Biohaven Pharmaceuticals

Protocol BHV3000-305

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

Statistical Analysis Plan

Version 9.0

Date: 09-Feb-2021

NCT Number: NCT03732638

SIGNATURE PAGE

Protocol Title:	BHV3000-305: A Phase 2/3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Rimegepant in Migraine Prevention
Sponsor:	Biohaven Pharmaceuticals, Inc.
Protocol Number:	BHV3000-305
Document Version/Date:	Version 9.0/09-Feb-2021
Author:	[redacted]

Sponsor Approval

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

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

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

Sponsor Signatories:

[redacted]

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

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

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

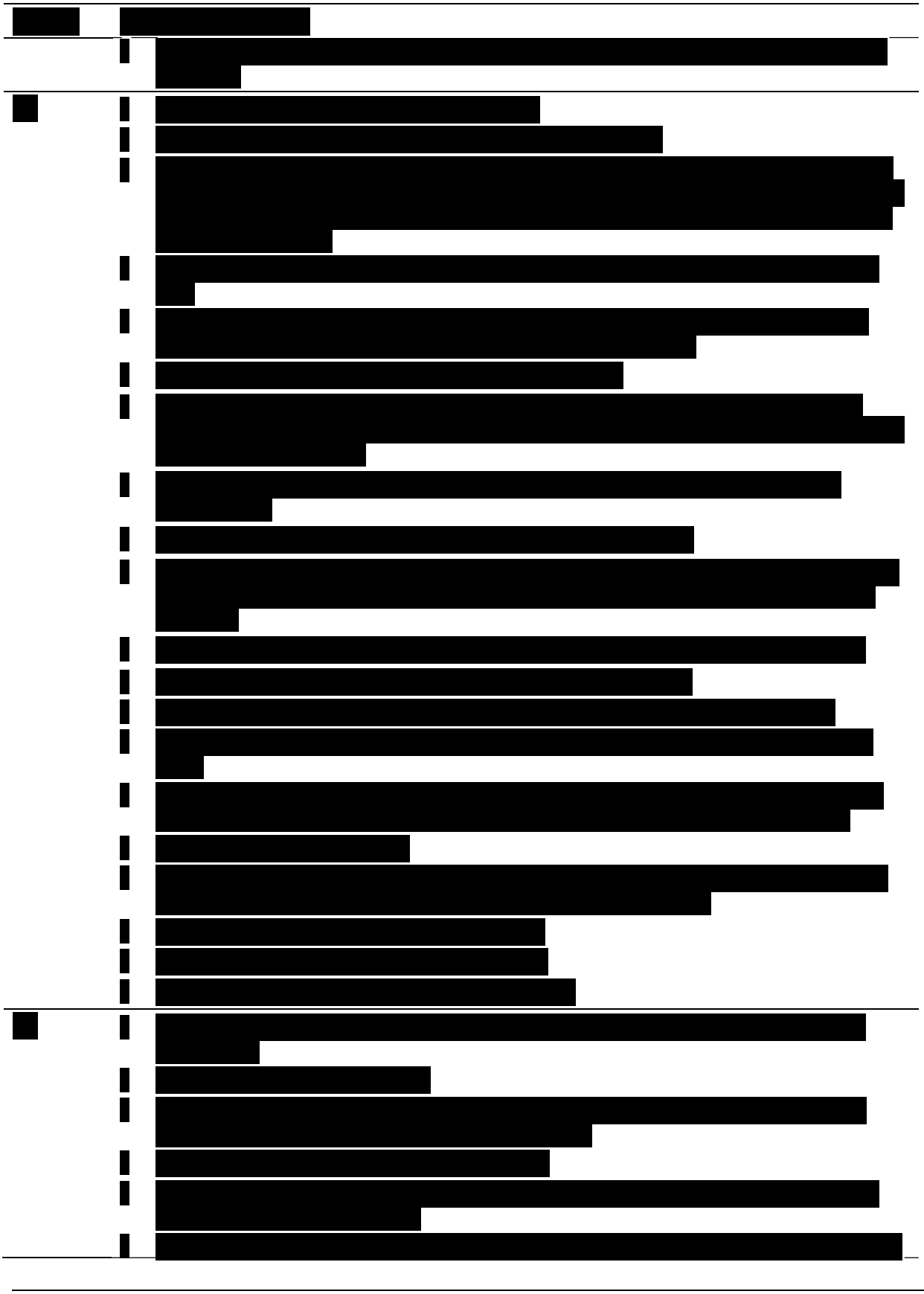
[redacted]

[redacted]

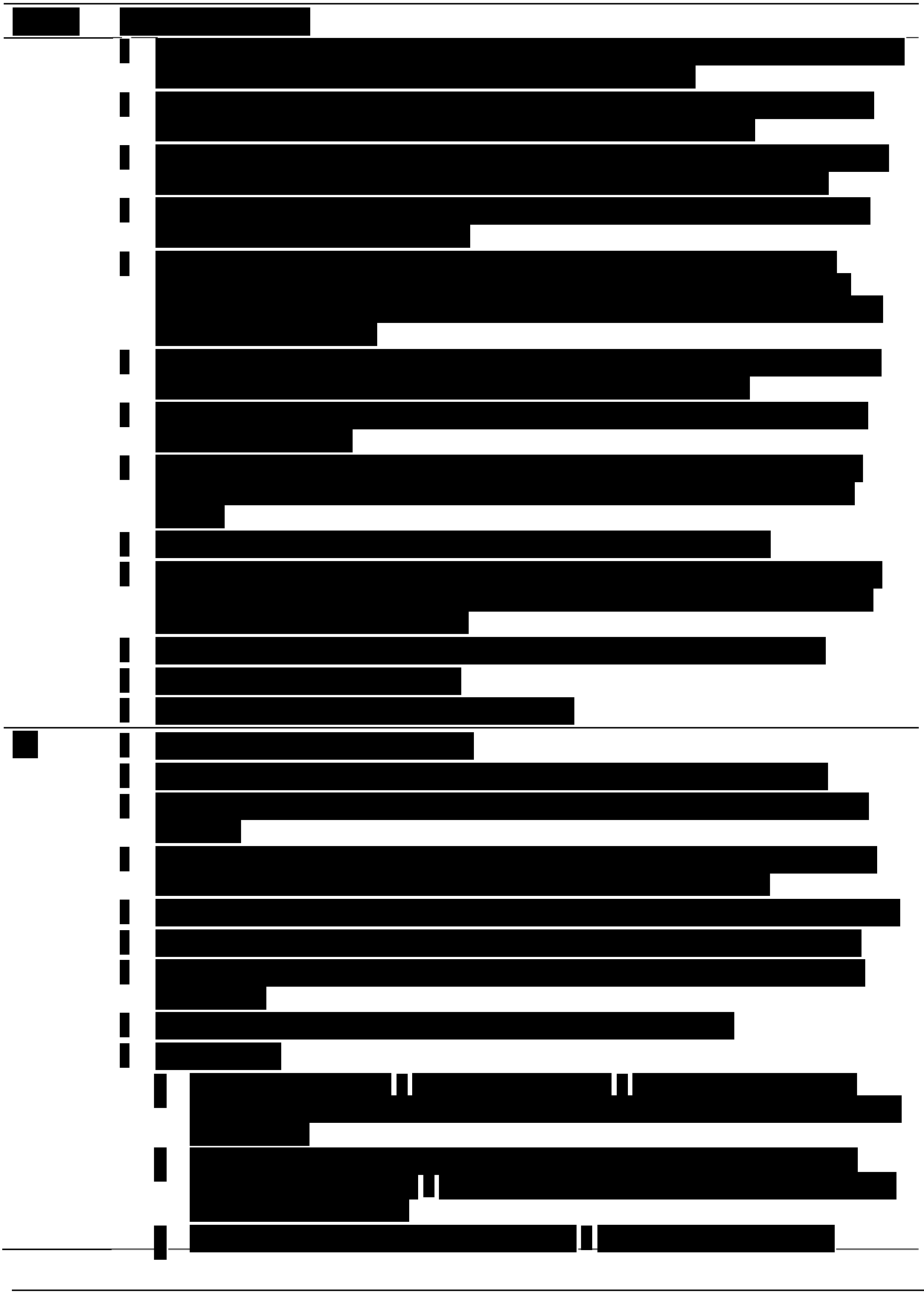
[redacted]

