Protocol BHV3000-317

A Phase 2/3, Double-Blind, Randomized, Placebo- Controlled, Safety and Efficacy Trial of BHV-3000 (rimegepant) Orally Disintegrating Tablet (ODT) for the Acute Treatment of Temporomandibular Disorders (TMD)

Statistical Analysis Plan

Version 2.0

Date: 14-Jun-2023

SIGNATURE PAGE

Protocol Title:	A Phase 2/3, Double-Blind, Randomized, Placebo-Controlled, Safety and Efficacy Trial of BHV-3000 (rimegepant) Orally Disintegrating Tablet (ODT) for the Acute Treatment of Temporomandibular Disorders (TMD)
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Author:	PPD Biostatistics Rho, Inc. Signature:_ Date:_____ **Sponsor**

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/project, are in accordance with the study/project 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 Statistics Group Lead
Pfizer, Inc

Signature:
Date:___

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REVISION HISTORY

Version	Description of Change
0.1	Created
0.2	Updated after initial review by PP
0.3	Incorporated Core SAP Version D2 updates
1.0	Final version after final sponsor review
2.0	Signature: Updated Author and Signatory from Pfizer
	Section 1: Added text on the study termination prematurely
	Section 2.4: Added SAP version 2.0 is also based on Protocol version 3.0
	Section 3.2.2 Table 2 Objective 3: Corrected stratified CMH into Mantel-Haenzel risk estimation
	Section 3.2.2 Table 2 Objective 4: Removed comparison using log-rank test
	Section 3.2.2 Table 2 Objective 5: Removed comparison using log-rank test
	Section 3.2.2 Table 2 Objective 6: Corrected stratified CMH into Mantel-Haenzel risk estimation
	Section 3.2.3: Removed all CCI [redacted] except for CCI
	Section 4.3: Removed text on p-values
	Section 5: Removed text on multiplicity when testing CCI [redacted]
	Section 6.2.4.2: Added a listing of significant protocol deviations based on CTMS.
	Section 6.3.1: Updated Table 6 to Table 5
	Section 6.3.2.1: Updated Table 4 to Table 3 and removed text on p-value for the ANCOVA
	Section 6.3.2.2: Removed section on sensitivity analyses as no sensitivity analysis will be done
	Section 6.3.3: Removed texts on p-values and texts on sensitivity analysis.
	Section 6.3.3.3: Corrected stratified CMH into Mantel-Haenzel risk estimation
	Section 6.3.3.4: Removed comparison using log-rank test
	Section 6.3.4: CCI [redacted] are not assessed
	Section 6.4: Removed ECG to be analyzed.
	Section 6.4.4: Removed section on ECG
	Section 6.4.5: Updated to Section 6.4.4

ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ASE	asymptotic standard error
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BUN	Blood Urea Nitrogen
CI	Confidence interval
CK	Creatine kinase
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Technical Criteria for Adverse Events
CTMS	clinical trial management system
ECG	electrocardiogram
eDISH	Evaluation of drug-induced serious hepatotoxicity
EOT	End of Treatment
FESS	functional endoscopic sinus surgery
ICH	International Conference on Harmonization
IP	investigational product
IWRS	Interactive web response system
LFT	Liver function test
LS	Least squares
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MCMC	Markov Chain Monte Carlo
MI	Multiple imputation
MNAR	Missing not at random
NRS	Numerical Rating Scale
NSAID	non-steroidal anti-inflammatory drug

CCI	[redacted]
PT	Preferred term
REML	Restricted maximum likelihood
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SI	Systeme Internationale
SOC	System organ class
TEAE	Treatment-emergent adverse event
TBL	Total bilirubin
TLF	Table listing figure
TMD	Temporomandibular Disorder
TMJ	Temporomandibular joint
ULN	Upper limit of normal
US	United States
WHO-DD	World Health Organization-Drug Dictionary

1 BACKGROUND AND RATIONALE

This document presents the statistical analysis plan (SAP) for Protocol BHV3000-317: A Phase 2/3, Double-Blind, Randomized, Placebo-Controlled, Safety and Efficacy Trial of BHV-3000 (rimegepant) Orally Disintegrating Tablet (ODT) for the Acute Treatment of Temporomandibular Disorders (TMD).

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).

The Rimegepant (BHV3000)/Zavegepant (BHV3500) Core Statistical Analysis Plan, v3.0 (the "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.

For purposes of applying the Core SAP, the following applies:

- BHV3000-317 is a single-dose study
- BHV3000-317 is not a study with a follow-up phase
- References in the Core SAP to "studies with a COVID-19 Visit Impact CRF" will not necessarily apply to BHV3000-317. COVID-19 impact will be addressed as specified in this SAP.

Note that the study was terminated prematurely in 1Q2023 due to low enrollment. As a result, the SAP is being amended from Version 1.0 to 2.0 to reduce the number of TLFs to focus only on the most important outputs.

