Protocol C4951011 (BHV3000-405)

A Phase 4, Open-Label Study to Evaluate the Safety and Tolerability of Daily Dosing of Rimegepant in Episodic Migraine Prevention

Statistical Analysis Plan

Version 8

Date: 05-Sep-2024

SIGNATURE PAGE

Protocol Title: A Phase 4, Open-Label Study to Evaluate the Safety and Tolerability of Daily Dosing of Rimegepant in Episodic Migraine Prevention

Document Version: 8

Date: 05-Sep-2024

Author: PPD

Signature: PPD

Date: 05-SEP-2024

Approval

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

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

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

PPD

Signature: PPD

Date:

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REVISION HISTORY

Version	Description of Change
1	Original version (11-May-2022) based on Protocol Version 3
2	Amended version (12-Jul-2022) based on Protocol Version 3 Abbreviations: Removed CK. Section 2.4: Specified that SAP Version 2 is based on Protocol Version 3. Section 3.2.1: Modified the "Safety Endpoint" and "Summary" rows of Table 1. Section 6.1.1.2: Specified additional criteria for displaying COVID-19 visit impact code in select by-subject listings. Section 6.2.5: Removed tables of baseline characteristics by subgroups. Section 6.2.5.2: Added an additional categorical parameter to the migraine history table and listing. Section 6.2.6.2: Added an additional categorical parameter to the treatment compliance table and listing. Section 6.2.6.3: Added a frequency table of non-study follow-up medications for the follow-up safety analysis set. Section 6.4.1: Specified additional criteria for displaying COVID-19 visit impact code in the AE listing. Section 6.4.1.6: Modified the section title. Sections 6.4.2 and 6.4.4: Modified the visit collection schedule to be consistent with the protocol. Section 6.4.7: Changed "enrolled analysis set" to "safety analysis set" for SAEs.
3	Amended version (31-Jan-2023) based on Protocol Version 4 General: Changed "Biohaven Pharmaceuticals" to "Pfizer Inc" and "BHV3000-305" to "C4951011 (BHV3000-405)" throughout. Signature page: Replaced PPD with PPD Abbreviations: Added SI. Removed TEAE. Section 1.2: Changed "CSR database" to "database", and specified that no interim analyses are planned. Removed the last sentence. Section 2.1: Specified that approximately 280 subjects will be enrolled to treat approximately 150 subjects with study drug to ensure that at least 100 subjects will complete 24 weeks of treatment. Section 2.4: Specified that SAP Version 3 is based on Protocol Version 4, and that the target sample size was increased from 125 to 150 subjects to ensure that at least 100 subjects would complete 24 weeks of treatment. Section 3.2: In the "Intercurrent Events" section, specified that all observed values of the endpoint of interest are used prior to study drug discontinuation plus 7 days. Section 4.3: Removed all text and specified "Not applicable". Section 5: Updated to align with Protocol Version 4. Section 6.1.1.1: Removed references to safety subgroups. Section 6.1.1.2: Removed COVID-19 visit impact codes from listings. Section 6.2.2: Removed the frequency tables of enrollment by age group and accrual by month and year of rimegepant start.

Version	Description of Change
	Section 6.2.3: Added the by-subject listing of subject discontinuation for the enrolled analysis set, and specified its contents.
	Section 6.2.3.1: Removed the by-subject listing of eligibility with inclusion/exclusion criteria.
	Section 6.2.3.2: Removed the by-subject listing of OLT subject disposition. Removed "the final".
	Section 6.2.3.3: Removed the by-subject listing of follow-up subject disposition.
	Section 6.2.3.4: Added reference to Section 6.2.3.1.
	Section 6.2.3.5: Removed the by-subject listing of rescreen and previous study participation.
	Section 6.2.4: Moved text from Section 6.2.4.1 here.
	Sections 6.2.4.1 and 6.2.4.2: Removed.
	Section 6.2.5: Removed tables of baseline characteristics for select analysis sets. Removed the by-subject listing of cardiac and other risk factors.
	Section 6.2.5.2: Removed the parameter "diagnosed with migraines for ≥ 1 year prior to screening from the migraine history table because the parameter was added to the Core SAP.
	Section 6.2.6.1: Renamed section as "Study Medication". Modified the contents of the by-subject listing of study drug. Removed tables of rimegepant exposure by subgroups.
	Section 6.2.6.3: Renamed section as "Non-study Concomitant Medications". Removed frequency table of non-study follow-up medications. Simplified the definition of migraine standard of care medications.
	Section 6.4: Removed tables during pretreatment for the enrolled analysis set by overall.
	Section 6.4.1: Removed by-subject listings of SAEs, AEs leading to study drug discontinuation, and AEs of special interest.
	Section 6.4.1.1: Removed the frequency table of deaths.
	Section 6.4.1.2: Removed AE overview frequency tables during pretreatment for the enrolled analysis set and by subgroups.
	Section 6.4.1.3: Removed AE frequency tables for the enrolled analysis set.
	Section 6.4.1.4: Removed frequency tables of TEAEs by intensity, TEAEs occurring with ≥ 2% frequency after rounding, exposure-adjusted multiple occurrences of unique SAEs, exposure-adjusted multiple occurrences of SAEs related to study drug, exposure-adjusted multiple occurrences of non-SAEs with ≥ 5% frequency, and by subgroups.
	Section 6.4.2: Specified that TLFs display results in SI units, if applicable, and the contents of the by-subject listing of LFT values and ratios. Removed by-subject listings of laboratory tests by laboratory test group and pregnancy tests. Added the by-subject listing of laboratory test results for subjects with select findings.
	Section 6.4.2.1: Removed frequency tables of laboratory test low/normal/high shift from baseline to any abnormal value, and by subgroups.
	Section 6.4.2.2: Removed frequency table of LFT elevations during pretreatment for the enrolled analysis set. Added study drug dosing days to the by-subject longitudinal LFT plot.
	Section 6.4.3: Removed the by-subject listing of vital signs and physical measurements.
	Section 6.4.4: Removed the by-subject listing of ECG results.
	Section 6.4.4.2: Removed.
	Section 6.4.4.3: Renumbered as Section 6.4.4.2.
	Section 6.4.5: Removed.
	Section 6.4.6: Renumbered as Section 6.4.5. Removed the by-subject listing of C-SSRS.

