the following criteria are classified as responders:

- Migraine headache pain intensity of none or mild at all time points from 2 to 24 hours postdose, i.e., in the 2 to 24-hour postdose analysis windows
- Missing migraine headache pain intensity at ≤1 time point only from 3 to 8 hours postdose, i.e., in the 3, 4, 6, or 8-hour postdose analysis window
- No rescue medication taken at or before the migraine headache pain intensity measurement in the 24-hour postdose analysis window (see Section 7.5).

Subjects who are not responders are classified as failures. Failure criteria include any of the following:

- Rescue medication taken at or before 24 hours postdose (RM=F; see Section 7.5)
- Moderate or severe migraine headache pain intensity at any time point from 2 to 24 hours postdose, i.e., in the 2, 3, 4, 6, 8, or 24-hour postdose analysis window
- Missing migraine headache pain intensity at 2 or 24 hours postdose (NC=F), i.e., in the 2 or 24-hour postdose analysis window
- Missing migraine headache pain intensity at >1 time point from 3 to 8 hours postdose (NC1=F), i.e., in the 3, 4, 6, or 8-hour postdose analysis window.

The percentage of subjects with sustained pain relief from 2 to 24 hours postdose during the DBT Phase is compared between treatment groups using analogous methods as the main analysis of the primary endpoint with NC=F, NC1=F, and RM=F (see Section 6.3.2.1). These results are presented together in the same table as those for sustained pain relief from 2 to 48 hours postdose during the DBT Phase (see Section 6.3.3.7).

6.3.3.7 Sustained Pain Relief From 2 to 48 Hours Postdose During the DBT Phase

Sustained pain relief from 2 to 48 hours postdose is defined as migraine headache pain intensity of none or mild at all time points from 2 to 48 hours postdose.

Subjects who meet all the following criteria are classified as responders:

- Migraine headache pain intensity of none or mild at all time points from 2 to 48 hours postdose, i.e., in the 2 to 48-hour postdose analysis windows
- Missing migraine headache pain intensity at ≤1 time point only from 3 to 8 hours postdose, i.e., in the 3, 4, 6, or 8-hour postdose analysis window
- No rescue medication taken at or before the migraine headache pain intensity measurement in the 48-hour postdose analysis window (see Section 7.5).

Subjects who are not responders are classified as failures. Failure criteria include any of the following:

- Rescue medication taken at or before 48 hours postdose (RM=F; see Section 7.5)
- Moderate or severe migraine headache pain intensity at any time point from 2 to 48 hours postdose, i.e., in the 2, 3, 4, 6, 8, 24, or 48-hour postdose analysis window
- Missing migraine headache pain intensity at 2, 24, or 48 hours postdose (NC=F), i.e., in the 2, 24, or 48-hour postdose analysis window
- Missing migraine headache pain intensity at >1 time point from 3 to 8 hours postdose (NC1=F), i.e., in the 3, 4, 6, or 8-hour postdose analysis window.

The percentage of subjects with sustained pain relief from 2 to 48 hours postdose during the DBT Phase is compared between treatment groups using analogous methods as the main analysis of the primary endpoint with NC=F, NC1=F, and RM=F (see Section 6.3.2.1). These results are presented together in the same table as those for sustained pain relief from 2 to 24 hours postdose during the DBT Phase (see Section 6.3.3.6).

6.3.3.8 Sustained Pain Freedom From 2 to 24 Hours Postdose During the DBT Phase

Sustained pain freedom from 2 to 24 hours postdose is defined as migraine headache pain intensity of none at all time points from 2 to 24 hours postdose.

Subjects who meet all the following criteria are classified as responders:

- Migraine headache pain intensity of none at all time points from 2 to 24 hours postdose, i.e., in the 2 to 24-hour postdose analysis windows
- Missing migraine headache pain intensity at ≤1 time point only from 3 to 8 hours postdose, i.e., in the 3, 4, 6, or 8-hour postdose analysis window

- No rescue medication taken at or before the migraine headache pain intensity measurement in the 24-hour postdose analysis window (see Section 7.5).

Subjects who are not responders are classified as failures. Failure criteria include any of the following:

- Rescue medication taken at or before 24 hours postdose (RM=F; see Section 7.5)
- Mild, moderate, or severe migraine headache pain intensity at any time point from 2 to 24 hours postdose, i.e., in the 2, 3, 4, 6, 8, or 24-hour postdose analysis window
- Missing migraine headache pain intensity at 2 or 24 hours postdose (NC=F), i.e., in the 2 or 24-hour postdose analysis window
- Missing migraine headache pain intensity at >1 time point from 3 to 8 hours postdose (NC1=F), i.e., in the 3, 4, 6, or 8-hour postdose analysis window.

The percentage of subjects with sustained pain freedom from 2 to 24 hours postdose during the DBT Phase is compared between treatment groups using analogous methods as the main analysis of the primary endpoint with NC=F, NC1=F, and RM=F (see Section 6.3.2.1). These results are presented together in the same table as those for sustained pain freedom from 2 to 48 hours postdose during the DBT Phase (see Section 6.3.3.9).

6.3.3.9 Sustained Pain Freedom From 2 to 48 Hours Postdose During the DBT Phase

Sustained pain freedom from 2 to 48 hours postdose is defined as migraine headache pain intensity of none at all time points from 2 to 48 hours postdose.

Subjects who meet all the following criteria are classified as responders:

- Migraine headache pain intensity of none at all time points from 2 to 48 hours postdose, i.e., in the 2 to 48-hour postdose analysis windows
- Missing migraine headache pain intensity at ≤1 time point only from 3 to 8 hours postdose, i.e., in the 3, 4, 6, or 8-hour postdose analysis window
- No rescue medication taken at or before the migraine headache pain intensity measurement in the 48-hour postdose analysis window (see Section 7.5).

Subjects who are not responders are classified as failures. Failure criteria include any of the following:

- Rescue medication taken at or before 48 hours postdose (RM=F; see Section 7.5)
- Mild, moderate, or severe migraine headache pain intensity at any time point from 2 to 48 hours postdose, i.e., in the 2, 3, 4, 6, 8, 24, or 48-hour postdose analysis window
- Missing migraine headache pain intensity at 2, 24, or 48 hours postdose (NC=F), i.e., in the 2, 24, or 48-hour postdose analysis window

- Missing migraine headache pain intensity at >1 time point from 3 to 8 hours postdose (NC1=F), i.e., in the 3, 4, 6, or 8-hour postdose analysis window.

The percentage of subjects with sustained pain freedom from 2 to 48 hours postdose during the DBT Phase is compared between treatment groups using analogous methods as the main analysis of the primary endpoint with NC=F, NC1=F, and RM=F (see Section 6.3.2.1). These results are presented together in the same table as those for sustained pain freedom from 2 to 24 hours postdose during the DBT Phase (see Section 6.3.3.8).

6.3.3.10 MBS Freedom at 2 Hours Postdose During the DBT Phase

MBS freedom at a single time point postdose is defined as the MBS reported on study before dosing that is absent at that time point, e.g., subjects who report nausea as the MBS before dosing and have nausea absent at 2 hours postdose. The MBS before dosing is reported as nausea, phonophobia, or photophobia. Symptom status is reported postdose as present or absent for each symptom (nausea, phonophobia, and photophobia).

The percentage of subjects with MBS freedom at 2 hours postdose during the DBT Phase is compared between treatment groups using analogous methods as the main analysis of the primary endpoint with NC=F and RM=F (see Section 6.3.2.1). These results are presented together in the same table as those for MBS freedom over time during the DBT Phase (see Section 6.3.5.1).

6.3.4 Other Secondary Efficacy Endpoints

6.3.4.1 Change From Historical Baseline in Number of Migraine Days per Month During the OLE Phase

Analyses are based on the OLE migraine analysis set, i.e., subjects in the OLE efficacy analysis set with time in the OLE Phase ≥14 days.

Migraine days during the OLE Phase are defined in Section 9.2.2.

Months in the OLE Phase are defined as follows:

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

See Section 7.3 for OLE days.

Migraine headache pain intensity categories are (1) total (i.e., none, mild, moderate, severe, or not reported) or (2) moderate or severe.

The number of total migraine days per month in the OLE Phase analysis period is examined relative to total historical baseline, defined as the number of migraine days per month of any pain intensity in the 3 months prior to screening from the Migraine History CRF.

The number of moderate or severe migraine days per month in the OLE Phase is examined relative to moderate or severe historical baseline, defined as the number of moderate to severe migraine days per month in the 3 months prior to screening from the Migraine History CRF.

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

- Month (i.e., 4-week interval) in the OLE Phase analysis period: 28 × (total number of migraine days in the month)/(time in the month). Subjects must have time in the specified month ≥14 days to be evaluable.
  - Time in Month X of the OLE Phase is defined as maximum(minimum[Y, 28], 0), where Y = {time in the OLE Phase} − (28 × [X − 1]) days and X = 1, 2, or 3.
  - Time in the OLE Phase (days) is defined in Section 6.2.6.1.
- Overall OLE: 28 × (total number of migraine days in the OLE Phase analysis period through OLE day 84)/minimum(time in the OLE Phase; 84 days).

The table of values and changes (both absolute and percent) from the historical baseline in the number of migraine days per month in the OLE Phase is provided for the OLE migraine analysis set, and summaries parameters descriptively as continuous variables (including 2-sided normal 95% CIs for mean change) by treatment group/OL rimegepant and overall and by headache pain intensity (total; moderate or severe) in each month of the OLE Phase and overall OLE. Headache pain intensity categories are (1) total (none, mild, moderate, severe, or not reported) and (2) moderate or severe. Results support other secondary objective #2.

6.3.4.2 *Percentages of Subjects With Reduction From Historical Baseline in Number of Migraine Days per Month During the OLE Phase*

Analyses are based on the OLE migraine analysis set.

Migraine days per month during the OLE Phase and the overall OLE are defined in Section 6.3.4.1.

In analyses by months, subjects must (1) achieve the reduction criterion from historical baseline in the number of migraine days, (2) have time in the specified month ≥14 days to be evaluable, and (3) have historical baseline number of migraine days per months >0 to be classified as responders in the specified month. Otherwise, subjects are classified as failures in the specified month.