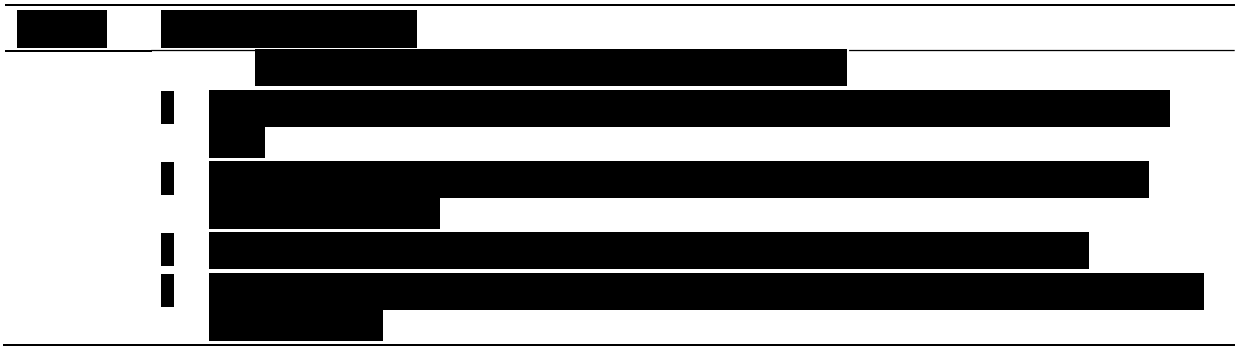
[redacted]

[redacted]



[redacted]





1 INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1 Introduction

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

This SAP [redacted] describes the analysis of the double-blind treatment (DBT), open-label extension (OLE), and follow-up phases of the study. It contains analysis details and methodology to answer the study objectives, including planned summary tables, by-subject listings, and figures, which will provide the basis for the results section of the 90-Day Safety Update and CSRs. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analyses.

1.2 Study Objectives

1.2.1 Primary Objectives

To compare the efficacy of rimegepant to placebo as a preventive treatment for migraine, as measured by the reduction from baseline in the mean number of migraine days per month in the last 4 weeks of the DBT phase (a month is defined as 4 weeks for the purpose of this protocol).

1.2.2 Secondary Objectives

- To compare the efficacy of rimegepant to placebo on the proportion of subjects who have at least a 50% reduction from baseline in the mean number of moderate or severe migraine days per month in the last 4 weeks of the DBT phase.
- To compare the efficacy of rimegepant to placebo on the reduction from baseline in the mean number of migraine days per month over the entire course of the double-blind treatment phase.
- To compare the frequency of use of rescue medications between rimegepant and placebo in the last 4 weeks of the DBT phase.
- To compare the efficacy of rimegepant to placebo on the reduction from baseline in the mean number of migraine days per month in the first 4 weeks of the DBT phase.
- To evaluate the safety and tolerability of rimegepant.
- To evaluate the frequency of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3x upper limit of normal (ULN) with concurrent elevations in total bilirubin (TBL) > 2x ULN in subjects treated with rimegepant.
- To evaluate the frequency of hepatic-related adverse events (AEs) and hepatic-related treatment discontinuations in subjects treated with rimegepant.

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

[redacted]

2 STUDY DESIGN

2.1 Synopsis of Study Design

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

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

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

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

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

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

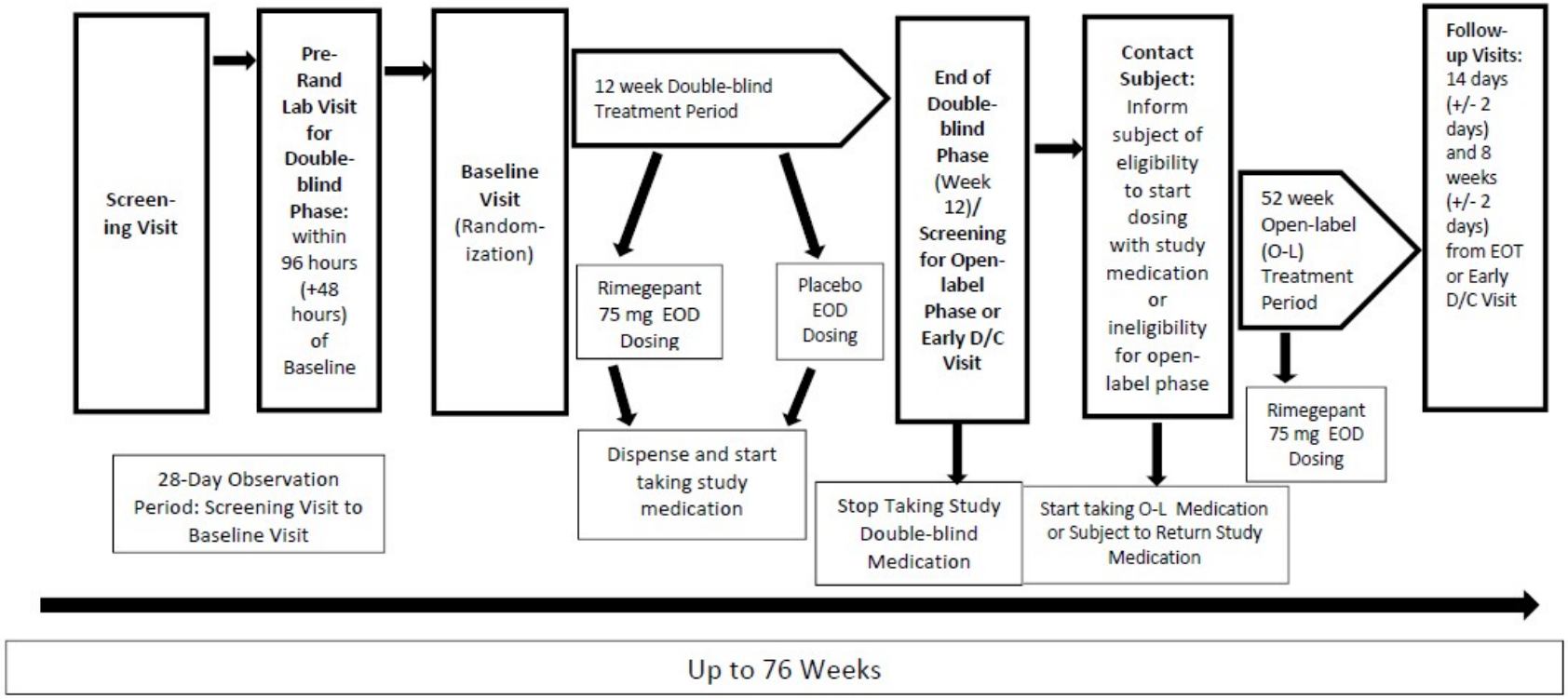
Study visits will occur at screening (enrollment), pre-randomization lab visit (which must occur within 96 hours of the baseline visit), baseline (randomization), Weeks 2, 4, 8, and 12. At the completion of the 12-week DBT phase, subjects may enter into the 12-week OLE phase if they continue to meet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