Version	Description of Change
	Section 6.4.7: Renumbered as Section 6.4.6.
	Section 6.5: Removed the by-subject listing of COVID-19 impact codes by visit. Renamed the by-subject listing of COVID-19 visit impact to visits impacted by COVID-19.
	Section 7.1: Added the death date.
	Section 7.3: Removed "Baseline #" row and corresponding footnote from Table 3.
	Section 8: Removed "the final".
	Section 9.1: Modified deviation about major depressive disorder. Changed "strong CYP3A4" to "moderate or strong CYP3A4".
4	Amended version (23-Mar-2023) based on Protocol Version 5
	General: Removed "Pfizer Inc". Changed "C4951011 (BHV3000-405)" to "BHV3000-405 (C4951011)". Added footer "Pfizer Confidential".
	Signature page: Removed all references to "sponsor". Removed PPD
	Section 1: Removed "Biohaven".
	Section 2.4: Specified that SAP Version 4 is based on Protocol Version 5, and that the target sample size was increased from 150 to 170 subjects to ensure that at least 100 subjects would complete 24 weeks of treatment.
	Section 5: Updated to align with Protocol Version 5 Section 9.1.
5	Amended version (21-Sep-2023) based on Protocol Version 6
	General: Applied Pfizer Global Style Guide throughout.
	Signature page: Changed "Hospital Products" to "Infectious Disease".
	Abbreviations: Added LSLV.
	Section 1.2: Specified that there is 1 planned database lock, LSLV database lock, which occurs when the last subject completes the Follow-Up Week 8 Visit, and that the LSLV final CSR is produced after the LSLV database lock.
	Section 2.1: Specified that a sufficient number of subjects will be enrolled to treat approximately 285 subjects with study drug to ensure that at least 170 subjects will complete 24 weeks of treatment.
	Section 2.3: Specified that all TLFs (draft or final) produced before or after the LSLV database lock are produced with the actual treatment group.
	Section 2.4: Specified that SAP Version 5 is based on Protocol Version 6, and described protocol changes that impacted statistical analyses.
	Section 5: Updated to align with Protocol Version 6 Section 9.1.
	Section 9.1: Changed "more than once and assigned" to "under". Removed "Gilbert's syndrome or any other".
	Section 6.2.4.1: Moved text from Section 6.2.4 here. Changed "enrolled" to "safety".
	Section 6.2.4.2: Added back entire section from SAP Version 1, but changed "enrolled" to "safety" and added a footnote description.
	Section 6.2.6.2: Modified the algorithm for required cumulative tablet count. Removed "No rimegepant taken for ≥ 3 days (not necessarily consecutive) in any 1 week."
	Section 7.3: Changed "Analysis-specified Interval" to "Analysis Visit Window" in Tble 3 column header.
	Section 8: Removed first sentence and modified second sentence as "All TLFs described in this SAP are produced for the LSLV final CSR (see Section 1.2)".

Version	Description of Change
	Section 9.1: Changed "Basilar migraine or hemiplegic migraine" to "Basilar migraine, hemiplegic migraine, or retinal migraine". For pretreatment eGFR and BMI, modified existing criteria and added new criteria to align with Protocol Version 6 Section 5.3. Changed "No rimegepant taken for ≥ 3 days (not necessarily consecutive) in any 1 week" to "Tablet count compliance < 80% from rimegepant start to later of last scheduled OLT Phase visit or rimegepant end". Specified how to determine the protocol version to which subjects originally consented.
6	Amended version (27-Mar-2024) based on Protocol Version 6 Signature page: Changed PPD General: Changed "BHV3000-405 (C4951011)" to "C4951011 (BHV3000-405)", and "BHV3000-405" to "C4951011" throughout. Abbreviations: Added CTCAE, DAIDS, FDA, and US. Removed COVID-19 and P-gp. Section 2.4: Specified that SAP Version 6 is based on Protocol Version 6. Section 4.1: Removed the COVID-19 impacted analysis set. Section 5: Changed "BHV3000-305 (C4951025)" to "C4951025 (BHV3000-305)". Section 6.1.1.3: Removed "All listings except administrative listings identify subjects who are impacted by COVID-19.", and "and visits impacted by COVID-19 visit impact". Section 6.2.1: Removed "(excluding COVID-19 impacted)". Section 6.2.3: Removed "Premature study termination due to COVID-19 status" from the by-subject listing of subject discontinuation. Section 6.2.3.1: Removed premature termination due to COVID-19. Sections 6.2.3.2 and 6.2.3.3: Removed premature termination due to COVID-19. Changed "database" to "LSLV database". Sections 6.2.3.4 and 6.2.3.5: Removed. Section 6.2.5: Removed "and in COVID-19 analyses by analysis visit (see Section 6.5)". Section 6.2.6.1: Removed the administrative listing of investigational drug batch numbers. Section 6.4.1.2: Modified the contents of the AE overview table. Removed the pretreatment AE overview table. Section 6.4.1.3: Removed. Section 6.4.1.4: Renumbered as Section 6.4.1.3. Changed "by intensity" to "by worst intensity". Removed tables of medication-overuse headache AEs and exposure-adjusted multiple occurrences of AEs. Section 6.4.1.5: Renumbered as Section 6.4.1.4. Changed "by intensity" to "by worst intensity". Section 6.4.1.6: Removed. Section 6.4.2: Specified that TLFs display results using both SI and US units, if applicable. Specified separate listings of laboratory test results for each toxicity grading scale (CTCAE/DAIDS in SI units; FDA in US units), and a separate listing of pregnancy test results. Section 6.4.2.1: Specified that separate tables are provided for each toxicity grading scale (CTCAE/DAIDS using SI units; and FDA using US units). Section 6.4.2.2: Specified that analyses use SI units. Removed tables of pretreatment LFT elevations and on-treatment exposure-adjusted cumulative LFT elevations. Section 6.4.2.3: Specified that a separate table is provided for each unit system (SI or US). Section 6.5: Removed.