In analyses of the overall OLE, subjects must (1) achieve the reduction criterion from historical baseline in the number of migraine days in the overall OLE, and (2) have historical baseline number of migraine days per months >0 to be classified as responders. Otherwise, subjects are classified as failures.

The frequency table of percentage reductions from historical baseline in the number of migraine days per month in the OLE Phase is provided by treatment group/OL rimegepant and overall and by headache pain intensity (total; moderate or severe) in each month of the OLE Phase and overall OLE (see Section 6.3.4.1 for months), and displays the following reduction categories:

≥30%, ≥50%, ≥75%, and 100%. Percentages are calculated against the number of subjects in the OLE migraine analysis set at each month and overall OLE. Results support other secondary objective #3.

6.3.5 Exploratory Efficacy Endpoints

Any p-values presented for exploratory efficacy endpoints during the DBT Phase are for descriptive purposes only, and not included in the hierarchical testing.

6.3.5.1 Efficacy at All Scheduled Time Points Postdose During the DBT Phase

Analyses are based on the DBT efficacy analysis set.

The table of efficacy at each planned time point from 15 minutes through 48 hours postdose during the DBT Phase is provided separately for each of the following efficacy endpoints: pain relief, pain freedom, MBS freedom, return to normal function, photophobia freedom, phonophobia freedom, and nausea freedom. Results support exploratory objectives #3 through #9.

At each planned time point postdose, the percentage of subjects achieving the endpoint during the DBT Phase is compared between treatment groups using analogous methods as the main analysis of the primary endpoint with NC=F and RM=F (see Section 6.3.2.1). For endpoints defined below, "rescue medication" denotes DBT rescue medication.

The line plot of pain relief over time during the DBT Phase displays percentage of subjects achieving pain relief on the y-axis versus time in minutes on the x-axis by treatment group. Error bars denote ± 1 ASE.

Let X denote a planned time point postdose: 15, 30, 45, 60, or 90 minutes; 2, 3, 4, 6, 8, 24, or 48 hours.

Pain Relief Over Time

At time point X, subjects who meet both of the following criteria are classified as responders:

- Migraine headache pain intensity of none or mild at X, i.e., in the X analysis window
- No rescue medication taken at or before the migraine headache pain intensity measurement in the X analysis window (see Section 7.5).

At time point X, subjects who are not responders are classified as failures. Failure criteria include any of the following:

- Rescue medication taken at or before X (RM=F; see Section 7.5)
- Moderate or severe migraine headache pain intensity at X
- Missing migraine headache pain intensity at X (NC=F).

Pain Freedom Over Time

At time point X, subjects who meet both of the following criteria are classified as responders:

- Migraine headache pain intensity of none at X, i.e., in the X analysis window
- No rescue medication taken at or before the migraine headache pain intensity measurement in the X analysis window (see Section 7.5).

At time point X, subjects who are not responders are classified as failures. Failure criteria include any of the following:

- Rescue medication taken at or before X (RM=F; see Section 7.5)
- Mild, moderate, or severe migraine headache pain intensity at X
- Missing migraine headache pain intensity at X (NC=F).

MBS Freedom Over Time

At time point X, subjects who meet both of the following criteria are classified as responders:

- MBS reported before DB study drug dosing that is absent at X, i.e., in the X analysis window
- No rescue medication taken at or before the MBS status measurement in the X analysis window (see Section 7.5).

At time point X, subjects who are not responders are classified as failures. Failure criteria include any of the following:

- Missing MBS before DB study drug dosing (see Section 7.4.2)
- Rescue medication taken at or before X (RM=F; see Section 7.5)
- MBS present at X, e.g., nausea reported as MBS before DB study drug dosing and nausea status of present in the X analysis window
- Missing MBS at X (NC=F), e.g., nausea reported as MBS before DB study drug dosing and missing nausea status in the X analysis window.

Return to Normal Function Over Time

This endpoint is evaluated in the subset of subjects with functional disability at the time of DB study drug dosing (see Section 6.3.3.3).

At time point X, subjects who meet both of the following criteria are classified as responders:

- Functional disability level of normal at X, i.e., in the X analysis window
- No rescue medication taken at or before the functional disability level measurement in the X analysis window (see Section 7.5).

At time point X, subjects who are not responders are classified as failures. Failure criteria include any of the following:

- Rescue medication taken at or before X (RM=F; see Section 7.5)
- Functional disability level of mildly impaired, severely impaired, or requires bedrest at X
- Missing functional disability level at X (NC=F).

Freedom From Photophobia, Phonophobia, or Nausea Over Time

Symptom freedom at a single time point postdose is defined as a symptom status of absent at that time point for the subset of subjects with symptom status of present at the time of dosing.

These endpoints are evaluated in the DBT efficacy analysis set with symptom status of present at the time of DB study drug dosing, e.g., nausea freedom is evaluated for subjects with nausea status of present at the time of DB study drug dosing.

For symptom freedom at X, subjects who meet both of the following criteria are classified as responders:

- Symptom status of absent at X, i.e., in the X analysis window
- No rescue medication taken at or before the symptom status measurement in the X analysis window (see Section 7.5)

For symptom freedom at X, subjects who are not responders are classified as failures. Failure criteria include any of the following:

- Rescue medication taken at or before X (RM=F; see Section 7.5)
- Symptom status of present at X
- Missing symptom status at X (NC=F).

6.3.5.2 Time to Migraine Headache Pain Relief Through 48 Hours Postdose During the DBT Phase

Pain relief during the DBT Phase is defined in Section 6.3.2.

Time to migraine headache pain relief through 48 hours postdose is assessed by treatment group as follows:

- Kaplan-Meier table and plot using the following postdose time intervals: 0 to ≤15, >15 to ≤30, > 30 to ≤45, >45 to ≤60, >60 to ≤90, >90 to ≤120, >120 to ≤180, >180 to ≤240, >240 to ≤360, >360 to ≤480, >480 to ≤1440, >1440 to ≤2940, and >2940 minutes. The Kaplan-Meier plot displays the percentage of subjects with migraine headache pain relief through 48 hours postdose on the y-axis versus time in minutes on the x-axis.
- Time-to-event distribution table (minutes), including a log-rank p-value (rimegepant versus placebo).

See Section 6.1.1.1 for time-to-event plot and table attributes. Results support exploratory objective #11.

Subjects are considered to have an event if (1) pain relief is achieved at ≥1 time point postdose in the DBT Phase, and (2) the first postdose eDiary finding date/time at which pain relief is achieved is before the imputed first DBT rescue medication date/time, if not missing (see Section 7.1).

Otherwise, subjects who do not have an event are censored at the earlier of the following: (1) upper bound of the 48-hour analysis window + 1 minute (i.e., 2941 minutes); (2) time from the DB study drug date/time to the imputed first DBT rescue medication date/time in minutes; (3) time from the DB study drug date/time to the last postdose eDiary finding date/time with nonmissing migraine headache pain intensity measurement in minutes.

6.3.5.3 Pain Relapse From 2 to 48 Hours Postdose During the DBT Phase

Pain relapse from 2 to 48 hours post DB dose is defined as migraine headache pain intensity of mild, moderate, or severe at any time point after 2 hours postdose for subjects with migraine headache pain intensity of none at 2 hours postdose. Thus, analyses of pain relapse are based on the DBT efficacy analysis set with pain freedom at 2 hours postdose in the DBT Phase.

Subjects who meet all the following criteria are classified as nonrelapsers:

- Migraine headache pain intensity of none at all time points after 2 hours postdose, i.e., in the 3 to 48-hour postdose analysis windows
- Missing migraine headache pain intensity at ≤1 time point only from 3 to 8 hours postdose, i.e., in the 3, 4, 6, or 8-hour postdose analysis window
- No rescue medication taken at or before the migraine headache pain intensity measurement in the 48-hour postdose analysis window (see Section 7.5).

Subjects who are not nonrelapsers are classified as relapsers. Relapse criteria include any of the following:

- Rescue medication taken at or before 48 hours postdose (RM=F; see Section 7.5)
- Mild, moderate, or severe migraine headache pain intensity at any time point after 2 hours postdose, i.e., in the 3, 4, 6, 8, 24, or 48-hour postdose analysis window
- Missing migraine headache pain intensity at 24 or 48 hours postdose (NC=F), i.e., in the 24 or 48-hour postdose analysis window
- Missing migraine headache pain intensity at >1 time point from 3 to 8 hours postdose (NC1=F), i.e., in the 3, 4, 6, or 8-hour postdose analysis window.

The percentage of subjects with pain relapse at 2 hours postdose during the DBT Phase is compared between treatment groups using analogous methods as the main analysis of the primary endpoint with NC1=F and RM=F (see Section 6.3.2.1). However, the RM=F method uses both criteria to classify subjects as failures (see Section 7.5).

In addition, the rate of rescue medication taken at or before 48 hours postdose (i.e., "n/N" and percentage) and 95% CI are also displayed by randomization stratum and overall for each treatment group.

Results support exploratory objective #10.

6.3.5.4 Acute Migraine Medication Days per Month During the OLE Phase

Analyses are based on the OLE migraine analysis set.

Acute migraine medication days are defined in Section 9.2.1.1.

Months in the OLE Phase are defined in Section 6.3.4.1.

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

- Month (i.e., 4-week interval) in the OLE Phase analysis period: 28 × (total number of acute migraine medication days in the month)/(time in the month). Subjects must have time in the specified month ≥14 days to be evaluable.
  - Time in Month X of the OLE Phase is defined as maximum(minimum[Y, 28], 0), where Y = {time in the OLE Phase} − (28 × [X − 1]) days and X = 1, 2, or 3.
  - Time in the OLE Phase (days) is defined in Section 6.2.6.1.
- Overall OLE: 28 × (total number of acute migraine medication days in the OLE Phase analysis period through OLE day 84)/minimum(time in the OLE Phase; 84 days).

The table of values for the number of acute migraine medication days per month in the OLE Phase is provided for the OLE migraine analysis set by treatment group/OL rimegepant and overall, and summaries parameters descriptively as continuous variables in each month of the OLE Phase and overall OLE. Results support exploratory objective #12.