2.2 Randomization Methodology

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

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

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



2.3 Study Estimands

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

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

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

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

2.3.1 Primary Objective Estimands

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

Table 1: Primary Objective Estimands

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

2.3.2 Secondary Objective Estimands

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

Table 2: Secondary Objective Estimands

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

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

[redacted]

[redacted]

3 POPULATION SAMPLES FOR ANALYSES

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

- **Enrolled subjects**: Subjects who sign an informed consent form and are assigned a subject identification number by IWRS, i.e., non-missing informed consent date.
- **Randomized subjects**: Enrolled subjects who are assigned a randomized treatment group and prophylactic medication use stratum by IWRS, i.e., non-missing IWRS randomization date.
- **Modified intent-to-treat (mITT) subjects**: Enrolled subjects who were randomized only once and received at least one dose of double-blind (DB) study medication (rimegepant or placebo), i.e., non-missing DBT start date. This corresponds to the Full Analysis Set in the BHV3000-305 Protocol.
    - **Evaluable mITT subjects**: mITT subjects with ≥ 14 days of eDiary efficacy data (not necessarily consecutive) in both the OP and at least one month (i.e., 4-week interval) in the DBT phase. This corresponds to the Efficacy Analysis Set in the BHV3000-305 Protocol.
    - **Evaluable first week mITT subjects**: mITT subjects with at least one day of eDiary efficacy data in both the OP and the first week of the DBT phase.
    - **Evaluable mITT menstruating female subjects**: mITT menstruating female subjects with at least one day of eDiary menstrually-related (MR) efficacy data in both the OP and at least one month (i.e., 4-week interval) in the DBT phase.

  - **OL rimegepant mITT subjects**: mITT subjects who received at least one dose of OL rimegepant, i.e., non-missing OL rimegepant start date.
    - **Evaluable OL rimegepant mITT subjects**: OL rimegepant mITT subjects with ≥ 14 days of eDiary efficacy data (not necessarily consecutive) in both the OP and at least one month (i.e., 4-week interval) in the OLE phase.
    - **Evaluable OL rimegepant mITT menstruating female subjects**: OL rimegepant mITT menstruating female subjects with at least one day of eDiary MR efficacy data in both the OP and at least one month (i.e., 4-week interval) in the OLE phase.

- **Treated subjects**: Enrolled subjects who received at least one dose of study drug (DB or OL), i.e., non-missing study drug start date. This corresponds to the Safety Analysis Set in the BHV3000-305 Protocol.
- **OL rimegepant treated subjects**: Enrolled subjects who received at least one dose of OL rimegepant, i.e., non-missing OL rimegepant start date.
  - **Interim subjects:** OL rimegepant treated subjects with OL rimegepant start date – DBT last date > 7 days.
- **DB or OL rimegepant treated subjects**: Enrolled subjects who received at least one dose of rimegepant (DB or OL) i.e., non-missing DB or OL rimegepant start date. This corresponds to the Rimegepant Safety Analysis Set in the BHV3000-305 Protocol.
- **Follow-up subjects**: Treated subjects whose last contact date is in the follow-up safety analysis period.
- Coronavirus Disease 2019 (COVID-19) impacted: Enrolled subjects who are impacted by COVID-19 [redacted]

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

4 SCHEDULE OF ANALYSES

The following planned analyses will be conducted:

- Blinded interim analysis for the 90-Day Safety Update with a scheduled database snapshot date of 13-June-2019. Analyses will focus on key safety endpoints (e.g., deaths, AEs by severity, SAEs, AEs leading to study drug discontinuation, worst laboratory test abnormalities, LFT elevations) and supportive endpoints (e.g., subject disposition, demographics and baseline characteristics, study drug exposure).
- Week 12 interim unblinded analysis for an interim CSR when the last treated subject completes the last visit in the DBT phase. All analyses described in this SAP will be performed.
- Final unblinded analysis for the final CSR when the last treated subject completes the last visit in the follow-up phase. Analyses will focus on efficacy during the OLE phase, and safety during the DB or OL rimegepant phase and follow-up phase.

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

5 SAMPLE SIZE AND POWER

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

6 STATISTICAL METHODS

6.1 General Methods

[redacted]

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

- Results for enrolled subjects will be presented only by overall without treatment group.
- Exposure, efficacy, and safety results for the DBT phase will be presented only by treatment group without overall.
- Results for follow-up subjects will be presented by 6 groups: rimegepant, placebo, placebo to open-label rimegepant, placebo no open-label rimegepant, double-blind or open-label rimegepant, and overall. "Placebo to open-label rimegepant" denotes as-treated placebo subjects who received open-label rimegepant, and "placebo no open-label rimegepant" denotes as-treated placebo subjects who never received open-label rimegepant; note that these 2 groups add to the "placebo" group. Also note that the "rimegepant" and "placebo to open-label rimegepant" groups add to the "double-blind or open-label rimegepant" group.

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

All listings except administrative listings will identify subjects who are impacted by COVID-19 [redacted]

Select listings of measurements over time will display COVID-19 visit impact code for visits that are impacted by COVID-19 [redacted]

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

6.1.1 Missing Data

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

6.1.2 Type 1 Error Control

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

1. Proportion of subjects with ≥ 50% reduction from OP in the mean number of moderate or severe migraine days per month in the last month of the DBT phase
2. Change from OP in the mean number of migraine days per month in the entire DBT phase
3. Mean number of rescue medications days per month in the last month of the DBT phase
4. Change from OP in the mean number of migraine days per month in the first month of the DBT phase
5. Change from baseline in MSQoL restrictive role function score at Week 12 of the DBT phase
6. Change from baseline in MIDAS total score at Week 12 of the DBT phase.

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

6.1.3 Subgroups

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

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

6.1.3.1 Efficacy Subgroups for Evaluable mITT Subjects

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

- Age: < 40, ≥ 40, < 65 , ≥ 65
- Sex: female, male
- Race: White, Black or African American, Other Including Asian, Asian
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino
- Baseline body mass index (BMI; kg/m^2): < 25, ≥ 25 to < 30, ≥ 30

- Historical number of moderate or severe migraine attacks per month: < 6, ≥ 6, < 8, ≥ 8, < 12, ≥ 12, < 15, ≥ 15
- Historical primary migraine type: migraine with aura, migraine without aura
- Historical chronic migraine: yes, no
- Prophylactic migraine medication use at randomization (i.e., IWRS randomization strata): yes, no
- Total migraine days per month in the OP: < 14, ≥ 14.

6.1.3.2 Safety Subgroups for Treated Subjects

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

- Age: < 40, ≥ 40, < 65 , ≥ 65
- Sex: female, male
- Sex and age: female < 40, female ≥ 40, male < 40, male ≥ 40
- Race: White, Black or African American, Other Including Asian, Asian
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino
- Baseline body mass index (BMI; kg/m^2): < 25, ≥ 25 to < 30, ≥ 30
- Prophylactic migraine medication use at randomization: yes, no.