Version	Description of Change
	Section 7.1: Changed “database” to “LSLV database”. Modified the definition of the last contact date to exclude COVID-19 visit date. Section 7.2: Removed “and to assess pretreatment safety endpoints”. Section 9.1: Changed “moderate or strong CYP3A4 inhibitor” to “strong CYP3A4 inhibitor”. Removed “Select strong permeability glycoprotein (P-gp) inhibitor taken on or after informed consent #”.
7	Amended version (20-Jun-2024) based on Protocol Version 6 Section 2.4: Specified that SAP Version 7 is based on Protocol Version 6. Section 6.2.5.4: Changed “migraine standard of care” to “acute migraine”. Section 6.2.6.3: Changed “migraine standard of care” to “acute migraine”. Modified the definition of acute migraine medications, and removed the definition of migraine standard of care medications. Section 6.4.2.2: Changed “anorexia” to “decreased appetite” in frequency tables of LFT elevations. Section 6.4.6: Changed “AE” to “non-SAE” in 4 places. Reordered events.
8	Amended version (05-Sep-2024) based on Protocol Version 6 Section 2.4: Specified that SAP Version 8 is based on Protocol Version 6. Section 6.4.2.2: Changed “longitudinal” to “line”. Section 9.1: Removed “medical history” and “cardiovascular disease risk factor”, Changed “females with a positive pregnancy test on or after informed consent” to “females with a positive pregnancy test during pretreatment”, and “study drug dosing error” to “study drug dosing noncompliance”.

ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
CGRP	Calcitonin gene-related peptide
CI	Confidence interval
CRF	Case report form
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Technical Criteria for Adverse Events
CYP3A4	Cytochrome P450 3A4
DAIDS	Division of Acquired Immune Deficiency Syndrome
ECG	Electrocardiogram
eDISH	Evaluation of drug-induced serious hepatotoxicity
eGFR	Estimated glomerular filtration rate
EOT	End of treatment
FDA	Food and Drug Administration
HDL	High-density lipoprotein
IWRS	Interactive web response system
LDL	Low-density lipoprotein
LFT	Liver function test
LSLV	Last subject last visit
MDRD	Modification of Diet in Renal Disease
ODT	Orally disintegrating tablet
OLT	Open-Label Treatment
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SI	Systeme Internationale
SOC	System organ class
TBL	Total bilirubin

Abbreviation	Definition
TLF	Table listing figure
ULN	Upper limit of normal
US	United States

1 BACKGROUND AND RATIONALE

This document presents the statistical analysis plan (SAP) for Pfizer Inc, Protocol BHV3000-405 (C4951011): A Phase 4, Open-Label Study to Evaluate the Safety and Tolerability of Daily Dosing of Rimegepant in Episodic Migraine Prevention.

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

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

1.1 Research Hypothesis

Rimegepant 75 mg orally disintegrating tablet (ODT) is well tolerated when taken daily for the prevention of migraine.

1.2 Schedule of Analyses

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

No interim analyses are planned.

2 STUDY DESCRIPTION

2.1 Study Design

This is a multicenter, open-label study to assess the long-term safety and tolerability of rimegepant in episodic migraine prevention.

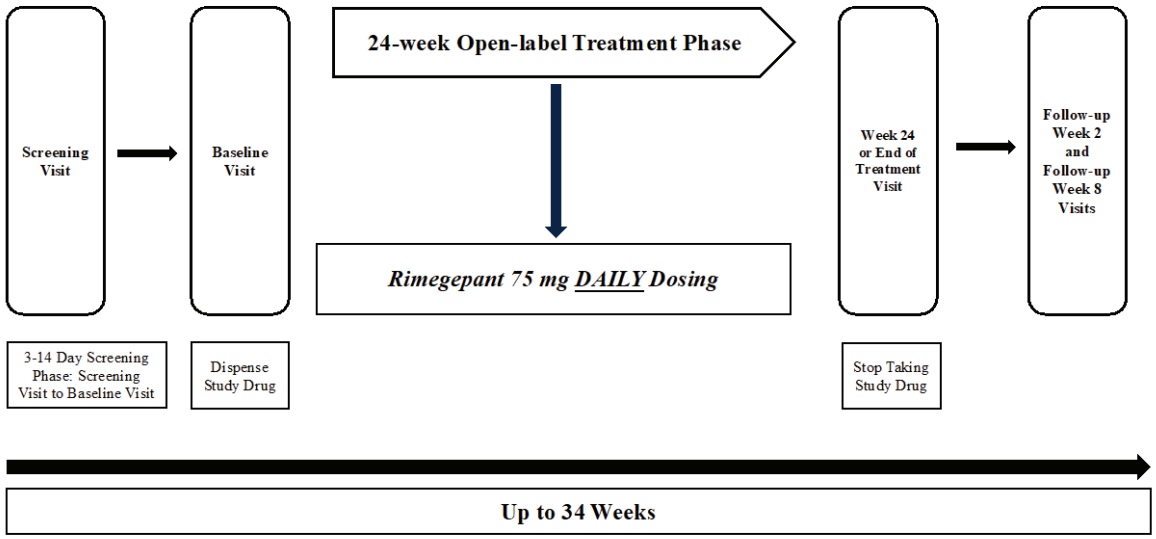
The study has 3 phases:

- Screening Phase: Lasts 3 to 14 days, and includes the Screening Visit.
- Open-Label Treatment (OLT) Phase:
  - Includes the Baseline, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, and End of Treatment (EOT) Visits.
  - Subjects are instructed to take study drug (i.e., rimegepant 75 mg ODT) daily for up to 24 weeks.
  - All subjects who take study drug and discontinue early from the OLT Phase should complete the EOT Visit. Otherwise, subjects should complete the Week 24 Visit.
- Follow-Up Phase:

- Includes Follow-Up Week 2 and Follow-Up Week 8 Visits primarily for safety assessments. These occur approximately 2 and 8 weeks respectively after the Week 24 or EOT Visit.
- All subjects who are treated with study drug should have both follow-up visits.

The design of the study is shown in Figure 1. A sufficient number of subjects will be enrolled to treat approximately 285 subjects with study drug to ensure that at least 170 subjects will complete 24 weeks of treatment.

Figure 1 Study Schematic



2.2 Treatment Assignment

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

If the subject is deemed eligible to participate in the study at the Baseline Visit, then the IWRS assigns specific container numbers for all open-label study drug to be dispensed at the Baseline Visit and subsequent visits in the OLT Phase.

2.3 Blinding and Unblinding

This is an open-label study. All TLFs (draft or final) produced before or after the LSLV database lock are produced with the actual treatment group.

2.4 Protocol and Protocol Amendments

C4951011 SAP Versions 1 and 2 are based on C4951011 Protocol Version 3 (08-Mar-2022).

C4951011 SAP Version 3 is based on C4951011 Protocol Version 4 (07-Nov-2022). The target sample size was increased from 125 to 150 subjects to ensure that at least 100 subjects will complete 24 weeks of treatment.

C4951011 SAP Version 4 is based on C4951011 Protocol Version 5 (14-Feb-2023). The target sample size was increased from 150 to 170 subjects to ensure that at least 100 subjects will complete 24 weeks of treatment.

C4951011 SAP Version 5 is based on C4951011 Protocol Version 6 (07-Aug-2023). Protocol changes that affected statistical analyses were the following: changing the sponsorship to Pfizer; stating that there is 1 planned database lock; increasing the target sample size to 285 treated subjects to ensure that at least 170 subjects will complete 24 weeks of treatment; and modifying exclusion criteria, which affects relevant protocol deviations.

C4951011 SAP Versions 6 and 7 are based on C4951011 Protocol Version 6 (07-Aug-2023). These SAPs incorporate project-level changes to the Core SAP.

C4951011 SAP Version 8 is based on C4951011 Protocol Version 6 (07-Aug-2023). This SAP modifies relevant protocol deviations.

3 STUDY OBJECTIVES AND ESTIMANDS

3.1 Objectives

3.1.1 Primary Objective

To evaluate the safety and tolerability of rimegepant taken daily for episodic migraine prevention during the OLT Phase.

3.1.2 Secondary Objectives

Not applicable.

3.1.3 Exploratory Objectives

1. To evaluate the frequency of adverse events (AEs) potentially associated with drug abuse during the OLT Phase.

2. To evaluate the frequency and intensity of hepatic-related AEs during the OLT Phase.

3. To evaluate the frequency of liver function test (LFT) elevations (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], and total bilirubin [TBL]) based on fold changes above upper limit of normal (ULN) during the OLT Phase.

4. To evaluate the frequency of ALT or AST > 3x ULN concurrent with TBL > 2x ULN during the OLT Phase.

5. To evaluate the frequency of ALT or AST > 3x ULN in temporal association with nausea, vomiting, anorexia, abdominal pain, or fatigue during the OLT Phase.

6. To evaluate the Columbia-Suicide Severity Rating Scale (C-SSRS) during the OLT Phase.

3.2 Estimands

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

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

Intercurrent Events

Intercurrent events are those that occur after treatment initiation and either preclude observation of the endpoint or affect its interpretation. Study drug discontinuation before the time point of interest defining the endpoint is considered an intercurrent event.

For safety objectives, study drug discontinuation is handled with a "while-on-treatment strategy," i.e., response to treatment prior to the occurrence of the intercurrent event of interest, such that all observed values of the endpoint of interest are used prior to study drug discontinuation plus 7 days (see Section 7.2 and the Core SAP).

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

Data Sources for Endpoints

AEs are determined from AE case report forms (CRFs).

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

C-SSRS parameters are derived from the C-SSRS CRF.

3.2.1 Primary Objective Estimand

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

Table 1 Primary Objective Estimand

Objective	**Safety and tolerability on treatment**
Safety Endpoint	Number and percentage of subjects with the following safety events and findings on treatment: AEs that occur in at least 5% of subjects by intensity; serious adverse events (SAEs); AEs leading to study drug discontinuation; and grade 3 to 4 laboratory test abnormalities
Summary	• AEs: Frequency for the safety analysis set • Laboratory test abnormalities: Frequency for the safety analysis set with laboratory test data on treatment
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy

3.2.2 Secondary Objective Estimands

Not applicable.