The table of values for the number of acute migraine-specific medication days per month in the OLE Phase is provided analogously. Acute migraine-specific medication days are defined in Section 9.2.1.2. The number of acute migraine medication days per month is prorated to 28 days and derived analogously.

6.3.5.5 Rescue Medication Use After Each of the First 5 Qualifying Migraine Attacks During the OLE Phase

The percentage of subjects with rescue medication use is assessed for the first 5 qualifying migraine attacks ≥23 hours apart in the OLE Phase analysis period for the OLE efficacy analysis set.

The table displays the rate (i.e., "n/N" and percentage) of rescue medication use, ASE, and 95% CI by treatment group/OL rimegepant and overall after each qualifying migraine attack.

A qualifying migraine attack is defined as a migraine attack of moderate or severe migraine headache pain intensity that is first treated with study drug.

First, the first 5 qualifying migraine attacks ≥23 hours apart in the OLE Phase are determined analogously to the first 5 EQMAs ≥23 hours apart in the OLE Phase, but regardless of 24-hour postdose MQoL data (see Section 9.3.1). Next, the reported OL rimegepant date/time (to which a given qualifying migraine attack is linked) is used to determine whether OLE rescue medication is used after that qualifying migraine attack (see Section 6.2.6.3).

Results support exploratory objective #13.

6.4 Safety

Safety analyses are based on the safety analysis set, unless otherwise noted. Safety parameters include the following: deaths; AEs; laboratory tests; vital signs; physical measurements; electrocardiograms (ECGs); and C-SSRS.

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

- 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
- Follow-up safety for the follow-up safety analysis set by treatment group/OL rimegepant status and overall.

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

Measurements are slotting safety parameters into analysis periods.

Select safety parameters are tabulated descriptively as continuous variables at baseline and each scheduled visit over time during the on-DBT and on-OL rimegepant safety analysis periods. Measurements are slotted into analysis periods and analysis visits using the following steps:

1) Measurements are slotted into the Screening Phase, DBT Phase, OLE Phase, and Follow-up Phase analysis periods.
2) Measurements are slotted into analysis visits in the analysis periods listed in the previous step.
3) Measurements are slotted into safety analysis periods (pretreatment, on-DBT, or on-OL rimegepant, or follow-up).

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

6.4.1 Adverse Events

Refer to the Core SAP for the following: AE start and end date imputation; death date derivation; counting and rounding rules in AE frequency tables; definitions of AEs related to study drug, and significant AEs; and TLF contents.j

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 is provided for the enrolled analysis set.

6.4.1.1 Deaths

Deaths are identified from any of the following sources:

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

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

6.4.1.2 AE Overviews

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

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

- On-DBT for the DBT safety analysis set
- On-DBT for the DBT safety analysis set by subgroup level and overall for all high-level safety subgroups of interest described in Section 4.3.2 for each treatment group. Results support exploratory objective #17.
- Post-DBT pre-OL rimegepant for the interim safety analysis set
- On-OL rimegepant for the OL rimegepant safety analysis set

- On-OL rimegepant for the OL rimegepant safety analysis set by subgroup level and overall for all high-level safety subgroups of interest specified in Section 4.3.2. Results support exploratory objective #17.
- Follow-up for the follow-up safety analysis set.

6.4.1.3 On-DBT AEs

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

- AEs by worst intensity (other secondary objective #4) *
- AEs related to study drug by worst intensity
- SAEs (other secondary objective #4)
- Hepatic-related AEs (exploratory objective #13)
- Potential drug abuse AEs, displayed in alphabetical order by worst intensity and PT without SOC
- Cardiovascular AEs
- Suicidality AEs
- Hypertension AEs
- Hypertension AEs for subjects with medical history of hypertension.

Frequency tables of on-DBT AEs by SOC and PT display AEs in descending order of rimegepant frequency within SOC and PT.

Frequency tables of endpoints marked with "*" are also provided by subgroup level and overall for all high-level safety subgroups of interest specified in Section 4.3.2 for each treatment group. Results support exploratory objective #17.

6.4.1.4 Post-DBT Pre-OL Rimegepant AEs

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

- AEs by worst intensity
- SAEs.

6.4.1.5 On-OL Rimegepant AEs

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

- AEs by worst intensity (other secondary objective #4) *
- AEs related to study drug by worst intensity

- SAEs (other secondary objective #4)
- AEs leading to study drug discontinuation (other secondary objective #4)
- Hepatic-related AEs (exploratory objective #13)
- Hepatic-related AEs leading to study drug discontinuation (exploratory objective #14)
- Potential drug abuse AEs, displayed in alphabetical order by worst intensity and PT without SOC
- Cardiovascular AEs
- Suicidality AEs
- Hypertension AEs
- Hypertension AEs for subjects with medical history of hypertension.

Frequency tables of endpoints marked with "*" are also provided by subgroup level and overall for all high-level safety subgroups of interest specified in Section 4.3.2. Results support exploratory objective #17.

6.4.1.6 Follow-Up AEs

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

- AEs by worst intensity
- SAEs.

6.4.2 Laboratory Tests

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

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

- Hematology: Screening; Baseline; DBT EOT; and Week 12/EOT
- Serum chemistry: Screening; Baseline; DBT EOT; and Week 12/EOT. Exceptions are for the following:
  - LFTs (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], total bilirubin [TBL], direct bilirubin, indirect bilirubin): Screening; Baseline; DBT EOT; Week 4; and Week 12/EOT.

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

- Laboratory test results using the Common Terminology Criteria for Adverse Events/ Division of Acquired Immune Deficiency Syndrome (CTCAE/DAIDS) toxicity grading scale

(SI units). The listing displays all test results over time for subjects with grade 3 to 4 laboratory test abnormalities at any time point.

- Laboratory test results using the Food and Drug Administration (FDA) toxicity grading scale (US units). The listing displays all test results over time for subjects with grade 3 to 4 laboratory test abnormalities at any time point.
- LFT values and ratios to ULN (i.e., ALT, AST, TBL and ALP) 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.
- Pregnancy test results (SI units). The listing displays all test results over time for subjects with positive pregnancy tests at any time point.

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

6.4.2.1 Laboratory Test Abnormalities

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

- On-DBT for the DBT safety analysis set
- On-DBT for the DBT safety analysis set by subgroup level and overall for all high-level safety subgroups of interest described in Section 4.3.2 for each treatment group. Results support exploratory objective #17.
- Post-DBT pre-OL rimegepant for the interim safety analysis set
- On-OL rimegepant for the OL rimegepant safety analysis set
- On-OL rimegepant for the OL rimegepant safety analysis set by subgroup level and overall for all high-level safety subgroups of interest specified in Section 4.3.2. Results support exploratory objective #17.
- Follow-up for the follow-up safety analysis set.

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

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

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

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

6.4.2.2 Liver Function Test Elevations

Analysis use SI units.

LFT Elevations

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

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

Results support exploratory objective #16.

LFT Shifts From Baseline to Worst Elevation

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

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

LFT Plots

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

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

By-subject LFT line plots are provided for the safety analysis set with select LFT elevations in any safety analysis period. Study weeks are defined as study day/7, where study day is derived from the laboratory test collection date (see Section 7.3). Each figure also displays DB study drug and OL rimegepant dosing days using symbols along the x-axis, 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. Study drug dosing days are days on which study drug was taken, i.e., nonmissing study drug date.

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; EOT in the on-DBT safety analysis period; Week 4 (LFTs only), Week 12, and EOT in the on-OL rimegepant safety analysis period. Results for overall are displayed only at baseline and time points in the on-OL rimegepant safety analysis period.

Note that scheduled visits vary according to laboratory test.

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

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

6.4.3 Vital Signs and Physical Measurements

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

Refer to the Core SAP for TLF contents.

BMI is derived as (weight in kg)/(baseline height in m^2) at all time points that weight is collected, where baseline height is derived as per Section 6.2.5.

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; EOT in the on-DBT safety analysis period; each scheduled visit through Week 12 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 safety analysis period.

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

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

6.4.3.2 Vital Sign and Physical Measurement Abnormalities

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

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

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

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

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

6.4.4 Electrocardiograms

ECG parameters include RR, QRS, PR, QT, QTcF, and ventricular heart rate. ECGs are measured by the external source Clario at the following visits: Screening; DBT EOT; OLE Week 12/EOT.

Refer to the Core SAP for TLF contents.

6.4.4.1 ECG Changes From Baseline Over Time

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

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

6.4.4.2 ECG Abnormalities

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

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

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

6.4.5 C-SSRS

The C-SSRS is a clinician administered questionnaire used to help immediate risk of suicide. The C-SSRS is administered at the following visits: Screening; Baseline; DBT EOT; OLE Weeks 4 and 12/EOT. At the Screening Visit, the recall period for completing is (1) 12 months and lifetime for suicidal ideation and (2) 10 years and lifetime for suicidal behavior; at all other visits, the recall period for completing the C-SSRS is since the last visit.

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

- On-DBT for the DBT safety analysis set

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

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

6.4.6 Safety Narrative Subject Identifiers

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

- Death in any analysis period for the enrolled analysis set
- SAE on DB or OL rimegepant or during follow-up for the DB or OL rimegepant safety analysis set
- Non-SAE leading to study drug discontinuation in any analysis period for the DB or OL rimegepant safety analysis set
- Other significant non-SAE on DB or OL rimegepant or during follow-up for the DB or OL rimegepant safety analysis set:
  - Select hepatic-related AE, i.e., PT containing cirrhosis, drug-induced liver injury, hepatic failure, hepatitis, jaundice, or liver failure
  - Cardiovascular AE
  - Suicidality AE
  - Hypertension AE
  - Raynaud's phenomenon AE
- LFT elevation on DB or OL rimegepant or during follow-up for the DB or OL rimegepant safety analysis set:
  - ALT or AST > 3x ULN
  - ALT or AST > 3x ULN concurrent with TBL > 2x ULN
  - ALP or TBL > 2x ULN.

Refer to the Core SAP for additional details.

6.5 Outcomes Research

Analyses are based on as-randomized treatment group for the DBT and OLE efficacy analysis sets.

Outcomes research questionnaires and rating scales are as follows:

- MQoL: 24 hours post dose after the single qualifying migraine attack in the DBT Phase and each of the first 5 qualifying migraine attacks in the OLE Phase using the eDiary
- MSQ: Baseline and Week 12/EOT using CRFs
- MIBS: Baseline; Weeks 4, 8, and 12/EOT using CRFs.