6.1.3.3 Safety Subgroups for DB or OL Rimegepant Treated Subjects

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

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

These apply to the final CSR.

6.1.3.4 Safety Subgroups for OL Rimegepant Treated Subjects

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

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

6.2 Study Population

6.2.1 Population Samples for Analyses

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

Inclusion and exclusion from the evaluable mITT sample population will be summarized by as-randomized treatment group and overall for randomized subjects. Reasons for exclusion categories are mutually exclusive and will include the following: (1) not mITT: not treated with

DBT; (2) not mITT: treated with DBT but randomized more than once; (3) mITT but not evaluable: < 14 days of efficacy data in OP only; (4) mITT but not evaluable: < 14 days of efficacy data in all 3 months of the DBT phase only; (5) mITT but not evaluable: < 14 days of efficacy data in both OP and in all 3 months of the DBT phase. See Section 6.3.1.1 for months.

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

6.2.2 Enrollment

Enrollment by (1) country and site and (2) age group will be tabulated for enrolled subjects. The enrollment by country and site table also displays results for randomized subjects and treated subjects. [redacted]

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

6.2.3 Subject Disposition

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

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

6.2.3.1 Subject Disposition From Enrollment to Randomization

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

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

6.2.3.2 Subject Disposition From Randomization to Treatment

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

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

6.2.3.3 Subject Disposition in the DBT Phase

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

- Ongoing in DBT phase (identified as subjects with missing response to the question about completing all DB visits on the DB Subject Status CRF)
- Completed DBT phase (identified as subjects with primary completion/discontinuation reason of "Completed Double Blind Phase" on the DB Subject Status CRF)
- Did not complete DBT phase (identified as subjects with "no" response to the question about completing all DB visits or primary completion/discontinuation reason not missing but not equal to "Completed Double Blind Phase" on the DB Subject Status CRF)
    - Reasons for not completing, including not reported
- Continuing to OLE phase (identified as subjects with "yes" response to the question about continuing to OL on the DB Subject Status CRF)
- Continuing to follow-up phase (identified as subjects with "yes" response to the question about continuing to follow-up on the DB Subject Status CRF)
- Not continuing to follow-up phase (identified as subjects with "no" response to the question about continuing to follow-up on the DB Subject Status CRF)
    - Reasons for not continuing, including not reported
- Completed DBT phase but not continuing to OLE phase (identified as subjects with primary completion/discontinuation reason of "Completed Double Blind Phase" and "no" response to the question about not continuing to OL on the DB Subject Status CRF)
    - Reasons for not continuing, including not reported.

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

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

6.2.3.4 Subject Disposition in the OLE Phase

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

- Ongoing in OLE phase (identified as subjects with missing response to the question about completing all OL visits on the OL Subject Status CRF)
- Completed OLE phase (identified as subjects with primary completion/discontinuation reason of "Completed Open Label Phase" on the OL Subject Status CRF)

- Did not complete OLE phase (identified as subjects with "no" response to the question about completing all OL visits or primary completion/discontinuation reason not missing but not equal to "Completed Open Label Phase" on the OL Subject Status CRF)
    - Reasons for not completing, including not reported
- Terminated OLE phase prematurely due to COVID-19 [redacted]
    - Reasons for termination, including not reported
- Continuing to follow-up phase (identified as subjects with "yes" response to the question about continuing to follow-up on the OL Subject Status CRF)
- Not continuing to follow-up phase (identified as subjects with "no" response to the question about continuing to follow-up on the OL Subject Status CRF)
    - Reasons for not continuing, including not reported.

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

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

6.2.3.5 Subject Disposition in the Follow-up Phase

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

- Did not formally enter the follow-up phase (identified as subjects with missing response to the question about completing all follow-up visits on the Follow-up Subject Status CRF and without "yes" response to the question about continuing to follow-up on the DB or OL Subject Status CRF)
- Ongoing in follow-up phase (identified as subjects with missing response to the question about completing all follow-up visits on the Follow-up Subject Status CRF and with "yes" response to the question about continuing to follow-up on the DB or OL Subject Status CRF)
- Completed follow-up phase (identified as subjects with "yes" response to the question about completing all follow-up visits on the Follow-up Subject Status CRF)
- Did not complete follow-up phase (identified as subjects with "no" response to the question about completing all follow-up visits on the Follow-up Subject Status CRF)
    - Reasons for not completing, including not reported
- Terminated follow-up phase prematurely due to COVID-19 [redacted]
    - Reasons for termination, including not reported.

6.2.4 Protocol Deviations

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

- Informed Consent
- Inclusion/Exclusion Criteria (specify #)
- Concomitant Medication
- SAE Reporting
- Regulatory
- Drug Storage/Preparation
- Drug Administration
- Visit Schedule
- EPro Diary Non-compliance
- Non-compliance (i.e., trends, missed assessments).

A significant protocol deviation is any deviation that could impact subject safety or the integrity of the trial. For the purposes of this study, significant protocol deviations will be defined as the following:

- Inadequate informed consent or initiation of study procedures prior to completing the informed consent
- Subjects receiving an enrollment date in IWRS, but not meeting the inclusion/exclusion criteria
- Unreported SAEs
- Use of prohibited medication as defined by the protocol
- eDiary non-compliance
- Repeated deviations of the same nature for a given site or subject.

The sponsor, or designee, will be responsible for producing the final significant protocol deviation file (formatted as a Microsoft Excel file). This file will include site, subject ID, deviation date, deviation type, and a description of the protocol deviation.

The number and percentage of randomized subjects with significant protocol deviations will be summarized by deviation type and by as-randomized treatment group and overall. Deviation types will be presented in descending order of overall frequency.

A by-subject listing of significant protocol deviations will be provided for enrolled subjects.

6.2.5 *Pre-Treatment Characteristics*

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

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

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

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

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

Demographics and DB or OL rimegepant baseline characteristics (including both age at informed consent and age at DB or OL rimegepant baseline), as well as migraine history and cardiac and other risk factors, will be summarized by as-treated treatment group and overall for DB or OL rimegepant treated subjects to support DB or OL rimegepant safety. Age at DB or OL rimegepant baseline is defined using DB or OL rimegepant start date as the reference date (see Section 7.7). These will also be summarized analogously by subgroup level and overall for all safety subgroups of interest described in Section 6.1.3.3.

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

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

Baseline will be defined according to population as follows:

- Enrolled subjects not randomized: Last non-missing value
- Randomized subjects not treated: Last non-missing value on or before the IWRS randomization date/time
- mITT subjects and treated subjects: Last non-missing value on or before the study drug start date/time (i.e., in the pre-treatment analysis period; see Sections 7.3 and 7.4)
- DB or OL rimegepant treated subjects: Last non-missing value on or before the DB or OL rimegepant start date (i.e., DB or OL rimegepant baseline)

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

The following listings will be provided for enrolled subjects:

- Demographics, including informed consent date. All reported races will be displayed for subjects who reported multiple races.
- Baseline characteristics, including previous BHV3000-305 subject identifier from the Rescreen CRF
- Medical history, displaying results by SOC and PT
- Migraine history split into general migraine history, migraine symptom history, and migraine aura history
- Cardiac and other risk factors for subjects with any risk factor present. Only records with "yes" responses to questions about having risk factors will be displayed.