3.2.3 Exploratory Objective Estimands

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

Table 2 Exploratory Objective Estimands

Objective	**Frequency of AEs potentially associated with drug abuse during the OLT Phase**
Safety Endpoint	Number and percentage of subjects with potential drug abuse AEs on treatment
Summary	Frequency for the safety analysis set
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy
Objective	**Frequency and intensity of hepatic-related AEs during the OLT Phase**
Safety Endpoint	Number and percentage of subjects with hepatic-related AEs by intensity on treatment
Summary	Frequency for the safety analysis set
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy
Objective	**Frequency of LFT elevations based on fold changes above ULN during the OLT Phase**
Safety Endpoint	Number and percentage of subjects with LFT elevations (ALT, AST, ALP, or TBL) based on fold changes above ULN on treatment
Summary	Frequency for the safety analysis set with LFT data on treatment
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy
Objective	**Frequency of ALT or AST > 3x ULN concurrent with TBL > 2x ULN during the OLT Phase**
Safety Endpoint	Number and percentage of subjects with ALT or AST > 3x ULN concurrent with TBL > 2x ULN on treatment
Summary	Frequency for the safety analysis set with LFT data on treatment
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy

Objective	**Frequency of ALT or AST > 3x ULN in temporal association with nausea, vomiting, anorexia, abdominal pain, or fatigue during the OLT Phase**
Safety Endpoint	Number and percentage of subjects with ALT or AST > 3x ULN concurrent with AEs of nausea, vomiting, anorexia, abdominal pain, or fatigue on treatment
Summary	Frequency for the safety analysis set with LFT data on treatment
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy
Objective	**C-SSRS during the OLT Phase**
Safety Endpoint	Number and percentage of subjects with any of the following findings on treatment: suicidal ideation; suicidal behavior; suicidal ideation or behavior; and non-suicidal self-injurious behavior.
Summary	Frequency for the safety analysis set with C-SSRS data on treatment
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy

4 ANALYSIS SETS, TREATMENT GROUPS, AND SUBGROUPS

4.1 Analysis Sets

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

- Enrolled: subjects who sign an informed consent form and are assigned a subject identification number, i.e., nonmissing informed consent date. This analysis set is used mainly to assess study population and in by-subject listings.
- Safety: subjects in the enrolled analysis set who take ≥ 1 dose of study drug (rimegepant), i.e., nonmissing study drug start date. This analysis set is used to assess study population, exposure, and on-treatment safety.
    - Follow-up safety: subjects in the safety analysis set whose last contact date is in the follow-up analysis period. This analysis set is used to assess follow-up safety.

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

4.2 Treatment Groups

The single treatment group is rimegepant 75 mg ODT.

4.3 Subgroups

Not applicable.

5 SAMPLE SIZE, POWER, AND TYPE 1 ERROR

With a target sample size of 285 subjects in the safety analysis set and no events observed, the upper bound of a 1-sided 95% confidence interval (CI) for zero observations is 0.01. Hence, this sample size is large enough to rule out events that occur at rates greater than 1 case per 100 subjects.

In C4951025 (BHV3000-305) migraine-prevention study with every-other-day dosing, 73% of subjects in the rimegepant treatment group had ≥ 6 months (defined as ≥ 23 weeks) of double-blind or open-label rimegepant (i.e., 27% noncompletion rate). In this study, it is expected that the 24-week noncompletion rate will be higher due to early termination from baseline laboratory test elevations. Assuming a 40% noncompletion rate, approximately 170 subjects in the safety analysis set are expected to complete 24 weeks of treatment.

6 STATISTICAL ANALYSES

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

6.1 General

6.1.1 Programmed Output

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

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

6.1.1.1 Tables

Tables display results in a single treatment group column as “Overall”, unless otherwise specified.

6.1.1.2 Listings

Unless otherwise specified, by-subject listings are sorted by treatment status (treated [i.e., in the safety analysis set], not treated), site-subject ID, and additional variables such as time points, as applicable. Treatment group is abbreviated as “RMG” for subjects in the safety analysis set, and “NTRT” for subjects not in the safety analysis set.

Listings of exposure and safety parameters include the following: abbreviated name of the analysis period in which the measurement was slotted (i.e., PRETRT, ONTRT, FU; this does not apply to exposure); analysis visit in which the measurement was slotted (this does not apply to exposure or AEs); measurement date/time; study day derived using the measurement date (see Section 7.3).

6.1.2 Statistical Methods

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

6.1.3 Missing Data

All analyses are based on observed data without using imputation.

6.2 Study Population

Refer to the Core SAP for TLF contents.

6.2.1 Analysis Sets

The frequency table of analysis sets described in Section 4.1 is provided.

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

6.2.2 Enrollment

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

6.2.3 Subject Disposition

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

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

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

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

6.2.3.1 Subject Disposition From Enrollment to Treatment

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

- Treated with rimegepant (identified as subjects with nonmissing study drug start date)

- Not treated with rimegepant (identified as subjects with missing study drug start date)
    - Reasons for early discontinuation (i.e., not completing the study), including not reported. For subjects whose reason is screen failure due to inclusion/exclusion criteria, the reasons for screen failure from the Inclusion/Exclusion Criteria CRF are also included as subcategories.

6.2.3.2 Subject Disposition During the OLT Phase

The frequency table of subject disposition during the OLT Phase is provided for the safety analysis set based on the Treatment Phase Subject Status CRF, and displays the following categories:

- Ongoing in the OLT Phase. These are identified as subjects with (1) missing response to the question "Did the subject complete the OLT Phase?" and (2) missing study drug last date. This category only exists before LSLV database lock. After LSLV database lock, subjects with missing response are categorized as "Did not complete the OLT Phase".
- Completed the OLT Phase. These are identified as subjects with (1) "yes" response to the question "Did the subject complete the OLT Phase?" and (2) nonmissing study drug last date.
- Did not complete the OLT Phase. These are identified as subjects with (1) "no" or missing response to the question "Did the subject complete the OLT Phase?" and (2) nonmissing study drug last date.
    - Reasons for not completing the OLT Phase, including not reported
- Continued to the Follow-Up Phase. These are identified as subjects with "yes" response to the question "Is the subject continuing to the Follow-Up Phase?".
- Did not continue to the Follow-Up Phase. These are identified as subjects with "no" or missing response to the question "Is the subject continuing to the Follow-Up Phase?".
    - Reasons for not continuing to the Follow-Up Phase, including not reported.