MSQ and MIBS measurements are slotted into analysis periods and analysis visits using the following steps:

1. Measurements are slotted into the pretreatment and OLE outcomes research analysis periods.
2. Measurements are slotted into the analysis visits (Weeks 4, 8, and 12) in the OLE outcomes research analysis period (see Table 6).

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 MQoL

Impact of treatment on patient-reported quality of life is assessed using the MQoL Version 3.0, which is a 16-item questionnaire that has been validated in migraine patients to measure the short-term impact of treatment within 24 hours. The MQoL consists of 15 items across the following 5 domains: (1) work functioning; (2) social functioning; (3) energy/vitality; (4) migraine symptoms; (5) feelings/concerns. Item (Question) 16 measures overall change in migraine symptoms since taking study medication. See Section 7.4.4 for additional details.

6.5.1.1 Reliability of Rimegepant Effect in the OLE Phase

Reliability of rimegepant effect in the OLE Phase is assessed using the proportions of subjects achieving response after (1) the single EQMA in the DBT Phase (i.e., π_{DBT}) for the DBT efficacy analysis set randomized to rimegepant, and (2) each of the first 5 EQMAs ≥23 hours apart in the OLE Phase (i.e., π_{OLEi}, i =1, …, 5) for the OLE efficacy analysis set.

An EQMA is defined as a qualifying migraine attack (see Section 6.3.5.5) with a nonmissing MQoL Question 16 value at 24 hours postdose.

Reliability of rimegepant effect in the OLE Phase is defined as percentages for ≥4 of the first 5 EQMAs ≥23 hours apart in the OLE Phase being no more than 7% less than the percentage in the DBT Phase, i.e., $\pi_{DBT} - \pi_{OLEi} \leq 7\%$ for ≥ 4 of the 5 π_{OLEi}.

Response is defined as a category (value) of "moderately better" or "very much better" for MQoL Question 16 (overall change in migraine symptoms since taking study medication) at 24 hours postdose.

For a given EQMA, subjects who meet all the following criteria are classified as responders:

- MQoL Question 16 value of "moderately better" or "very much better" at 24 hours postdose, i.e, in the 24-hour postdose analysis window
- No rescue medication taken at or before the MQoL Question 16 value in the 24-hour postdose analysis window (see Section 7.5)

- No intervening OL rimegepant taken at or before the MQoL Question 16 value in the 24-hour postdose analysis window (see Section 7.7). This applies only to MQoLs in the OLE Phase.

For a given EQMA, subjects who are not responders are classified as failures. Failure criteria include any of the following:

- Rescue medication taken at or before the MQoL Question 16 value in the 24-hour postdose analysis window (RM=F; see Section 7.5)
- Intervening OL rimegepant taken at or before the MQoL Question 16 value in the 24-hour postdose analysis window (Intervening OL Rimegepant = Failure [IOL=F]; see Section 7.7). This applies only to MQoLs in the OLE Phase.
- MQoL Question 16 value of "A little better", "No change", "A little worse", "Moderately worse" or "very much worse" at 24 hours postdose.

Thus, for a given EQMA, subjects with missing MQoL Question 16 value at 24 hours postdose are excluded, i.e., missing MQoL Question 16 data are not imputed. For a given EQMA, the percentage is calculated against the number of evaluable subjects, i.e., those defined as responders or failures.

For the single EQMA in the DBT Phase, analyses are based on the DBT efficacy analysis set randomized to rimegepant with EQMA and MQoL eDiary measurement dates in the DBT Phase analysis period.

For the first 5 EQMAs ≥23 hours apart in the OLE Phase, analyses are based on the OLE efficacy analysis set with EQMA and MQoL eDiary measurement dates in the OLE outcomes research analysis period.

The RM=F algorithm (criterion 1 only) is applied to the single EQMA in the DBT Phase, and to the first 5 EQMAs ≥23 hours apart in the OLE Phase. For a given EQMA, subjects who take rescue medication at or before the MQoL measurement at 24 hours post dose are classified as failures.

The IOL=F algorithm is applied only to the first 5 EQMAs ≥23 hours apart in the OLE Phase. For a given EQMA, subjects who take intervening OL rimegepant at or before the MQoL measurement at 24 hours post dose are classified as failures.

See Section 9.3.1 for additional details.

Table of Reliability of Rimegepant Effect

The table of reliability of rimegepant effect displays the following for each EQMA by overall:

- Response rate (i.e., "n/N" and percentage; π_{DBT}; π_{OLEi}, i =1, …, 5), ASE, and 95% CI. For a given EQMA, the percentage is calculated against the number of evaluable subjects ("N"), i.e., those defined as responders or failures.

- Percentage difference $\pi_{DBT} - \pi_{OLEi}$ for each EQMA in the OLE Phase. Percentage differences <7% are identified.

A footnote defines the reliability of rimegepant effect, and states whether it was achieved. CIs are based on the normal approximation to the binomial distribution.

Results support other secondary objective #1.

The table of reliability of rimegepant effect is also produced using the first 5 EQMAs ≥47 hours apart in the OLE Phase as a sensitivity analysis.

Frequency Table of MQoL Overall Change in Migraine Symptoms Outcomes by EQMA

The frequency table of MQoL overall change in migraine symptoms (Question 16) outcomes displays the number and percentage of subjects by treatment group/OL rimegepant and overall in the following categories and subcategories at each EQMA:

- Responder (π_{DBT}; π_{OLEi}, i =1, …, 5)
  - Moderately better
  - Very much better
- Failure
  - Rescue medication taken at or before the MQoL Question 16 value at 24 hours postdose (RM=F)
  - Intervening OL rimegepant taken at or before the MQoL Question 16 value at 24 hours postdose (IOL=F). This subcategory applies only to MQoLs in the OLE Phase.
  - Very much worse
  - Moderately worse
  - A little worse
  - No change
  - A little better.

Subjects may be in either or both RM=F or IOL=F subcategories, but can only be in 1 of the last 5 failure subcategories (very much worse, …, a little better).

For a given EQMA, percentages are calculated against the number of evaluable subjects, i.e., those defined as responders or failures.

The frequency table of MQoL overall change in migraine symptoms outcomes is also produced using the first 5 EQMAs ≥47 hours apart in the OLE Phase as a sensitivity analysis.

6.5.1.2 MQoL Scores by EQMA During the DBT and OLE Phases

The table of MQoL total, domain, and overall change (Question 16) scores at 24 hours postdose by EQMA is provided for the DBT efficacy analysis set by treatment group/OL rimegepant and

overall after (1) the single EQMA in the DBT Phase, and (2) each of the first 5 EQMAs ≥23 hours apart in the OLE Phase. Results support exploratory objectives #1 and #2.

For the single EQMA in the DBT Phase, analyses are based on the DBT efficacy analysis set with MQoL eDiary measurement dates in the DBT Phase analysis period.

For the first 5 EQMAs ≥23 hours apart in the OLE Phase, analyses are based on OLE efficacy analysis set with MQoL eDiary measurement dates in the OLE outcomes research analysis period.

Refer to the Core SAP for the calculation of the MQoL total and domain scores, and TLF contents.

6.5.1.3 MQoL Overall Change in Migraine Symptoms During the OLE Phase Using Model Estimation

Analyses are based on the first 5 EQMAs ≥23 hours apart in the OLE Phase for the OLE efficacy analysis set with ≥1 MQoL in the OLE outcomes research analysis period.

A linear mixed effects model with repeated measures and the following attributes is used:

- Variables: MQoL Question 16 value as the dependent variable; imputed randomization stratum, categorical EQMA (i.e., 1 to 5 of the OLE Phase), rescue medication or intervening OL rimegepant use at or before the MQoL Question 16 value (yes, no), and migraine attack-by-rescue medication/intervening OL rimegepant use as fixed effects. If there are sparse data within a randomization stratum, then this variable may be excluded.
- Covariance structure for repeated measures accounting for within-subject correlated errors: unstructured. If the model fails to converge or cannot be fit with an unstructured covariance structure, then a first-order autoregressive with homogeneous variances ("AR(1)") structure is used.
- Standard error (SE) estimation method: Huber-White "sandwich" (refer to the Core SAP).

The table displays the following model estimates by EQMA: least-squares mean (LSM), SE, and 95% CI. See Section 9.3.2 for the SAS code.

A line plot with error bars displays the LSM MQoL overall change in migraine symptoms on the y-axis versus EQMA during the OLE Phase on the x-axis by rescue medication/intervening OL rimegepant use at or before the MQoL Question 16 value (yes, no). Error bars denote 95% CIs for LSMs.

6.5.2 MSQ

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

The table of values and changes from baseline in scores is provided by treatment group/OL rimegepant and overall for each domain for the OLE efficacy analysis set at the following time points: baseline; Week 12 of the OLE outcomes research analysis period. Results support exploratory objective #15.

The frequency table of MSQoL domain score increase from baseline categories is provided by treatment group and overall for the OLE efficacy analysis set at Week 12 of the OLE outcomes research analysis period.

6.5.3 MIBS

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

The table of values and changes from baseline in scores is provided by treatment group/OL rimegepant and overall for each domain for the OLE analysis set at the following time points: baseline; Weeks 4, 8, and 12 of the OLE outcomes research analysis period.

Results support other secondary objective #5.

7 CONVENTIONS

Conventions may be further modified in dataset specifications documents instead of the SAP as needed.