1.1 Research Hypothesis

Rimegepant will have efficacy superior to placebo in the acute treatment of temporomandibular disorders (TMD) with a favorable safety profile.

1.2 Schedule of Analyses

During this study, safety and exposure data are monitored on an ongoing basis. The CSR is produced after the last patient last visit and final database lock. All analyses described in this SAP are performed after the final database lock. No interim unblinded analyses are planned.

2 STUDY DESCRIPTION

2.1 Study Design

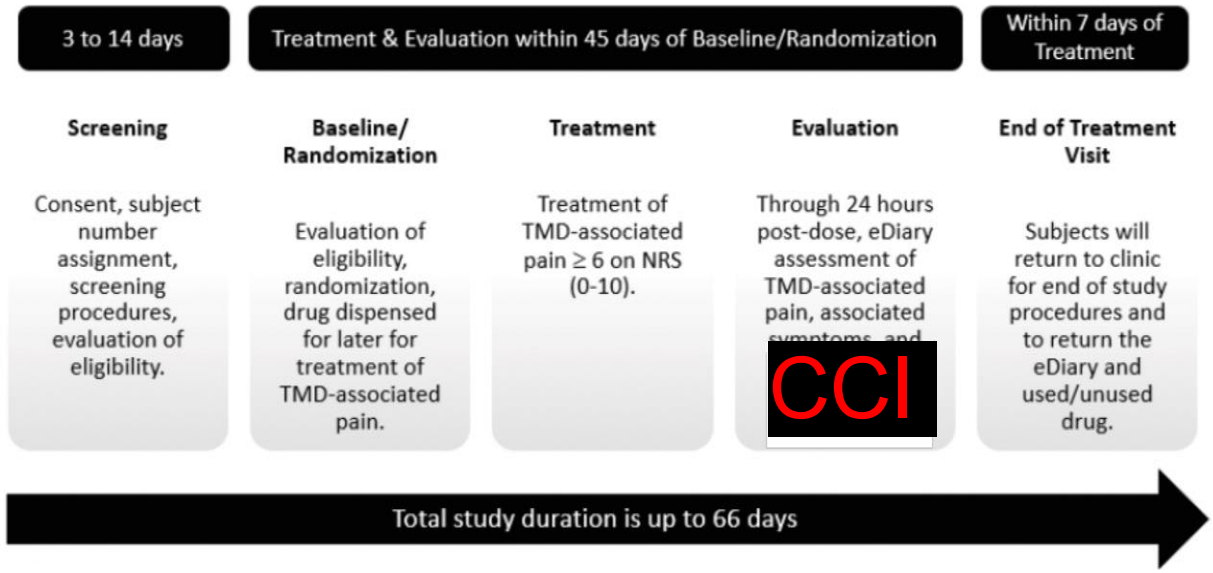
This is a Phase 2/3, double-blind, randomized, multicenter, outpatient evaluation of the safety and efficacy of rimegepant as compared to placebo for the acute treatment of temporomandibular disorders (TMD). The study drug will be rimegepant presented in a 75 mg ODT or matching placebo.

After obtaining informed consent, subjects will undergo all screening procedures as detailed in the schedule of assessments. After all screening procedures are complete, subjects may return 3 to 14 days (+2 days if needed for scheduling purposes) from signing informed consent to be randomized at the Baseline visit if they meet all eligibility criteria.

After randomization, the subject will be dispensed a single dose of the double-blind study medication to take home for up to 45 days. The subject will be instructed to take their study medication, as an outpatient, when (if) they have a TMD-associated pain in the jaw and/or temple area on either side which reaches pain intensity of 2: 6 on the NRS (0-10) after they answer eDiary questions about their current pain and symptoms; they should not dose until TMD-associated pain reaches a current intensity of 2: 6. The subject will complete an eDiary for 24 hours after taking study medication. The subject will be instructed to telephone the study center immediately if a severe or serious adverse event occurs.

Subjects will record efficacy data in their eDiary. CCI [redacted] Pain severity will be recorded using an NRS (0-10) at time of taking study medication and at 15, 30, 45, 60, and 90 minutes and 2, 4, 8 and 24 hours after dosing. CCI [redacted] Subjects will return to the study site within 7 days (+2) after taking study treatment for review of the eDiary, assessment of medication compliance, and monitoring of tolerability and safety. If a subject has NOT experienced a TMD-associated pain of sufficient severity within 45 days after randomization, they still are required to complete all end of treatment (EOT) visit procedures. All subjects must return empty medication packaging, any unused study medication, and the eDiary to the study center.

Figure 1: Study Schematic



2.2 Treatment Assignment

After completion of all screening evaluations, all eligible subjects will be randomized in a 1:1 ratio to the rimegepant or matching placebo treatment groups. Subjects will be randomized via the Interactive Web Response System (IWRS). The randomization will be stratified by the daily use of medications / oral devices to reduce intensity of TMD symptoms (yes or no) and will utilize block randomization with varying block sizes of 4 or 8. The number of blocks of each size will be blinded. It is important to correctly enter subjects who are using daily medications / oral devices in the IWRS system. Once a subject is stratified in the IWRS, this cannot be changed. Further detail is provided in the Randomization Plan v1.0, dated December 13, 2021.