6.2.5.1 Demographics and Baseline Characteristics

[redacted]

This table will also summarize the following parameters:

- Experiences menstrual periods (yes, no; if female)
- Screened for previous BHV3000 study (any previous study, BHV3000-111, BHV3000-201, BHV3000-301, BHV3000-302, BHV3000-303)
- Prophylactic migraine medication use at randomization (yes, no).

6.2.5.2 Medical History

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

6.2.5.3 Migraine History

[redacted]

6.2.5.4 Cardiac and Other Risk Factors

[redacted]

6.2.6 Exposure

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

6.2.6.1 Study Medication

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

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

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

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

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

eDiary Rimegepant or Placebo Exposure During Double-Blind Treatment

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

- Time on DBT (weeks), derived as (DBT end date – DBT start date + 1)/7
- Cumulative DB exposure (tablets), derived by summing number of tablets across DB study drug records

- Average DB exposure (tablets per month), derived as 4 × cumulative DB exposure/time on DBT
- Total DB exposure (tablets) summed across all subjects, derived by summing cumulative DB exposure across all subjects
- Total DB exposure (patient-years), derived by summing (DBT end date – DBT start date + 1)/365.25 across all subjects.
- Number and percentage of subjects in the following average DB exposure (tablets per month) categories:
  - > 16.8 (> 20% above EOD dosing)
  - > 15.4 (> 10% above EOD dosing)
  - ≥ 12.6 to ≤ 15.4 (± 10% of EOD dosing)
  - ≥ 11.2 to ≤ 16.8 (± 20% of EOD dosing)
  - ≥ 12.6 (≥ 90% compliant with EOD dosing)
  - ≥ 11.2 (≥ 80% compliant with EOD dosing)
- Number and percentage of subjects who took > 1 DB tablet on any 1 day. This could be from the same bottle or different bottles due to an unscheduled visit or erroneous eDiary usage.
  - Single study drug record (i.e., ≥ 2 tablets taken from a single source)
  - Multiple study drug records (i.e., ≥ 2 tablets taken based on multiple sources with the same study drug date)
    - Subject-reported duplicate data (i.e., duplicate study drug times from ≥ 2 eDiary subject-reported sources)
    - Subject-reported non-duplicate data (i.e., non-duplicate study drug times from ≥ 2 eDiary subject-reported sources)
    - Both site-reported data on medication reconciliation form and subject-reported data (i.e., duplicate study drug dates from the medication reconciliation form and an eDiary subject-reported source)
    - Site-reported data on medication reconciliation form only (i.e., duplicate study drug dates only from the medication reconciliation form)
- Number and percentage of subjects who took:
  - ≥ 12 DB tablets per month for 3 consecutive months, i.e., 3 consecutive 4-week intervals (see first paragraph below)
  - ≥ 13 , ≥ 14, ≥ 15, and ≥ 16 DB tablets per month for 3 consecutive months
- Number and percentage of subjects who took the incorrect DB study drug:
  - All the time (i.e., as-treated treatment group not equal to as-randomized treatment group)

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

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

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

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

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

A Kaplan-Meier mortality table will summarize time to DBT discontinuation in 4-week intervals (i.e., ≤ 4, > 4 to ≤ 8, > 8 to ≤ 12, > 12) by treatment group and overall for treated subjects. A Kaplan-Meier mortality plot by treatment group will display the percentage of treated subjects on DBT (y-axis) versus weeks (x-axis). Time to DBT discontinuation (weeks) is defined as (DBT end date – DBT start date + 1)/7. Subjects will be considered to have discontinued DBT if they have non-missing DBT last date. Otherwise, in an interim analysis or snapshot before the Week 12 interim analysis database lock, subjects will be censored at the DBT end date.

eDiary DB or OL Rimegepant Exposure During the Entire Study

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

- Time on DB or OL rimegepant (weeks), derived as (DB or OL rimegepant end date – DB or OL rimegepant start date + 1)/7
- Number and percentage of subjects in the following time on DB or OL rimegepant (weeks) categories: ≥ 11, < 23, ≥ 23, ≥ 51, ≥ 63. These correspond to using a 1-week lower bound on 3, 6, 12, and 15 months, respectively.
- Cumulative DB or OL rimegepant exposure (tablets), derived by summing number of DB or OL rimegepant tablets across records with non-missing DB or OL rimegepant date/times.

- Average DB or OL rimegepant exposure (tablets per month), derived as 4 × cumulative DB or OL rimegepant exposure/time on DB or OL rimegepant
- Total DB or OL rimegepant exposure (tablets) summed across all subjects, derived by summing cumulative DB or OL rimegepant exposure across all subjects
- Number and percentage of subjects who took > 1 DB or OL rimegepant tablet on any 1 day
  - Single study drug record
  - Multiple study drug records
    - Subject-reported duplicate data
    - Subject-reported non-duplicate data
    - Both site-reported data on medication reconciliation form and subject-reported data
    - Site-reported data on medication reconciliation form only

  Note that imputed OL rimegepant to treat headache date/time by definition will not contribute to taking more than 1 OL rimegepant tablet per day.
- Total DB or OL rimegepant exposure (patient-years), derived by summing (DB or OL rimegepant end date – DB or OL rimegepant start date + 1)/365.25 across all subjects.

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

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

eDiary Study Drug Exposure

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

- Time in the OP (weeks)
- Time from randomization to last contact (weeks), where study drug start date will be used if IWRS randomization date is missing
- Time on DBT (weeks)
- Cumulative DB exposure (tablets)

- Average DB exposure (tablets per month)
- Total DB exposure (tablets) summed across all subjects
- Time on OL rimegepant (weeks)
- Cumulative OL rimegepant exposure (tablets)
- Average OL rimegepant exposure (tablets per month)
- Total OL rimegepant exposure (tablets) summed across all subjects
- Time on study drug (weeks), derived as (study drug end date – study drug start date + 1)/7
- Number and percentage of subjects in the following time on study drug (weeks) categories: ≥ 11, ≥ 23, ≥ 51, ≥ 63. These correspond to using a 1-week lower bound on 3, 6, 12, and 15 months, respectively.
- Cumulative study drug exposure (tablets), derived by summing number of tablets across study drug records (DBT + OLE)
- Average study drug exposure (tablets per month), derived as 4 × cumulative study drug exposure/time on study drug
- Total study drug exposure (tablets) summed across all subjects, derived by summing cumulative study drug exposure across all subjects
- Total study drug exposure (patient-years), derived by summing (study drug end date – study drug start date + 1)/365.25 across all subjects
- Time in follow-up (weeks), derived as derived as (last contact date – study drug last date)/7, for follow-up subjects
- Time on study (weeks), derived as (last contact date – study drug start date + 1)/7
- Number and percentage of subjects in the following time on study (weeks) categories: ≥ 11, ≥ 23, ≥ 51, ≥ 63. These correspond to using a 1-week lower bound on 3, 6, 12, and 15 months, respectively.

