Protocol BHV3000-202

BHV3000-202: Phase 2: A Double-Blind, Placebo Controlled, Crossover Trial of BHV-3000 (Rimegepant) for Treatment Refractory Trigeminal Neuralgia

Statistical Analysis Plan

Version 2.0

Date: 28-Aug-2023

[redacted]

SIGNATURE PAGE

Protocol Title:	BHV3000-202: Phase 2: A Double-Blind, Placebo Controlled, Crossover Trial of BHV-3000 (Rimegepant) for Treatment Refractory Trigeminal Neuralgia
Document Version:	2.0
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Author:	PPD PPD PPD Signature: Date:

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:

PPD PPD	Signature:_ PPD Date:_____

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REVISION HISTORY

Version	Description of Change
1.0 (Final)	Initial version
2.0 (Final)	Amendment to incorporate the following changes: • Section 3.2 Estimands: Updated Intercurrent Events section with appropriate strategies for safety and secondary efficacy endpoints (Penn-FPS-R, Pain Disability Index). • Section 6.2.5 Baseline Characteristics: Added definition of OL baseline • Section 6.3 Efficacy: Updates on analysis visit window definitions • Section 6.4.1 Adverse Events: Added analysis period window definitions • Section 7.2 Analysis Periods: Updated definitions of analysis periods • Section 7.3 Analysis Visit Windows: Section removed; analysis visit windows no longer apply • Other minor wording and typographical updates throughout the document

ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body mass index
BUN	Blood urea nitrogen
CI	Confidence interval
COVID-19	Coronavirus Disease 2019
CPK	Creatine phosphokinase
CRF	Case Report Form
CSR	Clinical study report
DBT	Double-blind treatment
ECG	Electrocardiogram
eDISH	Evaluation of drug-induced serious hepatotoxicity
eGFR	Estimated glomerular filtration rate
GGT	Gamma-glutamyl transferase
HbA1C	Hemoglobin A1C
HDL	High-density lipoprotein
IR	Immediate release
IWRS	Interactive Web-based Response System
LDL	Low-density lipoprotein
LFT	Liver function test
LSMeans	Least square means
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mITT	Modified Intent to Treat
MMRM	Mixed-effect Model for Repeated Measures
NPRS	Numeric Pain Rating Scale
OLE	Open-label extension
Penn-FPS-R	Penn Facial Pain Scale-Revised
PGI-C	Patient Global Impression of Change Scale
PI	Principal Investigator
PID	Patient Identification Number

Abbreviation	Definition
●	
PT	Prefened te1m
QD	Once Daily
SAE	Serious Adverse Event
SAP	Statistical analvsis plan
SD	Standard deviation
SE	Standard enor
SI	Svsteme Internationale
SOC	System Organ Class
S-STS	Sheehan Suicidalitv Tracking Scale
T4	Thyroxine
TBL	Total bilirubin
TEAE	Treatment-Emergent Adverse Events
TLF	Tables, listings, and fomres
TN	Trigeminal Nemalgia
TSH	Thyroid stimulating honnone
ULN	Upper Limit ofN01mal
US	United States
WHO	World Health Organization

1 BACKGROUND AND RATIONALE

This document presents the statistical analysis plan (SAP) for Pfizer Inc. Protocol: BHV3000-202: Phase 2: A Double-Blind, Placebo Controlled, Crossover Trial of BHV-3000 (Rimegepant) for Treatment Refractory Trigeminal Neuralgia (TN).

This SAP is based on the final protocol version 9.0 dated April 8, 2022. It contains the analysis details and methodology to address the study objectives, including planned summary tables, by-subject listings, and figures, which will provide the basis for the results section of the clinical study report (CSR). Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analyses.

The Rimegepant (BHV3000) Core SAP describes analysis details and methodologies common to the BHV3000 program and is incorporated by reference. The Core SAP assumes primacy for any matter where this SAP is silent (and the relevant content of the Core SAP could feasibly apply) or where the Core SAP is directly referenced as applicable. Otherwise, should any discrepancy exist between the Core SAP and this SAP, this SAP assumes primacy.

Note that the study was terminated prematurely in 1Q2023 due to low enrollment. As a result, only critical data would be analyzed for the CSR.

1.1 Research Hypothesis

Rimegepant is superior to placebo in providing symptom relief for treatment-refractory patients with classical or idiopathic trigeminal neuralgia.

1.2 Schedule of Analyses

The final analysis of the Double-blind Treatment (DBT) Phase will occur after the last subject randomized has completed this phase of the study or discontinues from the DBT Phase. The study will be unblinded and analyses will summarize all efficacy, safety, laboratory and other data collected throughout the DBT phase of study.

A final analysis of the study will be completed after the last subject has completed their last study visit of the Open-Label Extension (OLE) Phase of the study. These analyses will summarize all efficacy, safety, laboratory and other data collected throughout the OLE Phase of the study. In addition throughout the study, data may be locked, analyses conducted, and reports produced as required to support safety monitoring or regulatory requirements.