6.2.3.3 Subject Disposition During the Follow-Up Phase

The frequency table of subject disposition during the Follow-Up Phase is provided for the follow-up safety analysis set based on the Follow-Up Subject Status CRF, and displays the following categories:

- Did not formally enter the Follow-Up Phase. These are identified as subjects with (1) missing response to the question "Did the subject complete the Follow-Up Phase?", and (2) "no" or missing response to the question "Is the subject continuing to the Follow-Up Phase?" on the Treatment Phase Subject Status CRF. A footnote explains that these are subjects with data in the follow-up safety analysis period who did not continue to the Follow-Up Phase as per Treatment Phase Subject Status CRF.
- Ongoing in the Follow-Up Phase. These are identified as subjects with (1) missing response to the question "Did the subject complete the Follow-Up Phase?", and (2) "yes" response to the question "Is the subject continuing to the Follow-Up Phase?" on the Treatment Phase

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

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

6.2.4 Protocol Deviations

6.2.4.1 Relevant Protocol Deviations

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

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

6.2.4.2 Significant Protocol Deviations

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

6.2.5 Baseline Characteristics

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

Tables of baseline characteristics are provided for the safety analysis set.

Baseline for a parameter collected over time (e.g., weight) is defined according to analysis set; refer to the Core SAP for details, including handling of ties on the same measurement date (entry date/time is the "earliest data creation time" variable in the raw CRF datasets). Note that the baseline value of a parameter is independent of the baseline analysis visit defined in Table 3; the latter is used only in by-subject listings that display visit(see Section 6.5).

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

6.2.5.1 Demographics and Other Relevant Baseline Characteristics

Refer to the Core SAP for the table of demographics and other relevant baseline characteristics. Previous study participation (e.g., any study, BHV3000-301, BHV3000-302, BHV3000-303, etc.) is also displayed.

6.2.5.2 Baseline Disease Characteristics

Refer to the Core SAP for the table of migraine history and frequency table of cardiac and other risk factors.".

6.2.5.3 Medical History

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

6.2.5.4 Nonstudy Prior Medications

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

- Current medications: all; acute migraine; prophylactic migraine
- Stable prophylactic migraine medications through study drug start.

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

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

6.2.6 Exposure

6.2.6.1 Study Medication

Study drug is rimegepant 75 mg ODT daily. Study drug is dispensed in a wallet-type blister card with a unique wallet ID. Each wallet has 8 tablets. Sites report the wallet ID, study medication start date, study medication end date, and number of tablets taken per day on the IP Dosing CRF.

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

- Time on rimegepant (weeks), derived as (study drug end date – study drug start date + 1)/7
- Time on rimegepant (weeks) categories: < 2, ≥ 2 to < 4, ≥ 4 to < 8, ≥ 8 to < 12, ≥ 12 to < 16, ≥ 16 to < 20, ≥ 20 to < 24, ≥ 24

- Time on rimegepant milestone categories:
  - ≥ 3 months, defined as ≥ 11 weeks
  - ≥ 6 months, defined as ≥ 23 weeks
- Cumulative rimegepant exposure (mg), derived by summing {number of days × number of tablets taken per day × 75} across records with complete study medication start dates.
  - Number of days for a record is derived as imputed study medication end date – study medication start date + 1.
- Average rimegepant exposure (mg per day), derived as cumulative rimegepant exposure/time on rimegepant (days)
- Total rimegepant exposure (mg) summed across all subjects, derived by summing cumulative exposure across all subjects
- Total rimegepant exposure (patient-years), derived by summing (study drug end date – study drug start date + 1)/365.25 across all subjects.

See Section 7.1 for derived dates.

The by-subject listing of study drug is provided for the safety analysis set based on the IP Dosing CRF, and displays wallet ID, study medication start date, study medication end date, study day derived from study medication start date, and number of tablets taken per day ≥ 0. The listing also displays study drug start and end dates and rimegepant exposure parameters (time on rimegepant, cumulative rimegepant exposure, and average rimegepant exposure), and identifies invalid wallet IDs. Valid wallet IDs are those that are in the kit list file. The listing is sorted by site-subject ID, study medication start date, wallet ID, and study medication end date.

6.2.6.2 Measurements of Treatment Compliance

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

- Tablet count compliance ≥ 80% from rimegepant start to later of last scheduled OLT Phase visit or rimegepant end. Tablet count compliance is derived as 100 × actual cumulative tablet count/required cumulative tablet count, where
  - Actual cumulative tablet count is derived by summing the {number of days × number of tablets taken per day} across records with complete study medication start dates.
    - Number of days for a record is derived as imputed study medication end date – study medication start date + 1.
  - Required cumulative tablet count is derived as {maxdate – study drug start date + 1}, where maxdate is defined as the latest of the (1) scheduled Week 2, 4, 8, 12, 16, 20, and Week 24/EOT visit dates, and (2) study drug end date.
    - Scheduled visits are identified from visit labels, and therefore exclude those containing “unscheduled” in the visit label.

  - If the required cumulative tablet count is < 14, then it is reset to {study drug end date – study drug start date + 1} to account for early OLT Phase termination due to baseline laboratory test exclusion criteria.

- > 1 tablet taken on any 1 day. This is determined from either of the following:
  - Records with complete study medication start date and number of tablets taken per day > 1
  - Overlapping records (see Section 9.2)
- Time on rimegepant > 26 weeks.

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

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

6.2.6.3 Nonstudy Concomitant Medications

Frequency tables of the following nonstudy concomitant medications are provided by therapeutic class and preferred name for the safety analysis set: all; acute migraine; prophylactic migraine.

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

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

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

The following conventions apply to nonstudy medications:

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

6.3 Efficacy

Not applicable.