2.3 Blinding and Unblinding

The study is double-blinded.

Randomization schedules are generated and kept by the IWRS vendor in a secure network folder with access limited to only unblinded team members. Each subject who is qualified for treatment is randomized via the IWRS randomization option. Subjects will maintain their subject number assigned at screening throughout the trial. The IWRS provides the double-blind treatment assignments. Further detail is provided in the BHV3000-317 Unblinding Plan v1.0 (as amended).

Dummy coding of treatment groups is used for purposes of blinded statistical programming and data review. Blinding of subjects is maintained until the database has been locked and unblinding has been approved.

Unblinding of individual subject(s) may occur in events of medical emergencies or pregnancies as specified in Section 7.3 of the protocol.

2.4 Protocol and Protocol Amendments

The versions 1.0 and 2.0 of the SAP are based on Version 3.0 of the protocol (31 March 2022).

3 STUDY OBJECTIVES AND ESTIMANDS

3.1 Objectives

3.1.1 Primary Objectives

To evaluate the efficacy of rimegepant compared with placebo in the acute treatment of Temporomandibular Disorders on the time-weighted sum of pain intensity difference (SPID) from baseline scores for the first 2 hours post-dose (SPID-2).

3.1.2 Secondary Objectives

1. To evaluate rimegepant compared with placebo on the time-weighted sum of pain intensity difference from baseline scores for the first 24 hours post-dose (SPID-24).

2. To evaluate rimegepant compared to placebo on change from baseline of pain on NRS (0-10) score at 2 hours post-dose.

3. To evaluate rimegepant compared to placebo on the proportion of subjects that are pain free at 2 hours post-dose.

4. To evaluate rimegepant compared to placebo on time to onset of meaningful pain relief post-dose.

5. To evaluate rimegepant compared to placebo on time to onset of initial pain relief post-dose.

6. To evaluate rimegepant compared to placebo on the probability of requiring rescue medication within 24 hours of initial treatment.

CCI [redacted]

CCI [redacted]

3.2 Estimands

An estimand is the target of estimation to address the scientific question of interest posed by a study objective. The four attributes of an estimand include the population of interest, endpoint of interest, 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. Use of non-study rescue medications on or before the time point of interest is considered an intercurrent event; intercurrent events are discussed in Table 1, Table 2 and Section 3.2.3 as applicable.

Refer to the specific sections below for additional detail on estimands for each endpoint. Refer to Section 4.1 for analysis sets that are used to assess endpoints.

3.2.1 Primary Objective Estimand

Table 1: Primary Objective Estimand

Objective	To evaluate the efficacy of rimegepant compared with placebo in the acute treatment of temporomandibular disorders on the time-weighted sum of pain intensity difference from baseline scores for the first 2 hours post-dose (SPID-2).
Efficacy Endpoint	Difference in SPID-2 scores between rimegepant and placebo groups assessed across the first 2 hours post-dose in treated subjects.
Summary	Difference in time-weighted SPID-2 between the rimegepant and placebo groups using an analysis of covariance (ANCOVA) model.
Intercurrent Events	1) Use of non-study rescue medications on or before two hours post-dose Composite strategy: All data points after rescue medication use are set to the last available observation prior to rescue medication usage when a subject uses a rescue medication on or before two hours post-dose. It is assumed that subjects who use rescue medication within the first two hours after dosing would not have experienced additional pain relief without the use of rescue medication. 2) Failure to log pain score at any time after study drug is administered through two hours post dose Composite strategy: All missing data points are set to the last available observation for subjects that fail to enter pain score(s) in the eDiary any time on or before the two hour post-dose pain assessment. It is assumed that subject who fail to enter pain scores would not have experienced additional efficacy at the missing timepoints. 3) All other intercurrent events Treatment policy strategy: All available assessments on the subject are used regardless of other intercurrent events.

3.2.2 Secondary Objective Estimands

Table 2: Secondary Objective Estimands

1	**Objective**	To evaluate rimegepant compared with placebo on the time-weighted sum of pain intensity difference (SPID) from baseline scores for the first 24 hours post-dose (SPID-24).
	Efficacy Endpoint	Difference in SPID-24 scores between rimegepant and placebo assessed across the first 24 hours post-dose in treated subjects
	Summary	Same as that of primary estimand, with respect to time-weighted SPID-24.
	Intercurrent Events	Same as that of primary estimand.
2	Objective	To evaluate rimegepant compared to placebo on change from baseline on NRS (0-10) score at 2 hours post-dose.
	Efficacy Endpoint	Change from baseline in NRS score to 2 hours post-dose in treated subjects.
	Summary	Difference in change from baseline in the NRS score between the rimegepant and placebo groups using a generalized linear mixed effect model.