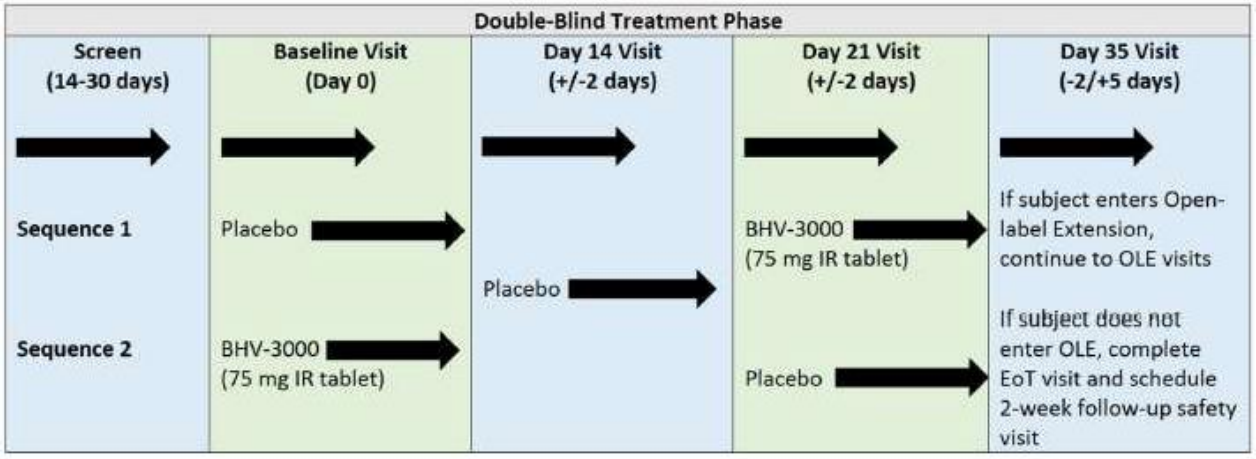
2 STUDY DESCRIPTION

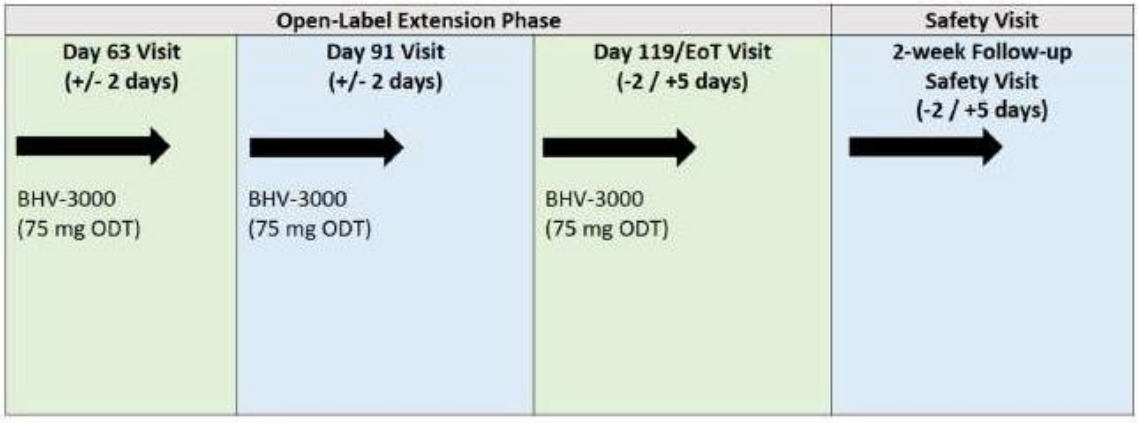
2.1 Study Design

BHV3000-202 is a phase 2, multi-center, double-blind, placebo controlled, crossover trial to assess the safety, tolerability, and efficacy of rimegepant in treating TN in patients who failed to respond adequately to or had intolerance or a contraindication to pharmacotherapy. Current inadequate response to therapy is defined by a daily pain score of greater than or equal to 4 on the "average intensity" on 11-point Numerical Pain Rating Scale (NPRS) during the 14 days prior to baseline. A crossover design with a placebo washout period of 7 days between treatments will be used due to the limited number of subjects, with each patient serving as their own control. The study will be conducted at multiple centers.

Figure 1 displays the study design.

Figure 1: Study Schematic





Prior to randomization, patients will enter a 14 to 30 day screening period during which they will complete daily self-reported assessments of pain intensity over a 24 hour period using an 11 point NPRS, ranging from 0 (for no pain) to 10 (for the worst imaginable pain). Throughout the

study, patients will be allowed to remain on their current medication regimens, provided they have been on a stable dose for a minimum of 4 weeks prior to the randomization visit.

Patients with a mean of ≥ 4 on the daily "average intensity" on the 11 point NPRS, during the last 14 days of the screening period, will be randomized to one of two treatment sequences to receive rimegepant 75 mg immediate release (IR) tablet administered orally vs placebo. Each sequence will include a 2-week treatment phase, with daily dosing of study drug or placebo. This will be followed by a 7-day placebo washout period. After the placebo washout period, another 2-week treatment phase will follow, again with once daily dosing of study drug or placebo. In the first sequence, patients will receive placebo for the first treatment period and rimegepant 75 mg IR tablet during the second treatment period. The second sequence will receive rimegepant 75 mg IR tablet during the first 2 week treatment period, followed by placebo in the second treatment phase.

During each 2 week treatment phase and during the 7 day placebo washout period, patients will complete the 11 point NPRS daily, as described above. In addition, patients will complete a paper diary daily to record efficacy data. The diary will include the daily recording of overall pain using the 11 point NPRS, a recording of daily use of rescue medications, and a daily rating of worst pain episode using the 11 point NPRS. Other secondary endpoints will be assessed at the beginning and end of each treatment period, including the Penn Facial Pain Scale (a 12-item activities of daily living scale designed specifically to assess impact of TN symptoms on daily activities), the Pain Disability Index (which measures the degree to which chronic pain interferes with 7 categories of daily activities, measured on an 11 point scale ranging from 0 (no disability) to 10 (worst disability)). The Patient Global Impression of Change (PGI-C: a patient self-reported global index scale) will be assessed at the end of each treatment sequence. In addition, the Sheehan-Suicidality Tracking Scale (S-STS) will be administered as a safety measure at screening, as well as at every visit, as specified in the protocol.

In addition, subjects completing the DBT Phase of the study and who continue to meet inclusion/exclusion criteria may be offered up to 12 weeks of OLE treatment, provided the Principal Investigator (PI) believes open-label treatment offers an acceptable risk-benefit profile. Subjects who agree to enter the OLE Phase will not be required to have a wash-out period of drug, but instead should continue dosing as specified in the OLE Phase.

All subjects will undergo a post study Follow-up Safety Visit 14 days after the final EOT Visit and last dose of study drug/medication administration. Subjects who discontinue from the study at any time during either the DBT Phase or the OLE Phase are expected to complete the End of Treatment (day 119) Visit and the 2-Week Follow-up Safety Visit.

2.2 Treatment Assignment

Approximately 120 patients will be screened to randomize 60 patients in a 1:1 ratio into 2 treatment sequences receiving 75 mg rimegepant vs placebo, using a 2-period, 2-sequence, crossover design. Patients with atypical TN and typical TN will be stratified equally into each of the two treatment sequences, with atypical TN patients not exceeding 50 percent of the subjects. Treatment assignments will be obtained by the investigator (or designee) via the Interactive Web-based Response System (IWRS).

2.3 Blinding and Unblinding

This study is blinded to study drug active status (rimegepant vs placebo) through the final analysis of the DBT Phase (see Section 1.2). Draft TLFs are produced with dummy treatment groups prior to the DBT Phase database lock. TLFs for the DBT Phase and subsequent database locks are produced unblinded.

2.4 Protocol and Protocol Amendments

BHV3000-202 SAP Version 2.0 is based on BHV3000-202 Protocol Version 9.0 (08-Apr-2022).

3 STUDY OBJECTIVES AND ESTIMANDS

3.1 Objectives

3.1.1 Primary Objective

To evaluate the efficacy of rimegepant compared to placebo in providing symptomatic pain relief in patients with refractory TN, defined as a reduction from baseline in the average daily NPRS between the two-week treatment phases.

3.1.2 Secondary Objectives

1. To assess the safety and tolerability of rimegepant relative to placebo in patients with TN
2. To evaluate the efficacy of rimegepant vs placebo for improving physical function in TN patients as measured by the Penn Facial Pain Scale-Revised (Penn-FPS-R)
3. To evaluate the efficacy of rimegepant vs placebo for improving functional disability in TN patients as measured by the Pain Disability Index
4. To evaluate the efficacy of rimegepant vs placebo on global functioning as measured by the PGI-C
5. To evaluate the efficacy of rimegepant vs placebo in providing symptomatic pain relief as captured by daily rating of worst pain episode as measured by the 11 point NPRS
6. To evaluate the efficacy of rimegepant vs placebo in providing symptomatic pain relief of clinical importance as defined by a 2-point or greater reduction in the 11 point NPRS

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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, specification of how intercurrent events are reflected in the scientific question of interest, and the 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 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. The following will be considered intercurrent events:

[redacted]

- Study drug discontinuation before the time point of interest defining the endpoint.
    - For safety objectives:
        - For AEs, 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 will be used prior to study drug discontinuation.
        - For all other safety endpoints, study drug discontinuation is 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.
    - For efficacy objectives:
        - For the NPRS objectives, study drug discontinuation is handled with a "while-on-treatment strategy".
        - For the Penn-FPS-R, PDI, and PGI-C efficacy objectives, study drug discontinuation is handled with a "treatment policy strategy".
    - For all other objectives (i.e., use of non-study TN standard of care medications on or before the time point of interest), this intercurrent event will be handled with a "while-on-treatment strategy"

3.2.1 Primary Objective Estimand

Table 1 presents the estimand for the primary objective.

Table 1: Primary Objective Estimand

Objective	**To evaluate the efficacy of rimegepant compared to placebo in providing symptomatic pain relief in patients with refractory TN, defined as a reduction from baseline in the average daily NPRS between the two-week treatment phases.**
Efficacy Endpoint	Change from baseline to the average of the 2-week treatment phase of the study in the average daily NPRS
Summary	Using the modified Intent to Treat (mITT) population: • Descriptive statistics for the averaged daily NPRS score and change from baseline score as a continuous variable by treatment group at each 2-week treatment phase • Difference in mean change from baseline in average daily NPRS scores between treatment groups estimated using a mixed-effect model for repeated measures (MMRM)
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy

3.2.2 Secondary Objective Estimands

Table 2 presents the estimands for secondary objectives.