7.1 Derived Dates

Derived dates are defined as follows:

- eDiary measurement date: derived for each record in the raw eDiary as follows:
  - eDiary reported study medication date if nonmissing, for any parameter in the Migraine question category at the time of study drug dosing (see Section 7.4.1.1)eDiary manual DCF study medication date, if nonmissing in the Manual DCF Study Medication question category (see Section 7.4.1.2)
  - eDiary finding date otherwise.
- DBT Phase start date: earlier of the RTSM randomization date or DB study drug date. This is an analysis period reference date.
- Study drug date/time: derived from either of the 2 following eDiary sources:
  - Reported: nonmissing eDiary reported study medication date/time (see Section 7.4.1.1)
  - Manual DCF: nonmissing eDiary manual DCF study medication date (see Section 7.4.1.2)

- Study drug start date/time: earliest study drug date/time. This is an analysis period reference date.
- Study drug end date: latest study drug date
- 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 question "Did the subject complete the DBT Phase?" from the DB Subject Status CRF, and "no" response to the question "Will the subject continue into the OLE Phase?" from the DB Subject Status CRF, and missing OL rimegepant start date
    - (2) "yes" or "no" response to the question "Did the subject complete the OLE Phase?" from the OLE Subject Status CRF
  - Final database lock: study drug end date

  This is an analysis period reference date.
- First OL wallet dispensed date: earliest nonmissing wallet dispensed date with valid OL wallet ID from the Drug Accountability CRF (see Section 6.2.6.1)
- DB study drug date/time: earliest study drug date/time, if any of the following is met:
  - Earliest study drug date is before the first OL wallet dispensed date
  - Earliest study drug date is equal to the first OL wallet dispensed date, and 00:00 ≤ earliest study drug time < 07:00. First OL wallet dispensed date is missing.

  This is an analysis period reference date. DB study drug date/time can be either reported (time is not missing) or manual DCF (time is missing).
- OL rimegepant date/time: study drug date/time (1) with study drug date on or after the first OL wallet dispensed date and (2) not classified as the DB study drug date/time. Note that although rare, it is possible for subjects to have multiple records on the same date. OL rimegepant date/time can be either reported (time is not missing) or manual DCF (time is missing).
- OL rimegepant start date/time: earliest OL rimegepant date/time. This is an analysis period reference date.
- OL rimegepant end date: latest OL rimegepant date. This is used to define OL rimegepant exposure.
- OL rimegepant last date:
  - Before the final database lock: OL rimegepant end date defined only for subjects with "yes" or "no" response to question "Did the subject complete the OLE Phase?" from the OLE Subject Status CRF.
  - Final database lock: OL rimegepant end date.

  This is an analysis period reference date.

- DB or OL rimegepant start date/time: study drug start date/time for subjects whose as-treated DB treatment group is rimegepant; OL rimegepant start date/time 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 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.
- OLE Phase start date: earlier of (1) DBT EOT visit date from the Visit Date CRF, or (2) OL rimegepant start date. This is an analysis period reference date.
- OLE Phase end date: latest of (1) OLE Phase start date, (2) OL rimegepant end date, or (3) latest complete visit date on or after the OLE Phase start date through the Week 12/EOT visit date (excluding the Follow-Up Week 2 visit date) from the Visit Date and Unscheduled Visit Checklist CRFs
- OLE Phase last date:
  - Before the final database lock: OLE Phase end date defined only for subjects with nonmissing study drug last date
  - Final database lock: OLE Phase end date.

  This is an analysis period reference date.
- First DBT rescue medication date/time: This date is used to assess the key secondary efficacy endpoint of rescue medication use through 24 hours postdose during the DBT Phase and the RM=F algorithm during the DBT Phase, and is derived using the following steps:
  - Records that meet the definition of DBT rescue medication are selected with both nonmissing medication date and time (see Section 6.2.6.3).
  - The earliest medication date/time is selected.

  Note that date and time are not imputed.
- Imputed first DBT rescue medication date/time: This date is used to assess exploratory time-to-event efficacy endpoints during the DBT Phase, and is derived using the following steps:
  - Records that meet the definition of DBT rescue medication are selected with non-missing medication date (see Section 6.2.6.3).
  - If medication time is missing, then time is imputed as follows:
    - If medication date = DB study drug date and DB study drug time is non-missing, then medication time = DB study drug time.
    - Otherwise, medication time is set to "00:00".
  - The earliest medication date/time is selected.

  Note that date is not imputed.

- Last contact date: (1) earliest complete death date from AE CRFs, if it exists; (2) otherwise, the maximum complete date of the following: AE start or end; ECG; eDiary finding; eDiary manual DCF study medication, eDiary reported study medication; informed consent; RTSM randomization; laboratory collection; nonstudy medication start or end; OLE Phase eligibility contact; physical measurement; procedure; rating scale; rescue medication; questionnaire; vital sign; visit. If the last contact date is after the most recent raw database creation date, then it is set to the most recent raw database creation date.
- Death date: refer to the Core SAP.

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

Missing time is considered to be earlier than nonmissing time on the same date.

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 as follows:

- General
  - Screening Phase:
    - If the DBT Phase start date is nonmissing: measurement date before the DBT Phase start date
    - If the DBT Phase start date is missing: measurement date

    This period is used to derive analysis visit windows for safety endpoints during the Screening Phase.
  - DBT Phase:
    - If the OLE Phase start date is nonmissing: measurement date on or after the DBT Phase start date through {OLE Phase start date – 1 day}
    - If the OLE Phase start date is missing: measurement date on or after the DBT Phase start date

    This period is used to assess efficacy endpoints and outcomes research MQoL endpoints during the DBT Phase, and also to derive analysis visit windows for safety endpoints during the DBT Phase.
  - OLE Phase:
    - If the OLE Phase last date is nonmissing: measurement date on or after the OLE Phase start date through the OLE Phase last date
    - If the OLE Phase last date is missing: measurement date on or after the OLE Phase start date

This period is used to assess efficacy endpoints during the OLE Phase, and also to derive analysis visit windows for safety endpoints during the OLE Phase.

- Follow-up Phase: measurement date on or after the OLE Phase last date.

- Pretreatment characteristics and safety endpoints
  - Pretreatment:
    - If the study drug start date is nonmissing: measurement date/time on or before the study drug start date/time.
    - If the study drug start date is missing: measurement date/time.

    This period is abbreviated as "PRETRT" in listings, and is used to derive baseline values. Note that AEs with imputed start date equal to the study drug start date are NOT part of this period.
  - On-DBT safety:
    - If the OL rimegepant start date is nonmissing: measurement date/time after the DB study drug date/time through the earlier of DB study drug date + 9 days and OL rimegepant start date/time
    - If the OL rimegepant start date is missing: measurement date/time after the DB study drug date/time

    This period is abbreviated as "DBT" in safety listings, and is used to assess safety endpoints on DBT for the DBT safety analysis set. The 9-day cut reflects the protocol-defined visit window of 7 (+2) days after DB study drug dosing for the DBT EOT Visit. Note that AEs with imputed start date equal to the DB study drug date are part of this period, and AEs with imputed start date equal to the OL rimegepant start date are NOT part of this period.
  - Post-DBT pre-OL rimegepant safety: measurement date after the DB study drug date + 9 days through the OL rimegepant start date/time.

    This period is abbreviated as "INT" in safety listings, and is used to assess safety endpoints during the interim period (i.e., post-DBT pre-OL rimegepant) for the interim safety analysis set (i.e., those with >9-day gap between DB study drug date and OL rimegepant start date). Note that AEs with imputed start date equal to the OL rimegepant start date are NOT part of this period.
  - On-OL rimegepant safety:
    - If the OL rimegepant last date is nonmissing: measurement date/time after the OL rimegepant start date/time through the OL rimegepant last date + 9 days
    - If the OL rimegepant last date is missing: measurement date/time after the OL rimegepant start date/time

    This period is abbreviated as "OLRMG" in safety listings, and is used to assess safety endpoints on OL rimegepant for the OL rimegepant safety analysis set. Note that AEs with imputed start date equal to the OL rimegepant start date are part of this period.

- On-DB or OL rimegepant safety:
  - If the DB or OL rimegepant last date is not missing: measurement date/time after the DB or OL rimegepant start date/time through the DB or OL rimegepant last date + 9 days
  - If the DB or OL rimegepant last date is missing: measurement date/time after the DB or OL rimegepant start date/time

  This period is used to assess safety endpoints on DB or OL rimegepant for the DB or OL rimegepant safety analysis set. Note that AEs with imputed start date equal to the DB or OL rimegepant start date are part of this period.
- Follow-up safety: measurement date after the study drug last date + 9 days. This period is abbreviated as "FU" in safety listings, and is used to assess safety endpoints during follow-up for the follow-up safety analysis set.
- OLE outcomes research: assessment date/eDiary measurement date on or after the OLE Phase start date. This period is used to assess outcomes research MQoL, MSQ, and MIBS endpoints.

See Section 7.1 for derived date/times for determining analysis periods.

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

7.3 Analysis Visit Windows

Study days are calculated from the DBT Phase start date as follows:

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

DBT days are calculated from the DB study drug start date as follows:

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

OLE days are calculated from the OLE Phase start date as follows:

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

OL rimegepant days are calculated from the OL rimegepant start date as follows:

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

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

Follow-up days are calculated from the OLE Phase last date as follows:

- Measurement date – OLE Phase last date + 1, if measurement date ≥ OLE Phase last date + 1
- Measurement date – OLE Phase last date, if measurement date < OLE Phase last date + 1.

General analysis visit windows (e.g. for safety parameters, MSQ, MIBS) are shown in Table 6.

Table 6 General Analysis Visit Windows

Analysis Period Analysis Visit	Abbreviation in Listings	Analysis Day Analysis Visit Window	Target Day
Screening Phase		**Study Day**	
Screening *		≤-1	
Baseline *		1	
Post-randomization @	Postrand	≥2	
DBT Phase		**Study Day**	
DBT EOT		≥2	
OLE Phase/OLE Outcomes Research		**OLE Day**	
Week 2		1 to 21	14
Week 4		22 to 42	28
Week 8		43 to 70	56
Week 12		71 to 98	84
Extension @	OLE Ext	≥99	
Follow-Up Phase			
Follow-Up Week 2	FU Week 2	1 to 21	14
Follow-Up Extension @	FU Ext	≥22	

* 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

7.4 eDiary Data

The eDiary has the following question categories and key parameters which are used during the DBT and OLE Phases:

- Migraine question category:
  - Study medication parameters, from which the eDiary reported study medication date/time is derived (see Section 7.4.1.1)
  - Migraine characteristics parameters (see Section 7.4.2)

- Other medication taken to treat headache or aura status (yes or no).

- Headache (Non-migraine) question category: headache (nonmigraine) characteristics parameters (OLE Phase only; see Section 7.4.3)
- MQoL question category: MQoL question parameters at 24 hours postdose (see Section 7.4.4)
- Manual DCF Study medication question category: manual DCF study medication date (see Section 7.4.1.2).