	Intercurrent Events	Same as that of primary estimand.
3	Objective	To evaluate rimegepant compared to placebo on the proportion of subjects that are pain free at 2 hours post-dose.
	Efficacy Endpoint	The percentage of treated subjects that report no pain at 2 hours post-dose
	Summary	The difference between the rimegepant and placebo group in the percentage of subjects who are pain-free at 2 hours post-dose, analyzed using Mantel-Haenszel risk estimation. The definition of "pain free" is a subject that reports a zero on their 2 hour post-dose NRS assessment.
	Intercurrent Events	1) Use of non-study rescue medications on or before two hours post-dose Composite strategy: Subjects who use rescue medication on or before assessment of pain at two hours are imputed as a failure. 2) Failure to report eDiary assessments at two-hours post-dose Composite strategy: Subjects with missing data at two hours post-dose are imputed as a failure. 3) All other intercurrent events: Treatment policy strategy: All available assessments on the subject are used regardless of other intercurrent events.
4	Objective	To evaluate rimegepant compared to placebo on time to onset of meaningful pain relief post-dose.
	Efficacy Endpoint	The time to first nominal timepoint at which pain on NRS (0-10) decreases by 30% from baseline in treated subjects.
	Summary	Descriptive analysis by treatment group of the time to first nominal timepoint at which pain on NRS (0-10) decreases by 30% from baseline using Kaplan-Meier method. Meaningful pain reduction will be measured as a two-point reduction in NRS (0-10) score for subjects with a baseline pain score of 6, 7, or 8 and a 3 point reduction in NRS (0-10) score for subjects with a baseline pain score of 9 or 10.
	Intercurrent Events	1) Use of non-study rescue medications on or before onset of meaningful pain relief Composite strategy: Subjects who use rescue medication on or before onset of meaningful pain relief are censored at the time of rescue medication use. 2) Failure to report eDiary assessments. Composite strategy: Subjects who do not complete all post-dose assessment will be censored at the time of the last completed NRS pain assessment. 3) All other intercurrent events: Treatment policy strategy: All available assessments on the subject are used regardless of other intercurrent events.
5	Objective	To evaluate rimegepant compared to placebo on time to onset of initial pain relief post-dose.
	Efficacy Endpoint	The time to first nominal timepoint at which pain on NRS (0-10) decreases by 1 point from baseline in treated subjects.
	Summary	Descriptive analysis by treatment group of the time to first nominal timepoint at which pain on NRS (0-10) decreases by 1 point from baseline using the Kaplan-Meier method.

	Intercurrent Events	Same as secondary endpoint # 4
6	Objective	To evaluate rimegepant compared to placebo on the probability of requiring rescue medication within 24 hours of initial treatment.
	Efficacy Endpoint	Percentage of treated subjects that use rescue medication within 24 hours after administration of study drug.
	Summary	The difference in the percentage of subjects that take study drug and then take rescue medication within 24 hours, analyzed using Mantel-Haenszel risk estimation.
	Intercurrent Events	Treatment policy strategy: All available assessments on the subject are used regardless of intercurrent events.

CCI [redacted]

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 signed the informed consent form and were assigned a subject identification number by the IWRS; i.e., non-missing informed consent date. This analysis set is used mainly to assess study population and in by-subject listings.

- Full: Enrolled subjects who were assigned a randomized treatment group; i.e., non-missing IWRS randomization date. This analysis set is used mainly to assess study population.

- Treated: Enrolled subjects who took study therapy (rimegepant or placebo); i.e., non-missing study drug start date. This is the primary efficacy analysis set and used to assess study population, exposure, and on-treatment safety, and produce select by-subject listings.

4.2 Treatment Groups

The two treatment groups are rimegepant 75 mg and placebo. The treated analysis set is assessed by the as-randomized treatment group for efficacy presentations and as-treated for safety presentations. The randomized analysis set is assessed by as-randomized treatment groups. The enrolled analysis set is assessed overall. If there are non-randomized subjects who took study drug, then the treatment group of "not randomized" is included in the full analysis set.

4.3 Subgroups

Stratification factor (use of daily medications / oral devices to reduce the intensity of TMD symptoms), as randomized is a subgroup of interest for the treated analysis set.

Subgroup analyses are performed for the primary efficacy endpoint only, following the methods specified in Section 6.3.2.1 with respect to each subgroup level. Stratification factor is removed as a covariate from the model as appropriate.

5 SAMPLE SIZE, POWER, AND TYPE I ERROR

If 80% of the 200 randomized (100 per treatment arm) treat with study drug, we expect roughly 160 total or 80 per treatment group in the randomized and treated population for analysis.

Assuming rimegepant provides a 2-point reduction in NRS pain, and a 1.5-point advantage over placebo on the primary endpoint, and a common standard deviation of 3.0, then the study will have roughly 88% power on the primary endpoint.