Table 2: Secondary Objective Estimands

Objective 1	**To assess the safety and tolerability of rimegepant relative to placebo in patients with TN**
Safety Endpoint	Frequency of unique subjects with: SAEs, AEs leading to discontinuation, AEs judged to be related to study medication, S-STS total score, and clinically significant electrocardiogram (ECG) and laboratory abnormalities observed during the randomization phase of the study
Summary	Using the treated subjects population: • Number and percentage of subjects with these events or findings
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy for AEs; treatment policy strategy for all other safety endpoints
Objective 2	**To evaluate the efficacy of rimegepant vs placebo for improving physical function in TN patients as measured by Penn-FPS-R**
Efficacy Endpoint	Change in Penn-FPS-R total score from baseline to the end of the 2-week treatment phase of the study
Summary	Using the mITT population: • Descriptive statistics for Penn-FPS-R and change from baseline as a continuous variable by treatment group at each visit • Difference in mean change from baseline in Penn-FPS-R scores between treatment groups estimated using MMRM
Intercurrent Events	Study drug discontinuation: treatment policy strategy
Objective 3	**To evaluate the efficacy of rimegepant vs placebo for improving functional disability in TN patients as measured by the Pain Disability Index**
Efficacy Endpoint	Change in Pain Disability Index total score from baseline to the end of the 2-week treatment phase of the study
Summary	Using the mITT population: • Descriptive statistics for Pain Disability Index and change from baseline as a continuous variable by treatment group at each visit • Difference in mean change from baseline in Pain Disability Index between treatment groups estimated using MMRM
Intercurrent Events	Study drug discontinuation: treatment policy strategy
Objective 4	**To evaluate the efficacy of rimegepant vs placebo on global functioning as measured by the PGI-C**
Outcomes Research Endpoint	PGI-C Scale at the end of the 2-week treatment phase of the study
Summary	Using the mITT population: • Descriptive statistics for PGI-C score as categorical variable by treatment group at each visit • Difference in PGI-C score between treatment groups estimated using MMRM

Intercurrent Events	Study drug discontinuation: treatment policy strategy
Objective 5	**To evaluate the efficacy of rimegepant vs placebo in providing symptomatic pain relief as captured by daily rating of worst pain episode as measured by the 11 point NPRS**
Effiacy Endpoint	Change from baseline to the average worst pain NPRS scores in a day in the 2-week treatment phase of the study
Summary	Using the mITT population: • Descriptive statistics for the average worst pain episode NPRS scores and change from baseline score as a continuous variable by treatment group for each 2-week treatment phase • Difference in mean change from baseline in the average worst pain episode NPRS scores between treatment groups estimated using MMRM
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy
Objective 6	**To evaluate the efficacy of rimegepant vs placebo in providing symptomatic pain relief of clinical importance as defined by a 2-point or greater reduction in the 11 point NPRS**
Effiacy Endpoint	Percentages of subjects with ≥ 2 point reduction from baseline in average daily NPRS score
Summary	Using the mITT population: • Number and percentages by treatment group and odds ratio between treatment groups using logistic regression
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy

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[redacted]

[redacted]

4 ANALYSIS SETS, TREATMENT GROUPS, AND SUBGROUPS

4.1 Analysis Sets

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

- Enrolled: Patients who signed an informed consent form and were assigned a Patient Identification number (PID).
- Full: Enrolled subjects who received a treatment assignment from the IWRS (rimegepant or placebo).
- Treated: Enrolled subjects who received at least 1 dose of study therapy (rimegepant or placebo).
    - DBT treated: Subjects in the treated analysis set who took ≥ 1 dose of DB study drug (rimegepant or placebo), i.e., nonmissing study drug start date.
    - Interim treated: Subjects in the treated analysis set with safety data entered during the interim period (post-DBT pre-OL period).
    - OL rimegepant treated: Subjects in the treated analysis set who took ≥ 1 dose of OL rimegepant, i.e., nonmissing OL rimegepant start date.
    - DB or OL rimegepant treated: Subjects in the treated analysis set who took ≥ 1 dose of DB or OL rimegepant, i.e., nonmissing DB or OL rimegepant start date.
    - Follow-up treated: subjects in the treated analysis set whose last contact date is in the follow-up period.
- Modified Intent to Treat (mITT): Randomized subjects who received at least 1 dose of study therapy and provided a baseline and at least one post-baseline efficacy assessment in each sequence.

4.2 Treatment Groups

Treatment groups in the DBT phase are rimegepant 75 mg and placebo. The treatment group in the OLE phase is rimegepant 75 mg.

Populations of treated subjects will be assessed by the as-treated treatment group; i.e., by the treatment actually received. Otherwise, all other populations and all efficacy analyses will be assessed by the as-randomized treatment group. The enrolled population will be assessed overall.

5 SAMPLE, POWER, AND TYPE I ERROR

The sample size for this study will be approximately 60 randomized patients. Approximately 120 patients will be screened, assuming no more than 50 percent of patients would be ineligible for randomization.

The calculation for the sample size was based on a paired t-test crossover design, assuming a low correlation (r = 0.2) between the active and placebo response to treatment. Assuming a paired difference standard deviation of 3.8, 60 randomized patients will provide >90% power to detect a 2-point difference between rimegepant and placebo using a two-sided significance level of 0.05 and a 20% dropout rate with no imputation.

Type 1 error is not applicable. The significance of the primary and secondary endpoints will not be evaluated.

6 STATISTICAL ANALYSES

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.

Medical history and AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA) most recent version available.

Concomitant medications are coded using the World Health Organization Drug Global Dictionary (WHODrug Global), most recent version available.

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

6.1.1.1 Tables

Tables will be summarized by treatment sequence and period, rimegepant pooled, placebo pooled, and overall. Exceptions are specified in subsequent sections as needed.

6.1.1.2 By-Subject Listings

By-subject listings will present all data by randomization status (randomized, not randomized), site-subject ID, and additional variables such as time points, as applicable. Listings display as-randomized treatment sequence abbreviated as (1) "RMG-PBO" for Sequence 1 subjects,"PBO-RMG" for Sequence 2 subjects, and (2) "NRND" for subjects who are not randomized.

Refer to the Core SAP for additional details about listings.

6.1.2 Statistical Methods

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

Categorical variables will be tabulated with the count and percentage within each category (with a 'Missing' category if applicable). Continuous variables will be summarized with univariate statistics (e.g., n, mean, median, standard deviation (SD), minimum, and maximum).

Tabulations of the following endpoints present the number of unique subjects with an event: protocol deviations; non-study medications; AEs; and laboratory abnormalities. Thus, for these endpoints, multiple occurrences of the same event are counted only once per subject.

6.1.3 Handling of Missing Data

Unless otherwise noted, efficacy analyses will be based on observed data only. For the main analyses of efficacy for primary and secondary endpoints, no imputation will be performed to impute data following discontinuation from study.

For efficacy analyses, partial or missing dates will not be imputed. The relative study days, where determined, will be calculated for full dates only.

6.2 Study Population

6.2.1 Analysis Sets

The number of subjects in each analysis set described in Section 4.1 is tabulated by treatment sequence (as-randomized for the full and mITT analysis sets; as-treated for the treated analysis set), not randomized, and overall.

A by-subject listing of analysis sets is provided for the enrolled analysis set, which includes the reason for exclusion (i.e., not treated with study drug). Treated subjects may have > 1 exclusion reason.

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

6.2.2 Enrollment

Enrollment by country and site is tabulated overall for the enrolled analysis set, full analysis set, and safety analysis set.

6.2.3 Subject Disposition

Results are based on the Study Termination Summary case report form (CRF). A by-subject listing of subject disposition by study phase will be produced for the enrolled analysis set. Refer to Section 6.2.3.1 of the Core SAP for more details.