A set of eDiary parameters is defined as those with the same eDiary finding date/time and eDiary completion date/time. The eDiary finding date/time is an internal date/time that is derived by YPrime after the subject answers the first question in the set. The eDiary completion date/time is an internal date/time that is derived by YPrime after the subject answers the last question in the set and saves the results.

Refer to the latest versions of the YPrime C4951004 Data Transfer Specification and eCOA System Requirements Document for additional details.

7.4.1 eDiary Study Medication

7.4.1.1 eDiary Reported Study Medication Date/time

The raw eDiary dataset has a reported study medication date/time parameter (DOSDATIM) with a value that is derived by YPrime from data entered by subjects in study medication parameters the Migraine question category. Date and time are both nonmissing.

Each distinct reported study medication date/time is derived from a distinct set of Migraine question category parameters at the time of prospective or retrospective study drug dosing.

A set of Migraine question category parameters at the time of prospective study drug dosing is defined as one in which (1) there is a "no" response to the eDiary question about already taking study medication, and (2) there is a "yes" response to the eDiary question about confirming that study medication was taken, and (3) eDiary planned time point is missing. The reported study medication date/time is derived by YPrime as the eDiary completion date/time.

A set of Migraine question category parameters at the time of retrospective study drug dosing is defined as one in which (1) there is a "yes" response to the eDiary question about already taking study medication, and (2) eDiary planned time point is missing. Subjects may enter study medication parameters retrospectively on or 1 day before the eDiary finding date as follows:

- During the DBT Phase, subjects must first report taking study medication either "today" or "other".
  - If the response is "today", then subjects must report the study medication time. The eDiary considers the date for "today" to be the same date as the corresponding eDiary finding date.

- If the response is "other", then subjects must report both the study medication date and time.

- During the OLE Phase, subjects must report both the study medication date and time.

The reported study medication date/time is derived by YPrime from these subject-reported study medication parameter values, and seconds are set to "00". Each distinct set of Migraine question category parameters at the time of study drug dosing is linked to a distinct eDiary reported study medication date/time as follows:

- A set of Migraine question category parameters at the time of retrospective study drug dosing is checked against eDiary reported study medication date/times. If the subject-reported study medication parameter values (with seconds of "00") match the date/time components of a reported study medication date/time, then the set of Migraine question category parameters is considered linked to that "retrospective" eDiary reported study medication date/time.
- A set of Migraine question category parameters at the time of prospective study drug dosing is checked against reported study medication date/times that have not been already linked to Migraine question category parameters at the time of retrospective study drug dosing. If the eDiary completion date/time of the set of Migraine question category parameters matches an eDiary reported study medication date/time within ± 1 second, then the set of Migraine question category parameters is considered linked to that "prospective" eDiary reported study medication date/time.

For each reported study medication date/time record with distinct eDiary finding date/time, it is assumed that the subject took 1 tablet of study drug for that record.

The reported study medication date/time is used by the eDiary to collect (1) postdose data at 15 minutes through 48 minutes in the Migraine question category during the DBT Phase, and (2) MQoL data at 24 hours postdose in the MQoL question category during the DBT and OLE Phases.

7.4.1.2 eDiary Manual DCF Study Medication Date

The raw eDiary dataset has a manual DCF study medication date parameter (MDOSDAT) with a value that is entered by YPrime into the Manual DCF Study Medication question category. The data are provided from manual DCFs by sites on days subjects took study medication without using the eDiary.

For each manual DCF date record with distinct eDiary finding date/time, it is assumed that the subject took 1 tablet of study drug for that record.

The manual DCF medication date is not used by the eDiary to collect postdose data.

7.4.2 eDiary Migraine Characteristics

The following migraine characteristics parameters are collected in the Migraine question category (1) at the time of dosing during the DBT Phase and OLE Phases, and (2) at planned

time points postdose from 15 minutes through 48 hours (e.g., 15, 30, 45, 60, and 90 minutes; 2, 3, 4, 6, 8, 24 and 48 hours) during the DBT Phase for a single migraine attack:

- Migraine headache pain intensity (none, mild, moderate, severe)
- MBS (nausea, phonophobia, photophobia). Collected only before dosing (i.e., when there is a "no" response to the question about study medication already taken) during the DBT Phase.
- Nausea status (present, absent)
- Nausea intensity (mild, moderate, severe), if nausea status is present
- Phonophobia status (present, absent)
- Phonophobia intensity (mild, moderate, severe), if phonophobia status is present
- Photophobia status (present, absent)
- Photophobia intensity (mild, moderate, severe), if photophobia status is present
- Functional disability level (normal, mildly impaired, severely impaired, requires bedrest)
- Aura preceding or accompanying headache status (yes, no). Collected only at the time of dosing.

During the OLE Phase, the eDiary also collects migraine headache pain intensity regardless of study drug dosing.

Note that parameters collected "at the time of dosing" or without dosing in the Migraine question category have missing planned time point (see Section 7.4.1.1).

During the DBT Phase, the eDiary allows subjects to report 1 set of migraine characteristics parameters per planned time point.

During the OLE Phase, the eDiary allows subjects to report 1 set of migraine characteristics parameters per migraine attack per day. However, once a subject reports having a qualifying migraine attack on a given day (see Section 7.4.4), no additional sets of parameters can be reported that day. Thus, subjects may have multiple sets of migraine characteristics parameters (regardless of study drug dosing) on the same eDiary measurement date.

Analysis windows for postdose efficacy measurements (15, 30, 45, 60, 90 minutes; 2, 3, 4, 6, 8, 24, and 48 hours) during the DBT Phase are presented in Table 7. Postdose measurements are slotted into analysis windows using the difference between the reported DB study drug date/time and the eDiary finding date/time of the postdose measurement (see Sections 7.1 and 7.4.1.1).

The raw eDiary dataset contains a variable for planned time point with values that correspond to the analysis window target times.

Table 7 eDiary Automated Efficacy Analysis Windows

Planned Time Point Postdose	Analysis-Specified Interval
15 minutes	>10 to <21 minutes
30 minutes	>25 to <36 minutes
45 minutes	>40 to <51 minutes
60 minutes	>55 to <66 minutes
90 minutes	>85 to <96 minutes
2 hours	>1 hour 55 minutes to <2 hours 16 minutes
3 hours	>2 hours 45 minutes to <3 hours 16 minutes
4 hours	>3 hours 45 minutes to <4 hours 16 minutes
6 hours	>5 hours 45 minutes to <6 hours 16 minutes
8 hours	>7 hours 45 minutes to <8 hours 16 minutes
24 hours	>23 to <25 hours 1 minute
48 hours	>47 to <49 hours 1 minute

7.4.3 eDiary Nonmigraine Headache Characteristics

The eDiary collects the following nonmigraine headache characteristics parameters in the Headache (Non-migraine) question category:

- Headache (nonmigraine) status (yes)
- Headache pain intensity (none, mild, moderate, severe).

The eDiary allows subjects to report 1 set of nonmigraine headache characteristics parameters per day.

These records have missing planned time point.

Note that the eDiary allows subjects to report both nonmigraine headache characteristics and migraine characteristics parameters on the same date.

7.4.4 eDiary MQoL

The eDiary collects MQoL data at 24 hours postdose in the MQoL question category using the same analysis window as for 24-hour postdose migraine characteristics (see Table 7) in both the DBT and OLE Phases. The eDiary does not allow subjects to skip questions in the MQoL before saving the results.

- During the DBT Phase, the set of MQoL parameters is slotted into the 24-hour postdose analysis window using the difference between the reported DB study drug date/time and the eDiary finding date/time of the MQoL set (see Sections 7.1 and 7.4.1.1).

- During the OLE Phase, each distinct set of MQoL parameters is slotted into a 24-hour postdose analysis window using the difference between a reported OL rimegepant date/time and the eDiary finding date/time of the MQoL set (see Sections 7.1 and 7.4.1.1).

The eDiary collects MQoL data at 24 hours postdose in the MQoL question category only once during the DBT Phase, and up to 5 times during the OLE Phase.

Note that due to retrospective study drug dosing entry, subjects may have multiple sets of MQoL parameters in the same 24-hour postdose analysis window or on the same eDiary finding date during the OLE Phase.

Refer to the Core SAP for additional details about MQoL.

7.5 RM=F Algorithm

Efficacy measurements that are affected by the RM=F algorithm are migraine headache pain intensity, nausea status, photophobia status, phonophobia status, and functional disability level. Outcomes research measurements that are affected by the RM=F algorithm are MQoL Question 16, which is used to assess the reliability of rimegepant effect in the OLE Phase.

Let X denote a postdose time point: 15, 30, 45, 60, or 90 minutes; 2, 3, 4, 6, 8, 24, or 48 hours.

For a given measurement at time point X, the objective is to determine whether any rescue medication is taken at or before that measurement, even if the measurement is missing.

- For endpoints during the DBT Phase, the first DBT rescue medication date/time is compared to the reported DB study drug date/time and its corresponding postdose eDiary finding date/time for the measurement at time point X.
- For endpoints during the OLE Phase, all OLE rescue medication date/times are compared to each distinct reported OL rimegepant date/time and its corresponding postdose eDiary finding date/time for the measurement at time point X.

See Section 7.1 for the definitions of the reported DB study drug date/time, reported OL rimegepant date/time, and first DBT rescue medication date/time. See Section 6.2.6.3 for the definition of OLE rescue medications.

7.5.1 RM=F Algorithm During the DBT Phase

No DBT Rescue Medication Taken at or Before the Measurement in the X Analysis Window

No DBT rescue medication taken at or before the measurement in the X analysis window is defined as any of the following when the measurement is nonmissing in the X analysis window:

- No DBT rescue medication ever taken, i.e., missing first DBT rescue medication date (see Section 7.1)
- First DBT rescue medication date/time > {eDiary finding date/time for the measurement in the X analysis window}, if first DBT rescue medication time is not missing

- First DBT rescue medication date > {eDiary finding date for the measurement in the X analysis window}, if first DBT rescue medication time is missing.