6.4 Safety

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

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

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

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

6.4.1 Adverse Events

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

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

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

6.4.1.1 Deaths

Deaths are identified from any the following sources:

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

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

6.4.1.2 AE Overview

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

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

- On-treatment AEs for the safety analysis set
- Follow-up AEs for the follow-up safety analysis set.

6.4.1.3 On-Treatment AEs

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

- AEs by worst intensity
- AEs occurring with ≥ 5% frequency by worst intensity (supports the primary objective). The 5% cut applies only to total intensity.
- AEs related to study drug by worst intensity
- SAEs (supports the primary objective)
- AEs leading to study drug discontinuation (supports the primary objective)
- Potential drug abuse AEs, displayed in alphabetical order by worst intensity and PT without SOC (supports the exploratory objective #1)
- Hepatic-related AEs by intensity (supports exploratory objective #2)
- Hepatic-related AEs leading to study drug discontinuation
- Cardiovascular AEs
- Suicidality AEs.

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

6.4.1.4 Follow-Up AEs

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

- AEs by worst intensity
- SAEs.

6.4.2 Laboratory Tests

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

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

- Hematology: Screening; Weeks 2, 4, 8, 12, 16, 24, and EOT.
- Serum chemistry (including LFTs and lipids): Screening; Weeks 2, 4, 8, 12, 16, 24, and EOT. Exceptions are for the following:
  - LFTs (ALT, AST, ALP, TBL, direct bilirubin, indirect bilirubin): all visits during the study.
  - Lipids (total cholesterol, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, triglycerides): Screening; Week 12, Week 24, and EOT.
- Urinalysis: Screening; Week 24 and EOT.

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

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

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

6.4.2.1 Laboratory Test Abnormalities

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

- On-treatment for the safety analysis set
- Follow-up for the follow-up analysis set.

Grade 3 to 4 results support the primary objective.

The frequency table of laboratory test shift from baseline to the worst abnormality on treatment for each graded laboratory test is provided for the safety analysis set.

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

6.4.2.2 Liver Function Test Elevations

Analyses use SI units. Refer to the Core SAP for additional details.

LFT Elevations

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

- On-treatment for the safety analysis set (supports exploratory objectives #3, 4, and 5)
- Follow-up for the follow-up safety analysis set.

Note that in the analysis of ALT or AST > 3x ULN concurrent with a select AE, the AE PT of "anorexia" specified in the Core SAP is replaced with the PT of "decreased appetite" because "anorexia" is no longer in MedDRA.

LFT Shifts From Baseline to Worst Elevation

The frequency table of LFT shift from baseline to the worst (highest) on-treatment LFT elevation is provided for the safety analysis set.

Time to LFT Elevations

The frequency table of time to first on-treatment LFT elevations (ALT > 3x ULN; AST > 3x ULN; ALT or AST > 3x ULN) is provided for subjects in the safety analysis set with on-treatment LFT elevations in the following categories: ≤ 2, > 2 to ≤ 4, > 4 to ≤ 8, …, > 24 weeks. Time to elevation is calculated as (LFT collection date – study drug start date + 1)/7.

LFT Plots

The on-treatment evaluation of drug-induced serious hepatotoxicity (eDISH) scatter plot is provided for the safety analysis set with paired ALT and TBL ratios on treatment.

By-subject line LFT plots are provided for the safety analysis set with select LFT elevations in any analysis period. Study weeks are defined as study day/7, where study day is derived from the laboratory test collection date (see Section 7.3). Each figure also displays study drug dosing days using symbols along the x-axis (see Section 9.2), and additional study milestones (e.g., start of the on-treatment safety analysis period, and start of the follow-up safety analysis period) using vertical lines with their corresponding descriptions in footnotes.

6.4.2.3 Laboratory Test Changes From Baseline Over Time

The table of values and changes from baseline in all hematology and serum chemistry laboratory tests is provided for the safety analysis set at the following time points: baseline; each scheduled visit through Week 24 and EOT in the on-treatment safety analysis period; and each scheduled visit in the follow-up safety analysis period.

Note that scheduled visits vary according to laboratory test.

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

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

6.4.3 Vital Signs and Physical Measurements

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

Refer to the Core SAP for TLF contents.

6.4.3.1 Vital Sign and Physical Measurement Changes From Baseline Over Time

The table of values and changes from baseline in vital sign and physical measurement parameters is provided for the safety analysis set at the following time points: baseline; each scheduled visit through Week 24 and EOT in the on-treatment safety analysis period; and each scheduled visit in the follow-up safety analysis period.

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

6.4.3.2 Vital Sign and Physical Measurement Abnormalities

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

- On-treatment for the safety analysis set
- Follow-up for the follow-up safety analysis set.

6.4.4 Electrocardiogram

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

Refer to the Core SAP for TLF contents.

6.4.4.1 ECG Changes From Baseline Over Time

The table of values and changes from baseline in ECG parameters is provided for the safety analysis set at the following time points: baseline; and each scheduled visit through Week 24 and EOT in the on-treatment safety analysis period.

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

6.4.4.2 ECG Abnormalities

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

- On-treatment for the safety analysis set
- Follow-up for the follow-up safety analysis set.

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

6.4.5 C-SSRS

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

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

- On-treatment for the safety analysis set (supports exploratory objective #6)
- Follow-up for the follow-up safety analysis set.

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

6.4.6 Safety Narratives

The by-subject listing of safety narrative subject identifiers is provided for the following select events, analysis periods, and analysis sets as columns:

- Death in any safety analysis period for the enrolled analysis set
- SAE on treatment or during follow-up for the safety analysis set
- Non-SAE leading to study drug discontinuation in any safety analysis period for the safety analysis set
- Event of special interest on treatment for the safety analysis set:
  - Select hepatic-related non-SAE, i.e., PT containing cirrhosis, hepatic failure, hepatitis, jaundice, or liver failure
  - Cardiovascular non-SAE
  - Suicidality non-SAE

- ALT or AST > 3x ULN
- ALT or AST > 3x ULN concurrent with TBL > 2x ULN
- ALP or TBL > 2x ULN.