6.2.3.1 Subject Disposition during the DBT Phase

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

- Completed the first treatment period
- Withdrew from the first treatment period
    - Reasons for withdrawal, including not reported
- Completed the second treatment period
- Withdrew from the second treatment period
    - Reasons for withdrawal, including not reported.
- Continuing to the OLE phase
- Not continuing to the OLE phase

6.2.3.2 Subject Disposition during the OLE Phase

Subject disposition in the OLE phase will be summarized for OLE treated subjects overall as the number and percentage of subjects in the following categories:

- Completed the OLE Phase
- Withdrew from the OLE Phase
    - Reasons for withdrawal, including not reported.

6.2.3.3 Subject Disposition during the Follow-Up Phase

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

- Completed the follow-up safety visit
- Did not complete the follow-up safety visit
    - Reasons for not completing

6.2.4 Protocol Deviations

6.2.4.1 Relevant Protocol Deviations

The frequency table of relevant protocol deviations are provided as the number and percentage of subjects in deviation categories by treatment sequence and overall for the full analysis set. Results are shown by deviation type (eligibility, subject management), category, and subcategory in the order specified in Section 9.1. Results for all relevant protocol deviation categories and subcategories are displayed, even those with 0 counts, unless specified otherwise. See Section 6.2.4.1 of the Core SAP for further details.

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

6.2.4.2 Significant Protocol Deviations

Significant protocol deviations are non-programmable deviations that do not impact the interpretability of study data. A subject listing of significant protocol deviations is a manually generated appendix provided by clinical operations for inclusion in the CSR.

A by-subject listing of significant protocol deviations is provided for the enrolled analysis set. This includes visit, deviation type, deviation description, and specify, which are used as additional sorting variables.

6.2.5 Baseline Characteristics

Baseline characteristics include: (1) demographics and other relevant baseline characteristics, (2) neurological exam results, (3) medical history, and (4) non-study prior medications. Tables will be summarized by treatment sequence and overall, unless otherwise specified.

Tables of baseline characteristics are provided for the DBT treated analysis set.

The frequency table of randomization stratum (i.e., atypical and typical TN) is provided for the full analysis set by as-randomized treatment sequence and overall.

For the DB treated and Follow-up treated analysis set, baseline is defined as the last non-missing value at or before the study drug start date/time (rimegepant or placebo) during period 1 of the 2-period sequence. For other analysis sets, refer to the Core SAP for details on baseline for a parameter (e.g., weight), including handling of ties on the same measurement date. For the OL

rimegepant treated analysis set, baseline is defined as the last non-missing value at or before the OL study drug start date/time.

By-subject listings are provided for the enrolled analysis set for (1) through (4) above.

6.2.5.1 Demographics and Other Relevant Baseline Characteristics

Refer to the Core SAP for the table of demographics and other relevant baseline characteristics, and calculating age at a reference date. Other relevant characteristics also include the following: neuralgia type (typical, atypical), MRI confirmed Classical TN diagnosis (yes, no).

6.2.5.2 Medical History

The frequency table of medical history is provided by system organ class (SOC) and preferred term (PT), and displayed in descending order of overall frequency within SOC and PT. Refer to the Core SAP (Section 6.2.5.3) for medical history.

6.2.5.3 Non-study Prior Medications

Frequency tables of non-study prior medications (i.e., previous or current medications) is provided by therapeutic class and preferred name in descending order of overall frequency within therapeutic class and preferred name. The definitions of medication types in Section 6.2.6.3 of the Core SAP applies.

6.2.6 Exposure

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

6.2.6.1 Study Therapy

During the DBT Phase of the study, subjects will be randomized to a sequence of either rimegepant (75 mg QD) and then placebo or placebo then rimegepant (75 mg QD) in a 2-sequence, 2-period, crossover design. Study drug/medication will be dispensed at the baseline visit and at Days 14 and 21. Subjects should take the first dose the day of the baseline visit. Study drug/medication should be administered in the morning without regard to meals. Subjects who showed continued compliance during the DBT Phase may choose to enter a 12 week OLE Phase with daily dosing of rimegepant (75 mg QD) ODT. Open label study drug will be dispensed at the Day 35 visit for subjects who enter the OLE Phase. Subjects should take the first dose of OLE study drug on Day 36.

Subjects report study drug exposure in the subject paper study log (diary), whereas sites report study drug accountability on the Study Drug Dispensing Log CRF.

An administrative listing of IP batch numbers is provided for the treated analysis set. Refer to the Core SAP for listing contents.

DB Study Drug (Rimegepant or Placebo) Exposure

DB rimegepant or placebo exposure will be summarized descriptively by as-treated treatment groups for period 1 placebo, period 1 rimegepant, period 2 rimegepant, period 2 placebo, rimegepant pooled, placebo pooled and overall, and will include the following parameters:

- Time on DBT (days), derived as DBT end date – DBT start date + 1
- Time on DBT study drug category (weeks)
- Cumulative DBT exposure (mg), derived by summing number of DB mg across DB study drug records
- Average DBT exposure (mg per day), derived as cumulative DB exposure/time on DBT
- Total DBT exposure (tablets) summed across all subjects, derived by summing cumulative DB exposure across all subjects.
- Total DBT exposure (patient-years), derived by summing (DBT end date – DBT start date + 1)/365.25 across all subjects.

OL Rimegepant Exposure

OL rimegepant exposure will be summarized descriptively by treatment sequence and overall, and will include the following parameters:

- Time on OL rimegepant (days), derived as OL rimegepant end date – OL rimegepant start date + 1
- Time on OL rimegepant category (weeks)
- Cumulative OL rimegepant exposure (mg), derived by summing number of OL mg across records with non-missing OL rimegepant date/times.
- Average OL rimegepant exposure (mg per day), derived as cumulative OL rimegepant exposure/time on OL rimegepant
- Total OL rimegepant exposure (tablets) summed across all subjects, derived by summing cumulative OL rimegepant exposure across all subjects
- Total OL rimegepant exposure (patient-years), derived by summing (OL rimegepant end date – OL rimegepant start date + 1)/365.25 across all subjects.

DB or OL Rimegepant Exposure

DB or OL rimegepant exposure will be summarized descriptively by as-treated DB rimegepant pooled/OL rimegepant, DB placebo pooled/OL rimegepant and overall, and will include the following parameters:

- Time on DB or OL rimegepant (days), derived as DB or OL rimegepant end date – DB or OL rimegepant start date + 1
- Time on DB or OL study drug category (weeks)
- Cumulative DB or OL rimegepant exposure (mg), derived by summing number of DB or OL mg across records with non-missing DB or OL rimegepant date/times.
- Average DB or OL rimegepant exposure (mg per day), derived as cumulative DB or OL rimegepant exposure/time on DB or OL rimegepant.

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- Total DB or OL rimegepant exposure (tablets) summed across all subjects, derived by summing cumulative DB or OL rimegepant exposure across all subjects. Total DB or OL rimegepant exposure includes missed dose days within a study phase and excludes the dosing break between study phases (i.e., (last dose day of DB study drug – first dose date of DB study drug + 1) – (number of days with a dosing break between the DB and OL phases)).
- 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.

A by-subject listing of study drug exposure will be provided for the treated analysis set.