DBT Rescue Medication Taken at or Before Time Point X (RM=F)

DBT rescue medication taken at or before time point X (RM=F) is defined as either (1) or (2):

1) DBT rescue medication taken at or before the measurement in the X analysis window. Defined as either of the following if the measurement is nonmissing in the X analysis window:
   - First DBT rescue medication date/time ≤ {eDiary finding date/time for the measurement in the X analysis window}, if first DBT rescue medication time is not missing
   - First DBT rescue medication date ≤ {eDiary finding date for the measurement in the X analysis window}, if first DBT rescue medication time is missing
2) DBT rescue medication taken at or before time point X and the measurement is missing in the X analysis window. Defined as either of the following:
   - (first DBT rescue medication date/time – reported DB study drug date/time) < upper bound of the X analysis window (see Table 7), if first DBT rescue medication time is not missing
   - First DBT rescue medication date ≤ reported DB study drug date + Y days, if first DBT rescue medication time is missing
     - If X < 24 hours, then Y = 0.
     - If X = 24 hours, then Y = 1.
     - If X = 48 hours, then Y = 2.

Note that criterion (2) is used only in sensitivity analyses of the primary efficacy endpoint (see Section 6.3.2.2).

7.5.2 RM=F Algorithm During the OLE Phase

During the OLE Phase, subjects may have multiple reported OL rimegepant date/times and multiple OLE rescue medication date/times.

Let [reported OL rimegepant date/time, MQoL eDiary finding date/time] denote an interval, where the MQoL data have been slotted into a 24-hour postdose analysis window based on the reported OL rimegepant date/time and MQoL eDiary finding date/time (see Section 7.4.4).

No OLE Rescue Medication Taken at or Before the MQoL Measurement in the 24-Hour Postdose Analysis Window

No OLE rescue medication taken at or before the nonmissing MQoL measurement in the 24-hour postdose analysis window is defined as any of the following when the measurement is nonmissing in the 24-hour postdose analysis window:

- There does not exist any OLE rescue medication date/time such that reported OL rimegepant date/time < OLE rescue medication date/time ≤ MQoL eDiary finding date/time, if OLE rescue medication time is not missing.
- There does not exist any OLE rescue medication date such that reported OL rimegepant date ≤ OLE rescue medication date ≤ MQoL eDiary finding date, if OLE rescue medication time is missing.

OLE Rescue Medication Taken at or Before the MQoL Measurement in the 24-Hour Postdose Analysis Window (RM=F)

OLE rescue medication taken at or before the nonmissing MQoL measurement in the 24-hour postdose analysis window (RM=F) is defined as any of the following when the measurement is nonmissing in the 24-hour postdose analysis window:

- There exists ≥1 OLE rescue medication date/time such that reported OL rimegepant date/time < OLE rescue medication date/time ≤ MQoL eDiary finding date/time, if OLE rescue medication time is not missing.
- There exists ≥1 OLE rescue medication date such that reported OL rimegepant date ≤ OLE rescue medication date ≤ MQoL eDiary finding date, if OLE rescue medication time is missing.

7.6 Nonstudy Medication Types

See Section 7.1 for derived dates.

DBT Concomitant Medications

DBT concomitant medications are defined as nonstudy medications taken within 9 days after DB study drug dosing and before the first dose of OL rimegepant, i.e., those meeting any of the following criteria:

- DB study drug date ≤ imputed start or imputed end date ≤ minimum {DB study drug date + 9 days; OL rimegepant start date − 1 day}
- DB study drug date ≤ imputed start or imputed end date ≤ DB study drug date + 9 days, if OL rimegepant start date is missing
- Imputed start date ≤ DB study drug date ≤ minimum {DB study drug date + 9 days; OL rimegepant start date − 1 day} ≤ imputed end date
- Imputed start date ≤ DB study drug date ≤ DB study drug date + 9 days ≤ imputed end date, if OL rimegepant start date is missing.

The 9-day window is chosen to align with the on-DBT safety analysis period (see Section 7.2).

Post-DBT Pre-OL Rimegepant Medications

Post-DBT pre-OL rimegepant medications are defined as nonstudy medications taken after DB study drug dosing + 9 days and before the first dose of OL rimegepant, i.e., those meeting any of the following criteria:

- DB study drug date + 9 days < imputed start or imputed end date < OL rimegepant start date
- Imputed start date < DB study drug date + 9 days < OL rimegepant start date < imputed end date.

OL Rimegepant Concomitant Medications

OL rimegepant concomitant medications are defined as nonstudy medications taken from the first dose of OL rimegepant through the last dose of OL rimegepant + 9 days, i.e., those meeting any of the following criteria:

- OL rimegepant start date ≤ imputed start or imputed end date ≤ OL rimegepant last date + 9 days
- OL rimegepant start date ≤ imputed start or imputed end date, and OL rimegepant last date is missing
- Imputed start date ≤ OL rimegepant start date ≤ OL rimegepant last date + 9 days ≤ imputed end date
- Imputed start date ≤ OL rimegepant start date ≤ imputed end date, and OL rimegepant last date is missing.

The 9-day window is chosen to align with the on-OL rimegepant safety analysis period (see Section 7.2).

Follow-Up Medications

Follow-up medications are defined as nonstudy medications taken after study drug discontinuation + 9 days, i.e., study drug last date + 9 days < imputed start date or imputed end date.

7.7 IOL=F Algorithm During the OLE Phase

Outcomes research measurements that are affected by the IOL=F algorithm are MQoL Question 16, which is used to assess the reliability of rimegepant effect in the OLE Phase.

During the OLE Phase, subjects may have multiple reported OL rimegepant date/times and multiple manual DCF OL rimegepant dates (see Section 7.1).

Let [reported OL rimegepant date/time_i, MQoL eDiary finding date/time] denote an interval, where the MQoL data have been slotted into a 24-hour postdose analysis window based on the ith reported OL rimegepant date/time_i and MQoL eDiary finding date/time (see Section 7.4.4).

No Intervening OL Rimegepant Taken at or Before the MQoL Measurement in the 24-Hour Postdose Analysis Window

No intervening OL rimegepant taken at or before the MQoL measurement in the 24-hour postdose analysis window is defined as any of the following when the measurement is nonmissing in the 24-hour postdose analysis window:

- There does not exist any reported OL rimegepant date/time_j such that reported OL rimegepant date/time_i < OL rimegepant date/time_j ≤ MQoL eDiary finding date/time, where $i \neq j$.
- There does not exist any manual DCF OL rimegepant date such that reported OL rimegepant date_i ≤ manual DCF OL rimegepant date ≤ MQoL eDiary finding date.

Intervening OL Rimegepant Taken at or Before the MQoL Measurement in the 24-Hour Postdose Analysis Window (IOL=F)

Intervening OL rimegepant taken at or before the MQoL measurement in the 24-hour postdose analysis window (IOL=F) is defined as any of the following when the measurement is nonmissing in the 24-hour postdose analysis window:

- There exists ≥1 reported OL rimegepant date/time_j such that reported OL rimegepant date/time_i < OL rimegepant date/time_j ≤ MQoL eDiary finding date/time, where $i \neq j$.
- There exists ≥1 manual DCF OL rimegepant date such that reported OL rimegepant date_i ≤ manual DCF OL rimegepant date ≤ MQoL eDiary finding date.

8 CONTENT OF REPORTS

8.1 PCD Final CSR

The following TLFs are produced for the PCD Final CSR (see Section 1.2):

- Section 6.2 Study Population: all TLFs
- Section 6.3 Efficacy: listing; tables of endpoints during the DBT Phase, i.e., those in Sections 6.3.1, 6.3.2, 6.3.3, 6.3.5.1, 6.3.5.2, and 6.3.5.3
- Section 6.3 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. No subgroup analyses.
  - Follow-up safety analysis period: tables of AE overview, AEs by worst intensity, and SAEs

- Section 6.4 Outcomes Research: table of MQoL total and domain scores at 24 hours postdose during the DBT Phase.

8.2 LSLV Final CSR

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

9 APPENDICES

9.1 Relevant Protocol Deviations

Relevant eligibility protocol deviations include the following categories:

- Previously treated with study drug in another BHV3000 (C495) multiple-dose study. Defined as subjects with (1) previous BHV3000 study subject identifiers from the Informed Consent/Demographic CRF, and (2) who took ≥1 dose of study drug (e.g., rimegepant or placebo) in a multiple-dose study.
- Randomized or treated with study drug under >1 subject identifier. These are identified from a Microsoft Excel file of protocol deviations extracted from the clinical trial management system (CTMS) by Sponsor Clinical Operations.
- No history of documented failure to ≥2 triptan medications or documented contraindication to the use of triptans (see Section 6.2.5.2)
- Migraine history issue, defined as any of the following subcategories:
  - ≤3 or ≥15 migraine days per month of any pain intensity in the 3 months prior to screening
  - ≥15 headache days per month in the 3 months prior to screening
  - ≥7 nonmigraine headache days per month in the 3 months prior to screening, if originally consented to Protocol Version 3 or higher. Defined as {number of headache days per month in the 3 months prior to screening} – {number of migraine days per month of any pain intensity in the 3 months prior to screening}.

  These are based on the Migraine History CRF.
- Finding out of range during pretreatment, defined any as any of the following subcategories:
  - Females with a positive pregnancy test (see Section 6.4.2)
  - Estimated glomerular filtration rate (eGFR) according to the re-expressed abbreviated (4-variable) Modification of Diet in Renal Disease (MDRD) Study equation ≤40 mL/min/1.73m^2, if originally consented to Protocol Version 3 or lower *
  - eGFR according to the re-expressed abbreviated (4-variable) MDRD Study equation <30 mL/min/1.73m^2, if originally consented to Protocol Version 4 or higher *
  - BMI ≥33 kg/m^2, if originally consented to Protocol Version 2 or lower *
  - BMI ≥35 kg/m^2, if originally consented to Protocol Version 3 or higher *

- C-SSRS suicidal ideation with active intent or plan to act, or suicidal behavior present. Defined as having a "yes" response to any of the following C-SSRS questions during pretreatment:
  - Suicidal ideation question 4 (active suicidal ideation with some intent to act, without specific) or 5 (active suicidal ideation with specific plan and intent)
  - Suicidal behavior question 1 (actual attempt), 3 (interrupted attempt), 4 (aborted attempt), 5 (preparatory acts or behavior), or 6 (suicidal behavior).