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

- Time to study drug discontinuation (weeks) is defined as (study drug end date – study drug start date + 1)/7. Subjects will be considered to have discontinued study drug if they have non-missing study drug last date/time. Otherwise, in an interim analysis or snapshot before the final database lock, subjects will be censored at the study drug end date.
- Time to study discontinuation (weeks) is defined as (last contact date – IWRS randomization date + 1)/7. If a subject is not randomized, then the study drug start date will be used instead of IWRS randomization date. In an interim analysis or snapshot before the final database

lock, subjects will be considered to have discontinued the study if any of the following criteria 1 through 4 are met:

1) All of the following criteria from the DB Subject Status CRF are met (see Section 6.2.3.3):
   a) Completed or did not complete the DB phase
   b) Not continuing to OLE phase
   c) Not continuing to follow-up phase
2) All of the following criteria from the OL Subject Status CRF are met (see Section 6.2.3.4)
   a) Completed or did not complete the OLE phase
   b) Not continuing to follow-up phase
3) Did not formally enter the follow-up phase (see Section 6.2.3.5)
4) Completed or did not complete the follow-up phase (see Section 6.2.3.5)

Otherwise, subjects will be censored at the last contact date. At the final database lock, all subjects will be considered to have discontinued the study. (This definition of study discontinuation was applied to the Interim Week 12 CSR.)

eDiary OL Rimegepant Exposure

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

- Time on OL rimegepant (weeks)
- Number and percentage of subjects in the following time on OL rimegepant (weeks) categories: ≥ 11, ≥ 23, ≥ 51. These correspond to using a 1-week lower bound on 3, 6, and 12 months, respectively.
- Cumulative OL rimegepant exposure (tablets)
- Average OL rimegepant exposure (tablets per month)
- Number and percentage of subjects in the subgroup categories defined in Section 6.1.3.4
- Number and percentage of subjects who took > 1 OL rimegepant tablet on any 1 day
  - Single study drug record
  - Multiple study drug records
    - Subject-reported duplicate data
    - Subject-reported non-duplicate data
    - Both site-reported data on medication reconciliation form and subject-reported data
    - Site-reported data on medication reconciliation form only

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

6.2.6.2 Drug Accountability

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

Drug Accountability Exposure

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

- Time from first DB kit dispensed to last DB kit returned (weeks), derived as (latest DB kit return date – earliest DB kit dispense date + 1)/7. Subjects who were dispensed ≥ 1 DB kit but never returned any DB kit will be credited with 1 day.
- Cumulative DB exposure (tablets) based on DB kits dispensed and returned, derived as summing (30 – number of tablets remaining) across records with non-missing DB kit dispense and return dates.
- Average DB exposure (tablets per month) based on DB kits dispensed and returned, derived as 4 × cumulative DB exposure based on DB kits dispensed and returned/time from first DB kit dispensed to last DB kit returned.
- Time from first OL kit dispensed to last OL kit returned (weeks), derived as (latest OL kit return date – earliest OL kit dispense date + 1)/7. Subjects who were dispensed ≥ 1 OL kit but never returned any OL kit will be credited with 1 day.
- Cumulative OL exposure (tablets) based on OL kits dispensed and returned, derived as summing (30 – number of tablets remaining) across records with non-missing OL kit dispense and return dates.
- Average OL exposure (tablets per month) based on OL kits dispensed and returned, derived as 4 × cumulative OL exposure based on OL kits dispensed and returned/time from first OL kit dispensed to last OL kit returned.
- Time from first DB or OL rimegepant kit dispensed to last DB or OL rimegepant kit returned (weeks). This is time from first DB kit dispensed to last DB kit returned for subjects whose as-treated treatment group is rimegepant. This is time from first OL kit dispensed to last OL kit returned for subjects whose as-treated treatment group is placebo.
- Cumulative DB or OL rimegepant exposure (tablets) based on DB or OL rimegepant kits dispensed and returned. This is cumulative DB and OL combined exposure for subjects whose as-treated treatment group is rimegepant, and cumulative OL exposure for subjects whose as-treated treatment group is placebo.
- Average DB or OL rimegepant exposure (tablets per month) based on DB or OL rimegepant kits dispensed and returned, derived as 4 × cumulative DB or OL rimegepant exposure based on DB or OL rimegepant kits dispensed and returned/time from first DB or OL rimegepant

kit dispensed to last DB or OL rimegepant kit returned.

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

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

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

Drug Accountability Compliance

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

- Any kit dispensed
- Did not return ≥ 1 kit dispensed and discontinued study drug, defined as any of the following:
  - Randomized subjects who were not treated and did not return ≥ 1 DB kit dispensed
  - Treated subjects who did not return ≥ 1 DB kit dispensed and discontinued DBT (i.e., non-missing DBT last date)
  - OL rimegepant treated subjects who did not return ≥ 1 OL rimegepant kit dispensed and discontinued OL rimegepant (i.e., non-missing OL rimegepant last date).
- Did not return any kit dispensed and discontinued study drug.

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

6.2.6.3 eDiary Compliance

eDiary Compliance During Pre-Randomization and in the DBT Phase

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

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

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

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

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

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

eDiary Compliance in the DB or OL Rimegepant Phase

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

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

6.2.6.4 Non-Study Medications

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

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

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

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

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

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

[redacted]

Non-Study Medications for Treated Subjects

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

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

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

Non-study prophylactic migraine standard of care medications will also be summarized analogously by treatment group for mITT subjects with prophylactic migraine medication use at randomization. Medications will be displayed in descending order of overall frequency within therapeutic class and preferred name. (This was an adhoc analysis for the Interim Week 12 CSR.)

Non-Study Medications for DB or OL Rimegepant Treated Subjects

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

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

Non-Study Medications for OL Rimegepant Treated Subjects

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

Non-Study Medications for Follow-up Subjects

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

6.3 Efficacy

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

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

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

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

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

- Subjects excluded from the efficacy analysis for randomized subjects not in the evaluable mITT population sample, including the reason for exclusion (see Section 3).
- Primary and secondary efficacy endpoints for randomized subjects, including the reason for exclusion from the evaluable mITT population sample (see Sections 6.3.1.1 and 6.3.2)
- [redacted]

6.3.1 Reduction in Migraine Days per Month

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

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

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

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

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

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

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

Months in the DBT phase are defined as follows:

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

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

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

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

Missing Efficacy Data

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

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

- < 14 days of efficacy data in the OP
- < 14 days of efficacy data in any of the following months (i.e., 4-week intervals) of the DBT phase:
  - Month 1: ≤ 4 weeks
  - Month 2: > 4 to ≤ 8 weeks
  - Month 3: > 8 to ≤ 12 weeks

Descriptive Analyses

Analyses will be based on evaluable mITT subjects.

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

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

The following scatter plots will be produced by treatment group:

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

Plots will include a horizontal reference line at 0. The last 2 plots were included as adhoc analyses in the Interim Week 12 CSR.

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

Treatment Group Comparisons

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

Principal Analysis

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

- Least-squares mean (LSM) change from OP, SE, and 95% CI by month and randomization stratum (yes, no, overall) for each treatment group
- Difference in LSM changes from OP between treatment groups (rimegepant – placebo), SE, 95% CI, and p-value by randomization stratum (yes, no) for each month
- Difference in LSM changes from OP between treatment groups (rimegepant – placebo), SE, 95% CI, and p-value for each month. Results in the last month will support the primary objective, results in the first month will support the fourth secondary objective, [redacted]
- Overall LSM change from OP, SE, and 95% CI by randomization stratum (yes, no, overall) for each treatment group
- Difference in overall LSM changes from OP between treatment groups (rimegepant – placebo), SE, 95% CI, and p-value by randomization stratum (yes, no)
- Difference in overall LSM changes from OP between treatment groups (rimegepant – placebo), SE, 95% CI, and p-value. Results will support the second secondary objective.