6.2.6.2 Drug Accountability and Compliance

DB study drug accountability and compliance will be tabulated by as-treated treatment groups for period 1 placebo, period 1 rimegepant, period 2 rimegepant, period 2 placebo, rimegepant pooled, placebo pooled, and overall with the number and percentage of subjects in the following categories for the DB phase:

- Any bottle dispensed (Yes, No, Not Reported)
- DB study drug taken but not randomized
- Tablet count compliance < 80% from study drug start to study drug end in DB phase
- More than the required number of tablets administered on 1 day
- Did not return ≥ 1 bottle dispensed and discontinued study drug, defined as any of the following:
    - Randomized subjects who were not treated and did not return DB bottle dispensed
    - Treated subjects who did not return ≥ 1 DB bottle dispensed and discontinued DBT (i.e., non-missing DBT last date)
- Did not return any bottle dispensed and discontinued study drug
- No study drug taken for ≥ 3 days (not necessarily consecutive) in any 1 week
- Incorrect study drug taken (all the time; at least once)

OL study drug accountability and compliance will be tabulated overall for the OLE phase:

- Tablet count compliance < 80% from study drug start to study drug end in OLE phase
- More than the required number of tablets administered on 1 day
- Did not return ≥ 1 bottle dispensed and discontinued study drug, defined as: OL rimegepant treated subjects who did not return ≥ 1 OL rimegepant bottle dispensed and discontinued OL rimegepant (i.e., non-missing OL rimegepant last date).
- Did not return any bottle dispensed and discontinued study drug
- No study drug taken for ≥ 3 days (not necessarily consecutive) in any 1 week

A by-subject listing of treatment compliance will be provided for the treated analysis set.

6.2.6.3 Non-study Medications

Non-study medications will be identified from the Concomitant Medications and Rescue Pain Medications CRFs. Recue medications are defined as non-study medications reported on the Rescue Pain Medication CRF. Rescue medication dates and times are not imputed.

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.

A by-subject listing of concomitant medications, inclusive of rescue medications, is provided by therapeutic class and preferred name for the enrolled subjects. Medication types are identified. Refer to the Core SAP for listing contents.

Refer to the Core SAP for non-study medication start and stop date imputation, listing content, and definition of concomitant medication.

DBT Period Non-study Medications

Frequency tables of the following DBT period non-study medications are provided by period 1 placebo, period 1 rimegepant, period 2 rimegepant, period 2 placebo, rimegepant pooled, and placebo pooled for the DBT treated subjects: concomitant medications, rescue medications. Medications are displayed in descending order of rimegepant pooled frequency within therapeutic class and preferred name.

OL Rimegepant Period Non-study Medications

OL rimegepant period non-study medications will be summarized analogously by treatment sequence and overall for the OL rimegepant treated subjects and the following medications: concomitant medications, rescue medications.

6.3 Efficacy

Unless otherwise noted, the primary and secondary efficacy analyses will be conducted on the mITT population. DBT and OLE efficacy data will be included in listings by subject, treatment sequence and period, study phase and visit (as applicable). Descriptive summary statistics will be provided for DBT and OLE phase data. Statistical analyses outlined in Table 3: Primary and Secondary Efficacy Estimands and Analyses will only be done for the DBT phase data.

Table 3: Primary and Secondary Efficacy Estimands and Analyses

Index	Description	Variable Type	Statistical Model	On-Study Data
Primary Estimand				
P01	Difference between treatment groups in change from baseline in average daily NPRS scores at the end of the randomization phase	Continuous	MMRM	Baseline, Day 14, 21, 35
Secondary Estimand				
S01	Difference between treatment groups in change from baseline in Penn-FPS-R score at the end of the randomization phase	Continuous	MMRM	Baseline, Day 14, 21, 35
S02	Difference between treatment groups in change from baseline in Pain Disability Index at the end of the randomization phase	Continuous	MMRM	Baseline, Day 14, 21, 35
S03	Difference between treatment groups in PGI-C at the end of the randomization phase	Continuous	MMRM	Day 14, 21, 35
S04	Difference between treatment groups in change from baseline in worst pain episode measured by NPRS at the end of the randomization phase	Continuous	MMRM	Baseline, Day 14, 21, 35
S05	Difference between treatment groups in percentages of subjects with ≥ 2 point reduction from baseline in average daily NPRS score	Binary	Logistic Regression	Baseline, Day 14, 21, 35

MMRM = Mixed effects model for repeated measures

6.3.1 Continuous Efficacy Endpoints

Assessments are taken directly from reported CRF visits, aside from the NPRS endpoints which are only taken between treatment exposure start and end dates.

Descriptive Analyses

Summary statistics for parameter values are tabulated at select time points by treatment group (rimegepant pooled or placebo pooled).

MMRM

Treatment groups are assessed using MMRM with the following variables:

- Dependent variable: change from baseline of NPRS score averaged over each DBT period
- Fixed effects (categorical variables): treatment group, sequence, and period
- Covariate (continuous variable): baseline value of dependent variable

Random effect: subject error degrees of freedom are determined by the Kenward-Roger method.

The following statistics are tabulated from the MMRM:

- Least-squares mean (LSMean) with corresponding SE with 95% confidence intervals (CIs) of changes from baseline by treatment group (pooled rimegepant, pooled placebo).
- Difference in LSMeans between treatment groups (pooled rimegepant, pooled placebo) with corresponding SE, and 95% CI.

6.3.2 Continuous Efficacy Endpoints without Baseline Measurement

Assessments are taken directly from reported CRF visits.

Descriptive Analyses

Descriptive statistics will be presented at select time points by treatment group (rimegepant pooled or placebo pooled).

MMRM

Treatment groups are assessed using MMRM with the following variables:

- Dependent variable, e.g., PGI-C score at Day 14 (note that Day is relative to the start of each treatment period)
- Fixed effects (categorical variables): treatment group, sequence, and period
- Random effect: subject error degrees of freedom are determined by the Kenward-Roger method.

The following statistics are tabulated from the MMRM:

- LSMean with corresponding standard error (SE) with 95% CIs of values by treatment group
- Difference in LSMeans between treatment groups (rimegepant, placebo) with corresponding SE, and 95% CI.

6.3.3 Binary Efficacy Endpoints

Assessments are taken directly from reported CRF visits, aside from the NPRS endpoints which are only taken between treatment exposure start and end dates.

Descriptive Analyses

Descriptive statistics will be presented at select time points by treatment group (rimegepant pooled or placebo pooled).

Logistic Regression

Treatment groups are assessed using Logistic Regression with the following variables:

- Dependent variable, e.g., ≥ 2-point reduction in average daily NPRS score
- Fixed effects (categorical variables): treatment group, sequence, and period
- Covariate (continuous variable): baseline value of NPRS

The following statistics are tabulated from the logistic regression:

- Number and percentage of subjects with ≥ 2-point reduction in average NPRS score by treatment group
- Observed percentage difference (rimegepant vs. placebo)
- Odds ratio between rimegepant and placebo with corresponding 95% CI.

6.3.4 P01: Primary Efficacy Endpoint: NPRS

6.3.4.1 Main Analyses

The NPRS is a segmented, 11-item, numeric scale ranging from 0-10. The NPRS is anchored by items ranging from "0" which represents "no pain;" to "10" which reflects "worst pain imaginable."

Subjects were given a paper diary to record daily pain intensity on the NPRS. They were asked to keep a daily record of their average pain intensity over a 24 hour period.

The primary endpoint is the change in average daily NPRS from baseline to the end of the 2-week treatment phase of the study. Pain relief is defined as an improvement (reduction) from baseline. The primary endpoint will estimate the effect of rimegepant relative to placebo over 2 weeks of treatment when added to a standard of care therapy, and regardless of the effect of other concomitant medication. The pain score will be the average of the daily 11-point NPRS recorded within each period using the mITT population. This treatment effect will be

summarized as the difference in the average daily score in total NPRS between rimegepant and placebo.

The primary endpoint will be analyzed using the method specified in Section 6.3.1. The MMRM table has the same format as the one described in Section 6.3.1.

6.3.5 Secondary Efficacy Endpoints

6.3.5.1 S01: Penn Facial Pain Scale-Revised (Penn-FPS-R)

The Penn-FPS-R is a 12-item scale used to assess the impact of TN pain on health-related quality of life and activities of daily living. Developers of the original Penn-FPS-R applied standard validation metrics (e.g., concept elicitation, cognitive debrief, reliability, responsiveness) to the Penn-FPS-R as a measure for use in assessing treatment impacts on TN symptoms. The response categories for each of the 12 items range from 0 ('does not interfere') to 10 ('completely interferes'). The specified recall period is for the 'past week.' Anchors to scale 0 to 10 were added by the Sponsor.