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

6 STATISTICAL ANALYSES

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

6.1 General

6.1.1 Programmed Output

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

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

Adverse event (AE), medical history, medications, and procedures are coded using Medical Dictionary for Regulatory Activities (MedDRA) v. 25.0 and World Health Organization-Drug Dictionary (WHO-DD) version March 2022 B3.

6.1.1.1 Tables

Treatment Group Presentation

Tables present results by treatment group (i.e., rimegepant 75 mg and placebo) with the following exceptions:

- Results for the enrolled analysis set are presented only by overall, without treatment group.
- Results for study population parameters (see Section 6.2) and pre-treatment safety also include overall.

Time-to-event Tables

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

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

6.1.1.2 Listings

In general, by-subject listings are sorted by randomization status (randomized, not randomized), which is not displayed, followed by site-subject ID and visit and/or date/time, as applicable.

Unless specified otherwise, listings of significant protocol deviations, safety parameters, efficacy parameters, and COVID-19 visit impact include the following: analysis visit or assessment in which the measurement was slotted (where applicable); event or finding date/time (where applicable); and study day and/or treatment day derived using the event or finding date/time (see Section 7.2 of the Core SAP). Listings of significant protocol deviations, safety parameters, and COVID-19 visit impact also include the abbreviated name of the analysis period in which the measurement was slotted (i.e., PRETRT for pre-treatment and ONTRT for on-treatment; see Section 7.2).

Refer to the Core SAP for additional details about listings. The footnote for race abbreviations is provided in Section 3.6.2. of the Biohaven Biostatistics Global TLF Standards - GD-0056 and does not include ‘U’ for Unknown.

6.1.2 Statistical Methods

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

Notwithstanding Section 7.6 of the Core SAP, age in all instances is age recorded on the case report form (CRF).

6.1.3 Handling of Missing Data

All safety analyses are based on observed data without using imputation, except that partial or missing start and stop dates or datetimes for non-study medications and AEs are imputed solely for purposes of categorizing the events. See Section 7.1.2 for the imputation of partial or missing non-study medications and AE dates (except rescue medications).

Missing efficacy data are handled in the respective subsections of Section 6.3.

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 group (as-randomized for the full analysis set; 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, and an administrative listing of randomization scheme and codes is provided for all randomization numbers and block numbers, even those not assigned to a subject. Refer to the Core SAP for listing contents.

6.2.2 Enrollment

Enrollment by country and site is tabulated for the enrolled analysis set. Refer to the Core SAP for additional details.

6.2.3 Subject Disposition

6.2.3.1 Subject Disposition at Study Milestones

Subject disposition is based on the Disposition CRF, unless noted otherwise.

A subject disposition table is provided for treatment to completion/discontinuation for the treated analysis set. This includes the number and percentage of treated subjects completing the study (i.e. study status is marked “Complete” in the Disposition CRF) and not completing the study with reasons for non-completion, including whether or not the subject discontinued due to COVID-19.

A by-subject listing of subject disposition is provided for the enrolled analysis set based on the Disposition CRF and includes the following: date randomized (as applicable), date/time the study drug was administered (as applicable), an indication whether the subject completed the study (yes, no), reason for discontinuation if applicable (including an indication if the subject discontinued due to COVID-19), and last contact date (see Section 7.1.3). Notwithstanding Section 6.2.3 of the Core SAP, this listing will not be provided separately for each phase, and study milestone parameters will not be included.

A listing would be provided for all visits and assessments impacted by COVID-19 for the enrolled analysis set. The listing would include the visits and assessments that were impacted by COVID-19, impact (e.g. missed), and relationship to COVID-19 (e.g. subject diagnosed with COVID-19).

6.2.3.2 Overall Premature Study Termination due to COVID-19

Notwithstanding Section 6.2.3.2 of the Core SAP, a frequency table of overall premature study termination due to COVID-19 will not be produced.

6.2.4 Protocol Deviations

6.2.4.1 Relevant Protocol Deviations

A relevant protocol deviation is a deviation from the protocol which is programmed from the database and which could potentially affect the interpretability of the study results. This type of deviation includes but is not limited to: eligibility and subject management.

For purposes of identifying relevant protocol deviations related to medication use, partial or missing non-study medication dates are imputed as set forth in Section 7.1.2. Medical history dates are not imputed; however, ongoing medications with partial start dates will be considered ongoing for purposes of categorizing relevant protocol deviations related to medical history if the partial date(s) are consistent with the medication being ongoing at the time of Screening, or as specified in the relevant protocol deviation criteria (see Section 9.1 for further detail).

Relevant Protocol Deviation Frequency Table

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

Relevant Protocol Deviation Listing

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

6.2.4.2 Significant Protocol Deviations

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

A Microsoft Excel file of protocol deviations is provided by the data management vendor from the clinical trial management system (CTMS). This file serves as the raw data source of protocol deviations, and classifies deviation severity as major or minor. Significant protocol deviations are defined as those with major severity. A footnote describes the raw data source and how significant protocol deviations are identified, e.g., "Significant protocol deviations are those with major severity reported by the data management vendor in the clinical trial management system."