[redacted]

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

Sensitivity Analysis

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

Subgroup Analyses

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

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

[redacted]

[redacted]

6.3.2 Secondary Efficacy Endpoints

6.3.2.1 Percentages of Subjects with Reduction in Migraine Days per Month

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

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

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

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

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

Descriptive Analyses

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

- Non-Evaluable = Failure: Analyses will be based on all evaluable mITT subjects in all months. An additional reduction category "Not evaluable" will be included.
- Non-Evaluable = Missing: Evaluable mITT subjects with ≥ 1 migraine day of appropriate migraine severity in the OP analysis period and < 14 days of efficacy data in the specified month will be excluded from analyses of the specified month.

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

- Responder, i.e., subjects with ≥ 14 days of efficacy data in the specified month, ≥ *X*% reduction in the specified month, and ≥ 1 migraine day of appropriate migraine severity in the OP analysis period.
- Failure
  - No migraine days of appropriate migraine severity in the OP.
  - Evaluable but < *X*% reduction in the month, i.e., subjects with ≥ 14 days of efficacy data and < *X*% reduction in the specified month.
  - ≥ *X*% reduction but not evaluable in the month, i.e., subjects with ≥ *X*% reduction and ≥ 1 to < 14 days of efficacy data in the specified month.
  - < *X*% reduction but not evaluable in the month, i.e., subjects with < *X*% reduction and ≥ 1 to < 14 days of efficacy data in the specified month.
  - No days of efficacy data in the month.

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

- Responder, i.e., subjects with ≥ *X*% reduction in the overall DBT mean and ≥ 1 migraine day of appropriate migraine severity in the OP analysis period.
- Failure
  - No migraine days of appropriate migraine severity in the OP.
  - < *X*% reduction, i.e., subjects with < *X*% reduction in the overall DBT mean.

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

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

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

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

Treatment Group Comparisons

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

- Response rate ("n/N"), risk (i.e., percentage), ASE, and 95% normal CI by randomization stratum for each treatment group
- Overall response rate ("n/N"), stratified risk, ASE, and 95% normal CI for each treatment group
- Difference in risks between treatment groups (rimegepant – placebo), ASE, 95% CI, and p-value by randomization stratum
- Difference in overall stratified risks between treatment groups (rimegepant – placebo), ASE, 95% CI, and p-value.

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

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

- Response rate ("n/N"), risk (i.e., percentage), ASE, and 95% normal CI by treatment group
- Difference in risks between treatment groups (rimegepant – placebo), ASE, 95% CI, and p-value.

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

[redacted]

6.3.2.2 Rescue Medication Days per Month

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

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

Rescue Medication Days per Month in the DBT Phase

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

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

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

Descriptive Analyses

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

Treatment Group Comparisons

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

- LSM, SE, and 95% CI by month and randomization stratum (yes, no, overall) for each treatment group
- Difference in LSMs between treatment groups (rimegepant – placebo), SE, 95% CI, and p-value by randomization stratum (yes, no) for each month
- Difference in LSMs between treatment groups (rimegepant – placebo), SE, 95% CI, and p-value for each month. Results in the last month will support the third secondary objective, [redacted]
- Overall LSM, SE, and 95% CI by randomization stratum (yes, no, overall) for each treatment group
- Difference in overall LSMs between treatment groups (rimegepant – placebo), SE, 95% CI, and p-value by randomization stratum (yes, no)
- [redacted]

6.3.2.3 MSQoL in the DBT Phase

The MSQoL will be assessed at early termination and the following visits: baseline; Week 12 of the DBT phase; [redacted]

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

Measurements will be first selected from the on-DBT efficacy period, and then slotted into the Week 12 analysis visit window (see Week 12 of the analysis visit window for outcome research [OR] endpoints column in Table 4). If a subject has multiple values in the analysis visit window, then the non-missing value closest to the target date for the visit will be used; in the case of a tie, the latest value collected will be used.

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

Descriptive Analyses

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

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

Treatment Group Comparisons

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

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

- LSM change from baseline at Week 12, SE, and 95% CI by randomization stratum (yes, no, overall) for each treatment group
- Difference in LSM changes from baseline between treatment groups (rimegepant – placebo) at Week 12, SE, 95% CI, and p-value by randomization stratum (yes, no)
- Difference in LSM changes from baseline between treatment groups (rimegepant – placebo) at Week 12, SE, 95% CI, and p-value. Results will support the fifth secondary objective.

6.3.2.4 MIDAS in the DBT Phase

The MIDAS is a retrospective, patient-administered, 5-item questionnaire that measures headache-related disability as lost time due to headache from paid work or school, household work, and non-work activities. The MIDAS will be assessed at early termination and the following visits: baseline; Week 12 of the DBT phase; [redacted]

[redacted]

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

Descriptive Analyses

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

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

Treatment Group Comparisons

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

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

6.3.2.5 Overall Summary of Primary and Secondary Endpoints

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

- Continuous endpoints involving change from OP or baseline
  - Overall LSM change and 95% CI for each treatment group
  - Difference in overall LSM changes between treatment groups (rimegepant – placebo), 95% CI, and p-value.

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

- Continuous endpoints not involving change from OP or baseline
  - Overall LSM and 95% CI for each treatment group
  - Difference in overall LSMs between treatment groups (rimegepant – placebo), 95% CI, and p-value.

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

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

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

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

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.4 Pharmacokinetic Evaluations

No pharmacokinetic data were collected in this study.

6.5 Safety

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

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

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

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

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

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

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

If a subject has multiple values in an analysis visit window in a safety analysis period, then the non-missing value in the analysis period closest to the target date for the visit will be used; in the case of a tie, the latest value collected (from the central laboratory, if applicable) will be used. Results will also be shown at EOT for each phase, i.e., last non-missing measurement in the on-DBT, on-OL rimegepant, and on-DB or OL rimegepant safety analysis periods. Results will also be shown at end of follow-up (EOFU), i.e., last non-missing measurement in the follow-up safety analysis period.

In analyses of the worst abnormality or category in a safety analysis period, subjects must have a non-missing measurement in the safety analysis period to be included for a given parameter. In shift from baseline analyses, subjects must have a non-missing measurement at baseline and in the safety analysis period to be included for a given parameter.

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

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

A by-subject listing of safety narrative subject identifiers will be provided for enrolled subjects with select events [redacted] The listing will flag subjects with select events.

6.5.1 Adverse Events

[redacted]

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

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

6.5.1.1 Deaths

Deaths will be identified from any of the following sources:

- AE CRF: PT or reported term containing “death”, outcome of fatal, “yes” response to the question “Did the AE result in death?”, or non-missing death date.
- DB Subject Status CRF: death as primary reason for phase completion/discontinuation; or death as reason for completing the DB phase through Week 12 and not entering the OL phase.
- OL Subject Status CRF: death as primary reason for phase completion/discontinuation.
- Follow-up Subject Status CRF: death as primary reason for phase completion/discontinuation.

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

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

6.5.1.2 AE Overviews

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

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

- Pre-treatment for enrolled subjects (overall, not by treatment group)
- Pre-treatment for treated subjects
- Pre-rimegepant for DB or OL rimegepant treated subjects
- On-DBT for treated subjects (excluding overall)
- On-DBT for treated subjects limited to on-DBT TEAEs (excluding overall)
- On-DB or OL rimegepant for DB or OL rimegepant treated subjects
- On-DB or OL rimegepant for DB or OL rimegepant treated subjects limited to on-DB or OL rimegepant TEAEs
- Post-DBT pre-OL rimegepant for interim subjects
- Follow-up for follow-up subjects.