Subjects are asked to complete the Penn-FPS-R at the beginning and end of each treatment phase, as outlined in the Schedule of Assessments.

Change from baseline in Penn-FPS-R total score will be analyzed using the same methodology as the primary endpoint (see Section 6.3.4.1) with baseline total score as the covariate.

6.3.5.2 S02: Pain Disability Index

The Pain Disability Index is designe d to measure the degree to which a patient's daily life is disrupted by their pain. The seven items of the scale reflect different "life activities" and are scored on an 11-point Likert Scale, with "0" representing "no disability" and "10" representing "worst disability."

Subjects are asked to complete the Pain Disability Index at the beginning and end of each treatment phase, as outlined in the Schedule of Assessments.

Change from baseline in Pain Disability Index total score will be analyzed using the same methodology as the primary endpoint (see Section 6.3.4.1) with baseline index as the covariate.

6.3.5.3 S03: Patient Global Impression of Change Scale (PGI-C)

The PGI-C is a patient-rated scale which assesses how the subject's current illness state has improved or worsened relative to the baseline visit. The subject is asked to rate a change in their overall disease condition on a 7-point scale, from 1 ('no change') to 7 ('a great deal better'). The PGI-C is a global index scale that may be used to rate the response of a condition to a therapy.

The PGI-C will be conducted at the beginning and end of each treatment phase as indicated in the Schedule of Assessments.

The PGI-C will be analyzed using the method specified in Section 6.3.2. The MMRM table has the same format as the one described in Section 6.3.2.

6.3.5.4 S04: Worst Pain Episode

Using the 11-point NPRS described above, subjects are asked to record an intensity rating of their worst pain episode over a 24-hour period daily in their paper diary.

Worst pain episode score will be analyzed using the same methodology as the primary endpoint (see Section 6.3.4.1) with baseline score as covariate.

6.3.5.5 S05: ≥ 2-Point Reduction in the 11 Point NPRS

Achievement of ≥ 2-point reduction in average NPRS score will be analyzed using logistic regression, that will include terms for treatment group, randomization strata (typical/atypical), sequence, and baseline NPRS score. See Section 6.3.3 for details. The regression table has the same format as the one described in Section 6.3.3.

6.4 Safety Analyses

Safety outcome measures include: AEs, laboratory assessments, vital signs, ECGs, concomitant medications, and the S-STS questionnaire.

Tables of safety endpoints are provided according to safety analysis period and analysis set as follows, unless otherwise noted:

- On-DBT for the DBT treated analysis set by treatment sequence and period, rimegepant pooled, and placebo pooled
- Post-DBT pre-OL rimegepant for the interim treated analysis set by treatment sequence and period, rimegepant pooled, placebo pooled, and overall
- On-OL rimegepant for the OL rimegepant treated analysis set by DB rimegepant pooled/OL rimegepant, DB placebo pooled/OL rimegepant, and overall. Shifts from baseline are based on the OL rimegepant baseline.
- On-DB or OL rimegepant for the DB or OL rimegepant treated analysis set by DB rimegepant pooled/OL rimegepant, DB placebo pooled/OL rimegepant, and overall. Shifts from baseline are based on the DB or OL rimegepant baseline.
- Follow-up for the follow-up treated analysis set by DB rimegepant pooled/OL rimegepant, DB placebo pooled/OL rimegepant, and overall.

6.4.1 Adverse Events

Refer to the Core SAP for the following: AE start and end date imputation; death date derivation; rules for counting and rounding in frequency tables; definitions of treatment-emergent adverse events (TEAEs), AEs related to study drug, and exposure-adjusted multiple occurences of unique AEs; and TLF contents.

A by-subject AE listing is provided for the enrolled analysis set. TEAEs are identified.

6.4.1.1 Deaths

Deaths are identified from any of the following sources:

- AE CRF with any of the following: PT or reported term of "death"; outcome of fatal; "yes" response to any death-related question (e.g., "Did the SAE result in death?"; "Is a

death certificate available?"; "Is an autopsy report available?"); complete or partially complete death date

- Study Termination Summary CRF with any of the following: death as reason for discontinuation; complete or partially complete death date

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

6.4.1.2 AE Overviews

An AE overview frequency table displays the following categories without SOC and PT: any AE; mild AE; moderate AE; severe AE; moderate or severe AE; AE related to study drug; AE leading to study drug discontinuation; SAE; SAE leading to study drug discontinuation; hepatic-related AE; cardiovascular AE; and suicidality AE.

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

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

6.4.1.3 On-DBT AEs

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

- AEs by intensity
- AEs related to study drug by intensity
- AEs by relationship to study drug (related, possibly related, unlikely related, not related, not reported)
- SAEs
- AEs leading to study drug discontinuation
- Exposure-adjusted multiple occurrences of unique AEs
- Hepatic-related AEs by intensity *
- Cardiovascular AEs *
- Suicidality AEs *.

AEs of special interest are asterisked ("*").

AEs with a start date on or after the first dose date/time on the Day 1 visit and prior to the first dose date/time on the Day 21 visit is considered to be in the on-DBT analysis period 1. AEs with a start date on or after the first dose date/time on the Day 21 visit to the earlier of the last dose of the DBT + 7 or the first dose of OLE - 1 is considered to be in the on-DBT analysis period 2.

Calculations for on-DB rimegepant exposure-adjusted multiple occurrences of unique AEs use an analysis period reference start date = DB rimegepant start date, analysis period reference end date = DB rimegepant last date + 7 days.

6.4.1.4 On-OL Rimegepant AEs

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

- AEs by intensity
- AEs related to study drug by intensity
- AEs by relationship to study drug (related, possibly related, unlikely related, not related, not reported)
- SAEs
- AEs leading to study drug discontinuation

AEs with a start date on or after the first dose date/time of OL rimegepant and prior to the last dose date of the OL rimegepant + 7 is considered to be in the on-OL analysis period.

6.4.1.5 On-DB or OL Rimegepant AEs

On-DB or OL rimegepant AEs are provided for the DB or OL rimegepant treated analysis set by SOC and PT for the same endpoints listed in Section 6.4.1.3.

AEs with a start date on or after the first dose date/time of DB rimegepant or OL rimegepant and prior to the last dose date of the DB or OL rimegepant + 7 is considered to be in the on-DB or OL rimegepant analysis period.

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

6.4.1.6 Post-DBT Pre-OL Rimegepant AEs

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

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

AEs with a start date after the last dose date/time of DB + 7 and before the OL rimegepant start date is considered to be in the post-DB Pre-OL rimegepant analysis period.

6.4.1.7 Follow-up AEs

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

- AEs by intensity

- SAEs.

For subjects who did not continue into the OL rimegepant period, AEs with a start date after the last dose date/time of DB + 7 is considered to be in the follow-up analysis period. For subjects who continued into the OL rimegepant period, AEs with a start date after the last dose date/time of OL rimegepant + 7 days is considered to be in the follow-up analysis period.

6.4.1.8 AEs across All Study Phases Combined

Frequency tables of AEs are provided by SOC and PT for the treated analysis set across all safety analysis periods combined for the following endpoints:

- AEs leading to study drug discontinuation

6.4.2 Laboratory Tests

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

- Hematology: Screening, Baseline (Day 1), Day 35, Day 119, Follow-up safety visit (14 days post last dose) and early termination
- Serum chemistry: Screening, Baseline (Day 1), Day 35, Day 119, Follow-up safety visit (14 days post last dose) and early termination. Exceptions are for the following:
    - Liver function Tests (LFTs) (ALT, AST, ALP, TBL, direct bilirubin, indirect bilirubin): All visits except Day 21
    - Lipids (total cholesterol, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, triglycerides), folate, HbA1C, P-Amylase or Lipase, TSH, and T4: Screening
- Urinalysis: Screening, Baseline (Day 1), Day 35, Day 119, Follow-up safety visit (14 days post last dose) and early termination.