6.2.5 Baseline Characteristics

Baseline characteristics include (1) demographics and other relevant baseline characteristics, (2) baseline disease characteristics (i.e., Diagnostic Criteria for TMD Symptom Questionnaire, DC/TMD Examination), (3) medical history, and (4) prior non-study medications. These are tabulated by the treated analysis set.

By-subject listings are provided for the enrolled analysis set for the following: demographics, medical history, Diagnostic Criteria for TMD Symptom Questionnaire, and DC/TMD Examination.

See Section 7.5 for the derivation of the baseline value for a parameter (e.g., weight).

6.2.5.1 Demographics and Other Relevant Baseline Characteristics

Refer to the Core SAP (Section 6.2.5.1) for the table of demographics and other relevant baseline characteristics, with the following adjustments:

- Country is not tabulated.
- Triptan non-responders and cardiovascular risk factors contraindicating triptans are not tabulated, as these data are not directly collected.
- "Unknown" is not included as a race category.

Randomization Stratum Frequency Table

A frequency table of randomization stratum displays the number and percentage of subjects in each randomization stratum for the full analysis set to confirm whether balance was achieved across treatment groups.

Demographics Listing

Refer to Section 6.2.5.1 of the Core SAP for specifications on the demographics listings.

6.2.5.2 Baseline Disease Characteristics

With respect to reporting baseline disease characteristics, Section 6.2.5.2 "Baseline Disease Characteristics" of the Core SAP does not apply in its entirety; the following applies instead.

Diagnostic Criteria for TMD

Results are based on the Diagnostic Criteria for Temporomandibular Disorders Symptom Questionnaire CRF. Results will be tabulated and include the following parameters summarized as categorical or continuous variables, as applicable. The table includes a "not reported" category for missing categorical variables for any categories with at least one record of "not reported". For each high-level category, the denominator is the number of subjects in the relevant population. For each sub-level category the denominator is the number of subjects responding "yes" in the related high-level category.

- Ever had pain in jaw, temple, in the ear, or in the front of the ear (yes, no)
    - Number of years and/or months since pain onset (continuous)
    - Pain in the last 30 days (no pain, pain comes and goes, pain always present)
        - Chewing hard or tough food
        - Opening mouth, or moving jaw forward or to the side
        - Jaw habits such as holding teeth together, clenching/grinding teeth, or chewing gum
        - Other jaw activities such as talking, kissing, or yawning
- Headaches in the last 30 days that included the temple areas (yes, no)
    - Number of years and/or months since temple headache first begin (continuous)
    - Activities in the last 30 days that changed any headache (better or worse) in the temple area
        - Chewing hard or tough food
        - Opening mouth, or moving jaw forward or to the side
        - Jaw habits such as holding teeth together, clenching/grinding teeth, or chewing gum
        - Other jaw activities such as talking, kissing, or yawning
- Jaw joint noise(s) in the last 30 days when the jaw is moved or used (yes/no)
- Closed locking of the jaw so that it would not open all the way (yes, no)
    - Severe enough to interfere with eating (yes, no)
    - Jaw locked in the last 30 days and then unlocked (yes/no)

        - Jaw currently locked (yes, no)

- Open locking of jaw in the last 30 days so that it could not close from a wide-open position (yes, no)

    - Intervened to allow jaw to close including resting, moving, pushing, or maneuvering (yes, no)

A by-subject listing of responses to all Diagnostic Criteria for TMD is provided for enrolled subjects.

DC/TMD Examination

Results are based on the DC/TMD Examination CRF. Results are tabulated and includes the following parameters summarized as categorical or continuous variables, as applicable. The table includes a "not reported" category for missing categorical variables for any categories with at least one record of "not reported." For each high-level category, the denominator is the number of subjects in the relevant population. For each sub-level category, the denominator is the number of subjects responding "yes" the related high-level category.

- DC/TMD examination completed in entirety (yes, no)
- Opening movements
    - Pain free opening (mm) (continuous)
    - Maximum unassisted opening (mm) (continuous)
    - Maximum assisted opening (mm) (continuous)
    - Terminated (yes, no)
- Diagnoses – pain disorders
    - None (n, %)
    - Myalgia (n, %)
    - Myofascial pain with referral (n, %)
    - Right arthralgia (n, %)
    - Left arthralgia (n, %)
    - Headache attributed to TMD (n, %)
- Right temporomandibular joint (TMJ) disorders
    - None (n, %)
    - Disc displacement with reduction (n, %)
    - Disc displacement with reduction and intermittent locking (n, %)
    - Disc displacement without reduction, with limited opening (n, %)
    - Disc displacement without reduction, without limited opening (n, %)

  - Degenerative joint disease (n, %)
  - Subluxation (n, %)

- Left TMJ disorders
  - None (n, %)
  - Disc displacement with reduction (n, %)
  - Disc displacement with reduction and intermittent locking (n, %)
  - Disc displacement without reduction, with limited opening (n, %)
  - Disc displacement without reduction, without limited opening (n, %)
  - Degenerative joint disease (n, %)
  - Subluxation (n, %)
- Other diagnoses (non-primary)
  - Tendonitis (n, %)
  - Contracture (n, %)
  - Hypertrophy (n, %)

A by-subject listing of DC/TMD Examination is provided for enrolled subjects.