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

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

Relevant subject management protocol deviations include the following categories:

- Randomization stratum discrepancies between the RTSM system and actual data, defined as any of the following subcategories:
  - RTSM value of "yes" and CRF value of "no" or missing
  - RTSM value of "no" and CRF value of "yes" or missing.

  See Section 6.2.5.1 for history of clinically relevant CV disease status.
- Prophylactic migraine medication started or ended from 3 months before informed consent to randomization. Defined as either of the following:
  - informed consent date – 90 days ≤ imputed nonstudy medication start date ≤ RTSM randomization date
  - informed consent date – 90 days ≤ imputed nonstudy medication end date ≤ RTSM randomization date and nonstudy medication ongoing status is not "yes".

  See Section 6.2.6.3 for prophylactic migraine medications.
- DB study drug dosing noncompliance, defined as any of the following subcategories (see Section 6.2.6.2):
  - DB study drug taken but not randomized
  - DB study drug taken without having a qualifying migraine attack
  - DB study drug actually received different from randomized treatment assignment.
- OL rimegepant dosing noncompliance, defined as any of the following subcategories (see Section 6.2.6.2):
  - >1 OL rimegepant tablet taken on any 1 day
  - OL rimegepant taken without having a qualifying migraine attack
  - OL rimegepant taken but DB study drug never taken.
- Prohibited nonstudy medication taken on or after informed consent, defined as any of the following subcategories:

- Botulinum toxin type A
- Calcitonin gene-related peptide (CGRP) antagonist monoclonal antibody or small molecule #
- Ergotamine
- Lamotrigine
- Narcotic (barbiturate or opioid) #
- Paracetamol-containing product not taken as acute headache medication #. Defined as (1) preferred named name containing "paracetamol", and (2) not categorized as nonstudy acute headache medication (see Section 6.2.6.3).
- Select moderate or strong cytochrome P450 3A4 (CYP3A4) inducer #
- Select strong CYP3A4 inhibitor #
- Triptan #.

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

- DBT rescue medication usage issue, defined as any of the following subcategories:
  - DBT rescue medication taken at or before 2 hours postdose #. Defined as first DBT rescue medication date/time – DB study drug date/time ≤ 2 hours, where both first DBT rescue medication date/time and DB study drug date/time must have nonmissing date and time. Note that the upper bound of the 2-hour postdose analysis window is not used.
  - Nonpermitted DBT rescue medication taken #. Identified from the latest version of C495 Permitted Acute Migraine Medication.xlsx or equivalent.
  - Paracetamol >2000 mg taken on any 1 day as DBT rescue medication. Paracetamol may be a single drug or a component in any combination drug.
- OLE rescue medication usage issue, defined as any of the following subcategories:
  - Nonpermitted OLE rescue medication taken #
  - Paracetamol >2000 mg taken on any 1 day as OLE rescue medication. Paracetamol may be a single drug or a component in any combination drug.

For the subcategories marked with "#", preferred names are displayed alphabetically as additional subcategories. Refer to the Core SAP for additional details about prohibited nonstudy medication and permitted acute migraine (rescue) medication.

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

The protocol version to which subjects consented is determined from the Inclusion/Exclusion Criteria CRF.

9.2 Efficacy Day During the OLE Phase

For a given subject, each date during the OLE Phase analysis period is assessed whether it is an acute migraine medication day, acute migraine-specific medication day, or migraine day. Dates during the OLE Phase analysis period are defined by the interval [OLE Phase start date, OLE Phase end date] inclusive. See Section 7.1 for derived dates.

9.2.1 Medication Day During the OLE Phase

9.2.1.1 Acute Migraine Medication Day During the OLE Phase

Acute migraine (rescue or non-rescue) medication days are identified from nonstudy medication CRF data and eDiary data.

Nonstudy acute headache medications taken during the OLE Phase and eDiary measurement dates during the OLE Phase are selected (see Sections 6.2.6.3 and 7.1).

Let X denote a date in the OLE Phase interval defined in Section 9.2. Then X is classified as an acute migraine medication day during the OLE Phase if any of the following criteria is met:

- X is an acute migraine-specific medication day (see Section 9.2.1.2)
- X is a migraine day (see Section 9.2.2) on which any of the following also occur:
  - Imputed medication start date ≤ X ≤ imputed medication end date, if any given select nonstudy acute headache medication has medication frequency of QD, BID, TID, QID, QAM, or QHS
  - X is equal to the imputed start date or imputed end date, if any given select nonstudy acute headache medication does not have medication frequency of QD, BID, TID, QID, QAM, or QHS
  - X is an eDiary measurement date with "yes" response to the question about other medication taken to treat headache or aura from the eDiary Migraine question category (see Section 7.4).

All select nonstudy medication records and eDiary measurement dates are compared to X to determine whether X is an acute migraine medication day.

Acute migraine medication days are a subset of migraine days (see Section9.2.2).

9.2.1.2 Acute Migraine-Specific Medication Day During the OLE Phase

Acute migraine-specific medication days are identified from nonstudy medication CRF data and eDiary data.

Nonstudy acute migraine-specific medications taken during the OLE Phase and OL rimegepant dates are selected (see Sections 6.2.6.3 and 7.1).

Let X denote a date in the OLE Phase interval defined in Section 9.2. Then X is classified as an acute migraine-specific medication day during the OLE Phase if any of the following criteria is met:

- Imputed medication start date ≤ X ≤ imputed medication end date, if any given select medication has medication frequency of QD, BID, TID, QID, QAM, or QHS
- X is equal to the imputed start date or imputed end date, if any given select medication does not have medication frequency of QD, BID, TID, QID, QAM, or QHS
- X is an OL rimegepant date.

All select nonstudy medication records and OL rimegepant dates are compared to X to determine whether X is an acute migraine-specific medication day.

Acute migraine-specific medication days are a subset of acute migraine medication days and migraine days (see Sections 9.2.1.1 and 9.2.2).

9.2.2 Migraine Day During the OLE Phase

Let X denote a date in the interval defined in Section 9.2. Then X is classified as a migraine day during the OLE Phase if either of the following criteria is met:

- X is an eDiary measurement date with migraine headache pain intensity of mild, moderate, or severe from the eDiary Migraine question category (see Section 7.4.2)
- X is an acute migraine-specific medication day (see Section 9.2.1.2).

If there are multiple headache pain intensities from the Migraine or Headache (Non-migraine) question category on the same eDiary measurement date that is a migraine day, then the worst (greatest) headache pain intensity is selected based on the hierarchy of severe, moderate, or mild.

9.3 Analyses of Reliability of Rimegepant Effect in the OLE Phase

9.3.1 EQMAs

A qualifying migraine attack is defined as an attack of moderate or severe migraine headache pain intensity that is first treated with study drug. Each qualifying migraine attack is derived from a distinct set of Migraine question category parameters at the time of study drug dosing that has both of the following parameter values in the same set:

1) Migraine headache pain intensity of moderate or severe
2) Other medication taken to treat headache or aura status of "no".

The set of Migraine question category parameters at the time of study drug dosing is linked to an eDiary reported study medication date/time (see Sections 7.4 and 7.4.1.1).

An EQMA is defined as a qualifying migraine attack in the appropriate phase analysis period (DBT or OLE) with a nonmissing MQoL Question 16 value at 24 hours postdose in the appropriate outcomes research analysis period (DBT or OLE). The eDiary measurement date/time for a given qualifying migraine attack is the eDiary reported study medication

date/time to which it is linked, and is used to determine whether there is a nonmissing MQoL Question 16 value in the corresponding 24-hour analysis window (see Section 7.4.4) in the outcomes research analysis period. If a subject has >1 MQoL set in the same analysis window, then the MQoL set with the earliest eDiary finding date/time and nonmissing MQoL Question 16 value in the outcomes research analysis period is selected for that qualifying migraine attack.

During the OLE Phase, the first 5 EQMAs ≥ X hours apart in the OLE Phase are identified as follows:

1) All EQMAs during the OLE Phase are sorted by the (1) eDiary measurement date (ignoring time), and (2) eDiary finding date/time.
2) If a subject has >1 EQMA on the same eDiary measurement date, then the EQMA with the earliest eDiary finding date/time is selected.
3) The first 5 EQMAs ≥ X hours apart in the OLE Phase are selected based on the first 5 eDiary measurement date/times being ≥ X hours apart.
   - X = 23 in the main analysis, whereas X = 47 in the sensitivity analysis (see Section 6.5.1.1). The cutoffs of 23 and 47 hours align with the lower bounds of the 24-hour and 48-hour postdose analysis windows, respectively (see Table 7).
   - The first EQMA is included in both analyses, and is the starting point.
   - The next EQMA ≥ X hours apart from the first EQMA is included in the analysis, and becomes the new starting point.
   - The iterative process continues until the first 5 EQMAs ≥ X hours apart are selected. See example below.

Example:

EQMA	eDiary Measurement Date/Time	Include in Main Analysis	Include in Sensitivity Analysis
1	01JAN2024:10:25	Yes	Yes
2	02JAN2024:08:32	No	No
3	03JAN2024:08:35	Yes	No
4	04JAN2024:06:22	No	Yes
5	05JAN2024:11:26	Yes	No

9.3.2 SAS Code: Linear Mixed Effects Model With Repeated Measures

Consider the following variables used to evaluate the MQoL overall change using a linear mixed effects model with repeated measures:

- mqol: MQoL Question 16 value; continuous variable (integer)
- irndstr: imputed randomization stratum; categorical variable with levels of 1 and 2 to denote yes and no, respectively (see Section 6.2.5.1)
- eqma: EQMA; categorical variable with levels of 1 to 5

- resiol: OLE rescue medication or intervening OL rimegepant taken at or before the MQoL Question 16 value; categorical variable with levels of 1 and 2 to denote yes and no, respectively
- usubjid: unique subject identifier; categorical variable.

Then the SAS code is as follows:

```
proc mixed empirical;
class usubjid irndstr eqma resiol;
model mqol = irndstr resiol eqma eqma*resiol;
repeated eqma / subject=usubjid type=un; /* unstructured */
lsmeans eqma*resiol / alpha=0.05 cl;
run;
```

10 REFERENCES

Not applicable.