Laboratory tests of clinical interest for analyses include the following:

- Hematology: hemoglobin, hematocrit, platelets, CBC with differential and absolute neutrophil count
- Serum chemistry: sodium, potassium, chloride, calcium, ALT, AST, LDH, alkaline phosphatase, GGT, phosphorous, bicarbonate, CPK, total protein, albumin, total bilirubin, glucose, creatinine, BUN, uric acid, total cholesterol, LDL, HDL, triglycerides, folate, HbA1C, P-Amylase or Lipase, TSH, and T4
- Urinalysis: macroscopic examination, pH, specific gravity, ketones, nitrites, urobilinogen, leukocyte esterase, protein, glucose, and occult blood.
- LFTs: ALT, AST, TBL and ALP

Refer to the Core SAP for toxicity grading.

Estimated glomerular filtration rate (eGFR) will be derived using the modification of diet in renal disease (MDRD) formula; refer to the Core SAP for additional details.

TLFs will be provided to show data in Systeme Internationale (SI) unit system.

A by-subject listing of the following select laboratory tests will be provided for enrolled subjects with at least one laboratory assessment of grade 3 or 4 abnormality or a positive pregnancy test result: hematology; serum chemistry (including eGFR derived using MDRD); urinalysis. If there is a positive pregnancy test, defined as a serum or urine pregnancy test with either (1) "positive" character value, or (2) numeric value ≥25 U/L. The listing will also include all pregnancy test results over time.

In addition, a by-subject listing values and ratios to ULN (i.e., ALT, AST, TBL and ALP) will also be provided for enrolled subjects with select elevations (ALT or AST > 3 x ULN; ALP or TBL > 2 x ULN) at any time point. Refer to the Core SAP for listing content.

6.4.2.1 Laboratory Test Abnormalities

Frequency tables of laboratory test abnormalities are provided for the following endpoints:

- Worst laboratory test abnormality for each graded laboratory test.
- Laboratory test toxicity grade shift from baseline to the worst toxicity grade for each graded laboratory test

These 2 frequency tables are provided for the following analysis periods and analysis sets:

- On-DBT for the DBT treated analysis set
    - Summarized by rimegepant pooled, placebo pooled, and overall
- On-OL rimegepant for the OL rimegepant treated analysis set
- On-DB or OL rimegepant for the DB or OL rimegepant treated analysis set.

Worst laboratory test abnormality will also be provided for the following analysis periods and analysis sets:

- Follow-up for the follow-up treated analysis set.

6.4.2.2 LFT Elevations

Subjects must have non-missing LFT data (i.e., ALT, AST, TBL, or ALP) post-baseline to be included.

Refer to the Core SAP for additional details.

LFT Elevations: Cumulative, Mutually Exclusive, and Composite

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

- Pretreatment for the DBT treated analysis set
- On-DBT for the DBT treated analysis set

  On-OL rimegepant for the OL rimegepant treated analysis set

  On-DB or OL rimegepant for the DB or OL rimegepant treated analysis set

[redacted]

- Follow-up for the follow-up treated analysis set.

LFT ULN Shifts from Baseline to Worst Elevation

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

- On-DBT for the DBT treated analysis set
    - Summarized by rimegepant pooled, placebo pooled, and overall
- On-DB or OL rimegepant for the DB or OL rimegepant treated analysis set where shifts are based on DB or OL rimegepant baseline.

eDISH Scatter Plots

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

- On-DBT for the DBT treated analysis set with paired ALT and TBL ratios on DBT by treatment group
- On-OL rimegepant for the OL rimegepant treated analysis set with paired ALT and TBL ratios on OL rimegepant
- On-DB or OL rimegepant for the DB or OL rimegepant treated analysis set with paired ALT and TBL ratios on DB or OL rimegepant.

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 day of the laboratory test result (x-axis) for treated subjects with any of the following LFT elevations post-baseline: ALT > 3 x ULN, AST > 3 x ULN, TBL > 2 x ULN, or ALP > 2 x ULN. Each figure also displays additional study milestones (e.g., start of the on-DBT treated analysis period, start of the OL rimegepant safety analysis period, and start of the follow-up period) using vertical lines with their corresponding descriptions in footnotes.

6.4.2.3 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 at each scheduled visit.

The table of values and changes from baseline in hematology and serum chemistry laboratory tests is provided by rimegepant pooled, placebo pooled, and overall for the treated analysis set at the following time points: baseline; Day 35 in the on-DBT safety analysis period; and the 2-week follow-up safety visit.

The table of values and changes from DB or OL rimegepant baseline in all hematology and serum chemistry laboratory tests is provided analogously for the DB or OL rimegepant treated analysis set at the following time points: DB or OL rimegepant baseline; Day 35 in the on-DBT

safety analysis period; each scheduled visit from Day 63 through Day 119 and EOT in the on-OL rimegepant safety analysis period; and the 2-week follow-up safety visit.

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

6.4.3 Vital Signs and Physical Measurements

Vital signs and physical measurements will be measured at the following visits: Screening, Baseline (Day 1), Day 14, Day 21, Day 35, Day 63, Day 91, Day 119/EOT, and 2-week follow-up safety visit .

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 height, weight and BMI.

6.4.3.1 Vital Signs and Physical Measurements Changes From Baseline Over Time

Values and changes from baseline in vital sign and physical measurement parameters will be summarized as continuous parameters at each scheduled visit.

The table of values and changes from baseline in vital signs and physical measurements is provided by rimegepant pooled, placebo pooled, and overall for the DBT treated analysis set at the following time points: baseline; each scheduled visit through Day 35 in the on-DBT safety analysis period; 2-week follow-up safety visit.

The table of values and changes from DB or OL rimegepant baseline in vital sign and physical measurement parameters is provided analogously for the DB or OL rimegepant treated analysis set at the following time points: DB or OL rimegepant baseline; each scheduled visit through Day 35 in the on-DBT safety analysis period; each scheduled visit from Day 63 through Day 119 and EOT in the on-OL rimegepant safety analysis period; and 2-week follow-up safety visit.

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

6.4.3.2 Vital Signs and Physical Measurement Abnormalities

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

- On-DBT for the DBT treated analysis set
    - Summarized by rimegepant pooled, placebo pooled, and overall
- On-OL rimegepant for the OL rimegepant treated analysis set using OL rimegepant baseline
- On-DB or OL rimegepant for the DB or OL rimegepant treated analysis set using DB or OL rimegepant baseline

[redacted]

- Follow-up for the follow-up treated analysis set.

6.4.4 Electrocardiograms

12-Lead ECGs data will not be analyzed for the CSR.

6.4.5 Sheehan-Suicidality Tracking Scale (S-STS)

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 (Day 1), Day 14, Day 21, Day 35, Day 63, Day 91, Day 119/EOT, and 2-week follow-up safety visit.

S-STS scores are calculated as described in the Core SAP.

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 by rimegepant pooled, placebo pooled 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) will also be presented by rimegepant pooled, placebo pooled 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-OL rimegepant for OL rimegepant treated subject; (3) on-DB or OL rimegepant for DB or OL rimegepant treated subjects, using DB or OL rimegepant baseline; and (4) follow-up for follow-up treated subjects.

6.4.6 Concomitant Procedures

The by-subject listing of procedures is provided for the enrolled analysis set, and is based on the Concomitant Procedures CRF. Procedures are coded in MedDRA. Refer to the Core SAP for additional details.

6.4.7 Covid-19 Impact

Covid-19 impact will not be assessed for this CSR.