6.2.5.3 Medical History

Refer to the Core SAP (Section 6.2.5.3) for medical history.

6.2.5.4 Non-Study Prior Medications

The following prior non-study medications are tabulated by therapeutic class and preferred name:

- Previous medications
- Current medications
- Stable medications to reduce intensity of TMD symptoms through end of treatment.

The definitions of medication types in Section 6.2.6.3 of the Core SAP, as applicable to single-dose studies, applies. For clarity, prior (previous and current) medications do not include rescue medications (see Section 6.2.6.3).

Medications are displayed in descending order of overall frequency within therapeutic class and preferred name. See Section 6.2.6.3 for further detail on medication types.

Stable TMD medications through Screening are defined as TMD medications taken > 3 months before informed consent and through completion or discontinuation of the study, with no change in dose amount or frequency, i.e., (1) informed consent date – imputed medication start date > 91 days, and (2) completion or discontinuation σ; imputed medication stop date, with no change in dose amount or frequency. For purposes of this analysis, TMD medications are defined as follows:

- Tricyclic antidepressants (such as: amitriptyline, nortriptyline)
- Venlafaxine, desvenlafaxine, duloxetine, milnacipran
- Gabapentin, pregabalin
- Feverfew, magnesium (2: 600 mg/day), riboflavin (2: 100 mg/day)
- Botulinum therapy (e.g., onabotulinum toxin A, abobotulinum toxin A, and incobotulinum toxin A)

6.2.6 Exposure

6.2.6.1 Study Therapy

Study drug is dispensed in a subject-specific bottle containing one blister unit of drug. Exposure is measured by subjects providing self-reported study drug exposure information (see Section 7.1). As a check on this exposure data, study drug accountability data are provided on the Drug Accountability CRF.

The date/time of exposure is defined in Section 7.1.

The self-reported study drug exposure data are tabulated by treatment group and overall for randomized subjects and includes:

- The number (and percentage) of randomized subjects that took study medication
    - The number and percentage who mistakenly took drug. A medication is deemed taken mistakenly if the subject entered “Yes” to “Did you mistakenly take your study medication already?” in the “Initial pain” eDiary, or if the subject reported having mistakenly taken drug to the site without interacting with the eDiary.
    - The number and percentage that took study medication immediately after providing a qualifying pain NRS score (≥ 6) (i.e. the subject responded “Yes” to the question “Please confirm you took your Study Medication” in the “Initial pain” eDiary.

- The number and percentage of randomized subjects who never reported taking study medication
    - The number and percentage who never reported a qualifying pain NRS score (佯 6)
    - The number and percentage who reported a qualifying pain NRS score (2: 6) at least once

An administrative listing of investigational product (IP) batch numbers is provided for the randomized analysis set. Refer to the Core SAP for listing contents.

6.2.6.2 Measurements of Treatment Compliance

Section 6.2.6.2 of the Core SAP does not apply.

The study drug accountability data are tabulated by treatment group and overall, for randomized subjects and includes:

- The number and percentage of randomized subjects to whom kits were dispensed
- The number and percentage of randomized subjects who returned kits
    - The number and percentage of subjects with returned kits from which the IP was used
    - The number and percentage of subjects with returned kits from which the IP was not used
    - The number and percentage of subjects with returned kits from which IP use not reported (i.e., missing)
- The number and percentage of subjects who did not return kits
- The number and percentage of subjects who did not report returning kit (i.e., missing)

A by-subject listing is prepared that indicates the study drug exposure and accountability status for the treated analysis set; this listing includes study drug start date/time and study day, drug accountability kit dispensed date, kit returned date, kit ID, and IP used status (IP taken, IP not taken). A patient identifier listing is prepared if subjects had unknown exposure data, unknown accountability data, or for whom the exposure and accountability data did not match.

6.2.6.3 Concomitant and Rescue Medications

Concomitant non-study medications are tabulated by therapeutic class and preferred name for the treated analysis set. The definition of concomitant medication in Section 6.2.6.3 of the Core SAP, as applicable to single-dose studies, applies. For clarity, concomitant medications include

both medications recorded on the Concomitant Medications CRF that meet the definition of "concomitant" (see Section 6.2.6.3 of the Core SAP) and all rescue medications (defined below). Sites are instructed to exclude medications reported on the Rescue Medication CRF from the Concomitant Medications CRF.

Medications are displayed in descending order of overall frequency within therapeutic class and preferred name. Refer to the Sections 6.2.6.3 of the Core SAP for non-study medication counting rules in frequency tables.