Refer to the Core SAP for additional details.

7 CONVENTIONS

7.1 Derived Dates

Derived dates are defined as follows:

- Study drug start date: earliest complete study medication start date from IP Dosing CRF records with number of tablets taken per day > 0. This is an analysis period reference date.
- Imputed study medication end date: If the study medication end date is (1) noncomplete or (2) complete but before the study medication start date, then the imputed end date is set to the study medication start date. Otherwise, the imputed end date is set to the complete study medication end date. Derived only for IP Dosing CRF records with complete study medication start date and number of tablets taken > 0.
- Study drug end date: latest of (1) complete study medication start dates, or (2) complete study medication end dates from IP Dosing CRF records with number of tablets taken per day > 0.
- Study drug last date
  - Before LSLV database lock: study drug end date derived only for subjects with "yes" or "no" response to the phase completion question on the Treatment Phase Subject Status or Follow-up Subject Status CRF
  - LSLV database lock: study drug end date

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

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

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

7.2 Analysis Periods

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

Analysis periods are as follows:

- Pretreatment: This period is used to derive baseline values.
- On-treatment safety: This period is used to assess safety endpoints on treatment for the safety analysis set.
- Follow-up safety: This period is used to assess safety endpoints during follow-up for the follow-up safety analysis set.

Refer to the Core SAP for defining these analysis periods in Phase 2/3/4 multiple-dose (non-randomized non-PRN) studies with 1 treatment phase. See Section 7.1 for derived dates for determining analysis periods.

7.3 Analysis Visit Windows

Refer to Protocol Section 4.3 for the schedule of assessments.

Refer to the Core SAP for defining study days and follow-up days in Phase 2/3/4 multiple-dose (non-randomized non-PRN) studies with 1 treatment phase.

Note that the measurement date must be complete for the measurement to be slotted into an analysis visit.

Analysis visit windows are shown in Table 3.

Table 3 Analysis Visit Windows

Analysis Period Analysis Visit	Abbreviation in Listings	Analysis Day Analysis Visit Window	Target Day
Pretreatment	**PRETRT**	**Study Day**	
Screening *		≤ -2	
Baseline *		-1 or 1	
On-Treatment	**ONTRT**	**Study Day**	
Week 2		2 to 21	14
Week 4		22 to 42	28
Week 8		43 to 70	56
Week 12		71 to 98	84
Week 16		99 to 126	112
Week 20		127 to 154	140
Week 24		155 to 182	168
Extension @	Ext	≥ 183	
Follow-Up	**FU**	**Follow-Up Day**	
Follow-Up Week 2	FU Week 2	8 to 35	14
Follow-Up Week 8	FU Week 8	36 to 77	56
Follow-Up Extension @	FU Ext	≥ 78	

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

8 CONTENT OF REPORTS

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

9 APPENDICES

9.1 Relevant Protocol Deviations

Relevant eligibility protocol deviations include the following categories:

- Treated with study drug under > 1 subject identifier. These subjects are identified from the Protocol Deviations CRF.
- Finding out of range, defined any as any of the following subcategories:
  - Females with a positive pregnancy test during pretreatment (see Section 6.4.2)
  - Estimated glomerular filtration rate (eGFR) according to the re-expressed abbreviated (4-variable) Modification of Diet in Renal Disease (MDRD) Study equation ≤ 40

mL/min/1.73m^2 during pretreatment, if originally consented to Protocol Version 5 or lower *

- eGFR according to the re-expressed abbreviated (4-variable) MDRD Study equation < 30 mL/min/1.73m^2 during pretreatment, if originally consented to Protocol Version 6 or higher *
- BMI ≥ 33 kg/m^2 during pretreatment, if originally consented to Protocol Version 5 or lower *
- BMI > 35 kg/m^2 during pretreatment, if originally consented to Protocol Version 6 or higher *
- C-SSRS suicidal ideation with active intent or plan to act, or suicidal behavior present during pretreatment. Defined as having a "yes" response to any of the following C-SSRS questions during pretreatment:
  - Suicidal ideation question 4 (active suicidal ideation with some intent to act, without specific) or 5 (active suicidal ideation with specific plan and intent)
  - Suicidal behavior question 1 (actual attempt), 3 (interrupted attempt), 4 (aborted attempt), 5 (preparatory acts or behavior), or 6 (suicidal behavior).

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

Relevant subject management protocol deviations include the following categories:

- Study drug dosing noncompliance, defined as any of the following subcategories (see Section 6.2.6.2):
  - Tablet count compliance < 80% from rimegepant start to later of last scheduled OLT Phase visit or rimegepant end
  - > 1 tablet taken on any 1 day.
- Prohibited nonstudy medications, defined as any of the following subcategories:
  - Atypical antipsychotic, divalproex, valproic acid, or valproate taken on or after informed consent #
  - Butterbur root or extract taken up to 14 days before study drug start or afterward
  - Calcitonin gene-related peptide (CGRP) antagonist monoclonal antibody or small molecule taken on or after informed consent #
  - Ergotamine taken on or after informed consent
  - Lamotrigine taken on or after informed consent
  - Narcotic (barbiturate or opioid) taken up to 2 days before study drug start or afterward #
  - Rimegepant taken on or after study drug start
  - Select moderate or strong cytochrome P450 3A4 (CYP3A4) inducer taken on or after informed consent #

- Select strong CYP3A4 inhibitor taken on or after informed consent #.

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

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

9.2 Study Drug Dosing Day

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

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

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

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

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

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

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

Example:

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

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

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

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

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

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

10 REFERENCES

Not applicable.