6.5 Pharmacokinetics

PK will not be analyzed for this CSR.

7 CONVENTIONS

7.1 General

7.1.1 Output Layout

Refer to the Core SAP for TLF layout conventions.

[redacted]

For the final analysis of the DBT phase and the final analysis after the OLE phase, a list of TLFs and unique TLF templates will be provided in the Mock TLF document.

7.2 Analysis Periods

Analysis periods are defined as follows:

- Efficacy endpoints
  - On-DBT efficacy: This period is used to assess efficacy during the DBT Phase, and is abbreviated as "DBT" in the efficacy listing.
  - On-OL rimegepant efficacy: This period is abbreviated as "OLRMG" and used only in the efficacy listing.
  - Follow-up efficacy: This period is abbreviated as "FU" and used in the efficacy listing.
- Pretreatment characteristics and safety endpoints
  - Pretreatment: This period is abbreviated as "PRETRT" in listings, and is used to derive baseline values and to assess pretreatment safety endpoints.
  - Pre-OL rimegepant: This period is used to derive the OL rimegepant baseline value.
  - Pre-DB or OL rimegepant: This period is used to derive the DB or OL rimegepant baseline value.
  - On-DBT safety: This period is abbreviated as "DBT" in safety listings, and is used to assess safety endpoints on DBT for the DBT treated analysis set
  - Post-DBT pre-OL rimegepant safety: This period is abbreviated as "INT" in safety listings, and is used to assess safety endpoints during the interim period (i.e., post-DBT pre-OL rimegepant) for the interim treated analysis set.
  - On-OL rimegepant safety: This period is abbreviated as "OLRMG" in safety listings, and is used to assess safety endpoints for the OL rimegepant treated analysis set.
  - On-DB or OL rimegepant safety: This period is used to assess safety endpoints on DB or OL rimegepant treatment for the DB or OL rimegepant treated analysis set
  - Follow-up safety: This period is abbreviated as "FU" in safety listings, and is used to assess safety endpoints during follow-up.
- Outcomes research endpoints
  - DBT outcomes research: This period is abbreviated as "DBT" in outcomes research listings, and used to assess outcomes research endpoints during the DBT Phase
  - OL rimegepant outcomes research: This period is abbreviated as "OLRMG" in outcomes research listings, and used to assess outcomes research endpoints during the OLE Phase.

For endpoints using the "treatment strategy policy", analysis period 1 is defined as the Day 14 CRF visit, analysis period 2 is defined as the Day 35 or Day 35/ET CRF visit.

[redacted]

For endpoints using the "while-on-treatment strategy":

- For AEs, refer to Section 6.4.1 for analysis period definitions.
- For NPRS endpoints, analysis period 1 is defined as the Day 14 visit, analysis period 2 is defined as the Day 35 or Day 35/ET visit, with visits derived using treatment exposure start and end dates.

8 CONTENT OF REPORTS

The final CSR is planned after the last planned analysis.

All analyses described in this SAP are included.

9 APPENDICES

9.1 Relevant Protocol Deviations

Relevant eligibility protocol deviations include the following categories:

- A mean of < 4 on the daily "average intensity" score on the NPRS during the last 14 days in the Screening Period
- TN onset less than 3 months prior to Screening
- Classical TN not confirmed on neuroimaging
- Neurological examination not done or incomplete (i.e., cranial, facial, or trigeminal nerve assessment not done)
- Non-compliance with or inability to complete the paper diary during the Screening Period. Non-compliance is 2 or more missed evening reports during the Screening Phase. Subjects should be considered for discontinuation after discussion with the sponsor.
- Medical history, defined as any of the following subcategories:
    - Subjects with Myocardial Infarction (MI), Acute Coronary Syndrome (ACS), Percutaneous Coronary Intervention (PCI), cardiac surgery, stroke or transient focal neurological deficit during the 6 months prior to screening
    - Gilbert's syndrome or any other active hepatic or biliary disorder
    - Gastric or small intestinal surgery.

Finding out of range during the pretreatment period or Day 35 if entering OL phase, defined as any of the following:

- ALT/AST/Direct Bilirubin/Indirect Bilirubin/Total Bilirubin > 1 xULN
- GGT > 1.5 xULN
- ECG abnormalities as follows:

  - Corrected QT interval > 470 msec (QTc by method of Frederica)
  - Left Bundle Branch block
  - Right Bundle Branch Block with a QRS duration ≥ 150 msec
  - Intraventricular Conduction Defect with a QRS duration ≥ 150 msec

- Neutrophil count ≤ 1000/μL (or equivalent)
- HbA1c ≥ 8%
- Diastolic measurement of ≥96mmHg
- 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
- BMI ≥ 33 kg/m^2
- Positive for cocaine or PCPs at any visit
- Females with a positive pregnancy test at any visit
- Subject's score is > 1 ("a little") on Question 2 or > 0 ("Not at all") on any other question on the Sheehan Suicidality Tracking Scale at any visit

Relevant subject management protocol deviations include the following:

- Type of TN discrepant between IWRS and CRF data, defined as any of the following subcategories:
  - IWRS randomization stratum of "atypical", but CRF Neuralgia type "typical" (Demographics page)
  - IWRS randomization stratum of "typical", but CRF Neuralgia type "atypical" (Demographics page)
- Prohibited non-study medications, procedures, or therapies defined as any of the following:
  - Standard of care Trigeminal Neuralgia medications with dose change or with start date < 4 weeks prior to randomization (see Section 4.4.1 for the definition of standard of care Trigeminal Neuralgia medication)
  - Carbamazepine taken during the Screening Period or afterward

[redacted]

- St. John's Wort taken up to 14 days prior to the Baseline Visit (randomization) or afterward
- Barbiturate-containing products (e.g. Fioricet, Fiorinal, butalbital, phenobarbital) taken up to 14 days prior to the Baseline Visit (randomization) or afterward
- Modafinil (PROVIGIL®) taken up to 14 days prior to the Baseline Visit (randomization) or afterward
- Butterbur root or extracts taken up to 14 days prior to the Baseline Visit (randomization) or afterward
- Ergotamine medications taken on ≥ 10 days per month on a regular basis for ≥ 3 months
- Narcotic medication, such as opioids, taken up to 2 days prior to the Baseline Visit or afterward
- Acetaminophen or acetaminophen containing products taken within 2 days before randomization.
- Use of acetaminophen during the Screening Period (3 to 14 days) or throughout the study at daily dosing levels of greater than 1000 mg/day
- Muscle relaxants (except baclofen) taken during the Screening Period or throughout the study
- Baclofen with start date < 8 weeks prior to randomization
- Strong CYP3A4 inhibitors taken during the Screening Period or throughout the study
- Strong CYP3A4 inducers taken during the Screening Period or throughout the study
- Strong inhibitors of the P-gp transporter taken during the Screening Period or throughout the study
- CGRP antagonists (biologic or small molecule) taken during the Screening Period or throughout the study

Note: Medications taken up to *X* days before a reference date or afterward are defined as those with medication start date or stop date ≥ reference date – *X*. Refer to the Core SAP for additional details about prohibited non-study medications.

[redacted]

- DB study drug dosing issue, defined as any of the following subcategories (see Section 6.2.6):
    - DB study drug taken but not randomized
    - DB tablet count compliance < 80% from DB study drug start to later of last scheduled DBT Phase visit or DB study drug end
    - > 1 DB tablet taken on any 1 day
    - Incorrect DB study drug taken
- OLE rimegepant dosing issue, defined as any of the following subcategories (see Section 6.2.6):
    - OLE rimegepant tablet count compliance < 80% from OL rimegepant start to later of last scheduled OLE Phase visit or OL rimegepant end
    - > 1 OLE rimegepant tablet taken on any 1 day

[redacted]

10 REFERENCES

Not applicable.

[redacted]