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

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

6.5.1.3 Pre-Treatment AEs

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

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

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

- AEs by severity
- SAEs.

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

6.5.1.4 On-Treatment AEs

DBT Phase

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

- AEs by severity
- TEAEs by severity
- TEAEs occurring with ≥ 2% frequency on rimegepant and greater than placebo after rounding. Percentages will be displayed rounded to integers, and AEs will be displayed in alphabetical order by SOC and PT.
- AEs related to study drug by severity
- AEs related to study drug occurring with ≥ 2% frequency in any treatment group
- SAEs
- AEs leading to study drug discontinuation
- Hepatic-related AEs
- Hepatic-related AEs leading to study drug discontinuation
- Additional AEs of special interest: potential drug abuse, CV, and suicidality. Potential drug abuse AEs will be displayed in alphabetical order by severity and PT without SOC
- Exposure-adjusted multiple occurrences of unique AEs (see Section 7.6.1)
- Exposure-adjusted multiple occurrences of unique SAEs (see Section 7.6.1)
- Exposure-adjusted multiple occurrences of unique SAEs related to study drug (see Section 7.6.1)
- Exposure-adjusted multiple occurrences of unique non-SAEs occurring with ≥ 5% frequency in any treatment group (see Section 7.6.1).

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

DB or OL Rimegepant Phase

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

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

- AEs by severity
- AEs occurring with ≥ 5% frequency by severity. The 5% cut applies only to total severity in overall (not in each subgroup level).
- TEAEs by severity
- TEAEs occurring with ≥ 2% frequency overall after rounding. Percentages will be displayed rounded to integers, and AEs will be displayed in alphabetical order by SOC and PT.
- AEs related to study drug by severity
- SAEs
- AEs leading to study drug discontinuation
- Additional AEs of special interest: hepatic-related AEs; potential drug abuse AEs, cardiovascular AEs, and suicidality AEs. Potential drug abuse AEs will be displayed in alphabetical order by severity and PT without SOC.

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

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

- AEs by severity
- SAEs
- AEs leading to study drug discontinuation.

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

OLE Phase

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

- AEs by severity

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

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

- Exposure-adjusted multiple occurrences of unique AEs
- Exposure-adjusted multiple occurrences of unique SAEs
- Exposure-adjusted multiple occurrences of unique SAEs related to study drug
- Exposure-adjusted multiple occurrences of unique non-SAEs occurring with ≥ 5% frequency.

6.5.1.5 Follow-up AEs

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

- AEs by severity
- SAEs.

6.5.1.6 AEs Across All Study Phases Combined

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

- AEs leading to study drug discontinuation
- Hepatic-related AEs leading to study drug discontinuation.

6.5.1.7 Post-DBT Pre-OL Rimegepant AEs

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

- AEs by severity
- SAEs
- AEs leading to study drug discontinuation.

6.5.2 Laboratory Tests

Clinical safety laboratory testing will be performed at early termination and the following visits: screening; baseline; Weeks 4, 8, and 12 of the DBT phase; and Weeks 16, 24, 48 and 64 of the

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

Clinically significant laboratory abnormalities will be identified as grade 3 to 4 laboratory test results. [redacted] Laboratory test groups of clinical interest will include hematology, serum chemistry, and urinalysis.

LDL cholesterol and triglycerides will be analyzed as separate laboratory test parameters according to fasting status: fasting (i.e., fasting status of yes), not fasting (i.e., fasting status not equal to yes, including no, unknown, not reported, missing, etc.), and overall.

Estimated glomerular filtration rate (eGFR) will be derived using the modification of diet in renal disease (MDRD) formula [redacted]

Tables, listings, and figures (TLFs) will be provided to show data in both Systeme Internationale (SI) and United States (US) unit systems, if applicable.

Tables will present results by treatment group (and overall if applicable), and laboratory tests alphabetically within laboratory test group, as applicable.

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

6.5.2.1 Laboratory Test Abnormalities

[redacted]

Worst Laboratory Test Abnormalities

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

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

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

Laboratory Test Toxicity Grade Shifts From Baseline to Worst Abnormality

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

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

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

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

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

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

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

6.5.2.2 LFT Elevations

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

[redacted]

LFT Elevations

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

- Pre-treatment for treated subjects
- Pre-rimegepant treatment for DB or OL rimegepant treated subjects
- On-DBT for treated subjects (excluding overall)
- On-DB or OL rimegepant for DB or OL rimegepant treated subjects
- On-DB or OL rimegepant for DB or OL rimegepant treated subjects by subgroup level and overall for all safety subgroups of interest described in Sections 6.1.3.3
- Post-DBT pre-OL rimegepant for interim subjects
- On-OL rimegepant for OL rimegepant treated subjects by overall for the 90-Day Safety Update only
- On-OL rimegepant for OL rimegepant treated subjects by subgroup level and overall for all safety subgroups of interest described in Sections 6.1.3.4
- On-treatment for treated subjects by overall for the 90-Day Safety Update only
- Follow-up for follow-up subjects.

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

- Exposure-adjusted cumulative LFT elevations with the number and percentage of subjects with LFT elevations, along with patient-years and exposure-adjusted rates based on exposure up to time of first LFT elevation (see Section 7.6.1).
- Time to first LFT elevation with number and percentage of subjects with LFT elevations by time categories (weeks): ≤ 2, > 2 to ≤ 4, > 4 to ≤ 8, and additional 4-week intervals. LFT

elevations are ALT > 3 x ULN, AST > 3 x ULN, and ALT or AST > 3 x ULN. Subjects must have an LFT elevation in the safety analysis period to be included.

LFT ULN Shifts From Baseline to Worst Elevation

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

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

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

eDISH Scatter Plots

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

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

By-Subject Longitudinal LFT Plots

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

6.5.2.3 Laboratory Test Changes From Baseline Over Time

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

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

6.5.3 Vital Signs and Physical Measurements

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

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

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

6.5.3.1 Vital Sign and Physical Measurement Changes From Baseline Over Time

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

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

6.5.3.2 Vital Sign and Physical Measurement Abnormalities

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

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

6.5.4 Electrocardiograms

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

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

6.5.4.1 ECG Changes From Baseline Over Time

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

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

6.5.4.2 ECG Interpretation Shifts From Baseline to Worst Category

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

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

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

6.5.4.3 ECG Abnormalities

[redacted]

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

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

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

6.5.5 Sheehan-Suicidality Tracking Scale

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

[redacted]

Values and changes from baseline in the self-reported S-STS ideation subscale, behavior subscale, and total score will be summarized as continuous parameters at baseline and the worst (highest) score in safety analysis periods by treatment group and overall.

In addition, the number and percentage of subjects in the worst (highest) score change from baseline category (i.e., < -1, -1, no change, 1, > 1) in safety analysis periods will also be presented by treatment group and overall for the ideation subscale, behavior subscale, and total score.

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

A by-subject listing of the S-STS will be provided for enrolled subjects. [redacted]

[redacted]

6.6.1 MSQoL

See Section 6.3.2.3 for the description of the MSQoL.

Descriptive Analyses

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

[redacted]

[redacted]

6.6.2 MIDAS

See Section 6.3.2.4 for the description of the MIDAS.

Descriptive Analyses

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

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8 CHANGES TO PLANNED ANALYSES IN THE PROTOCOL

There are no changes to planned analyses in the protocol at this time.

9 APPENDICES

[redacted]

[redacted]

[redacted]