Rescue medications include any non-study medication recorded on the Rescue Medication CRF with complete medication dates, and either (1) medication date/time is after the study drug start date/time if the medication time and study drug start time are both not missing, or (2) medication date is on or after study drug start date if the medication time or study drug start time is missing. Rescue medication dates are not imputed. Rescue medication times are not imputed, except as provided in Section 7.1.5 for time-to-event analyses. Rescue medications are separately tabulated and displayed in descending order of overall frequency within therapeutic class and preferred name for the treated analysis set. Any medication recorded on the Rescue Medication CRF that does not meet the above definition of a "rescue medication" will be treated as a current or concomitant medication, as appropriate, based on the imputed medication start date.

A by-subject listing of non-study medications is provided by therapeutic class and preferred name for the enrolled analysis set. The listing displays medication type and treatment days derived from the imputed start date. For purposes of this listing, the start date/time of rescue medication use is the date/time of rescue medication use, and rescue medications are identified. Refer to the Core SAP for additional listing contents, except AE and medical history terms are not included.

Non-study medications are classified according to the World Health Organization Drug Dictionary (WHO-DD) and Anatomical Therapeutic Chemical (ATC) classification system B3 global format (March 2022).

6.2.6.4 Concomitant Oral Devices

Concomitant oral devices are tabulated by system organ class (SOC) and preferred term (PT) for the treated analysis set. The definition of concomitant oral devices is the same as that used for concomitant medication in Section 6.2.6.3 of the Core SAP, as applicable to single-dose studies.

A by-subject listing of concomitant oral devices is provided for the enrolled analysis consistent with section 6.2.5.3 of the Core SAP, as applicable for oral devices.

6.3 Efficacy

Unless otherwise noted, all efficacy analyses are conducted using the treated analysis set as outlined below. Efficacy tabulations present results by as-randomized treatment group only (excluding overall), unless specified otherwise. All key efficacy data are included in listings by subject, treatment group, and time point (as applicable).

Summary statistics (n, mean, median, SD, minimum, maximum) are reported for continuous variables at each time point, along with change from baseline, as applicable.

6.3.1 Rescue Medication

Rescue medications are defined in Section 6.2.6.3. For efficacy evaluations (except for the analysis set forth in Section 6.3.3.6), a rescue medication is considered used as of a given time point if the date/time of first rescue medication use is on or prior to the date/time of that efficacy evaluation or, if the eDiary assessment is missing at that time point, if the date/time of first rescue medication use is :S the upper limit of the window for that assessment as specified in Table 5. For instance, a subject is treated as having used rescue medication as of 2 hours post-dose if the date/time of first rescue medication use is prior or equal to the date/time of the 2-hour assessment, even if the date/time of first rescue medication is more than 2 hours post-dose, or, if the eDiary assessment at 2 hours is missing, if the date/time of first rescue medication use is :S 135 minutes. If the time of first rescue medication is missing, the rescue medication is considered used as of a given time point if the date of rescue medication is on or prior to the date of that efficacy evaluation.

For efficacy evaluations (except for the analysis set forth in Section 6.3.3.6), the first rescue medication date/time is defined as the earliest rescue medication date/time, where missing time is considered to be earlier than non-missing time on the same date.

For clarity, assessments after rescue medication administration are not set to missing for purposes of calculating summary statistics, even when the assessments are set to missing for model evaluation.

6.3.2 Primary Efficacy Endpoint

6.3.2.1 Primary Analysis

TMD pain is assessed using an NRS score ranging in integers from 0 to 10, with 0 being “no pain” and 10 being “worst imaginable pain.” Each subject indicates pain using the eDiary at each of the following nominal timepoints: 0 (baseline), 15, 30, 45, 60, 90 and 120 minutes post-dose.

The pain intensity difference at each post-baseline timepoint (PID_i) is calculated by finding the difference between the NRS score at each timepoint (PI_i) from the baseline NRS score (PI_o).

$$PID_i = PI_i - PI_O$$

The SPID-2 will be calculated by multiplying the PID score at each post-dose timepoint by the duration (in hours) since the preceding timepoint, then summing the values over the 2 hours.

$$SPID\text{-}2 = \sum_{i=1}^{6} (T_i - T_{(i-1)}) * PID_i$$

Where $T_0 = 0$, T_i = the nominal time as described in Table 3, $T_{(i-1)}$ = the preceding nominal time, PID_i = PID score at time T_i

Table 3: NRS Collection Nominal Timepoints

NRS collection timepoint	*i*	*Ti (hours)*
15 minutes	*1*	*0.25*
30 minutes	*2*	*0.50*
45 minutes	*3*	*0.75*
60 minutes	*4*	*1.00*
90 minutes	*5*	*1.50*
2 hours	*6*	*2.00*
4 hours	*7*	*4.00*
8 hours	*8*	*8.00*
24 hours	*9*	*24.00*

The SPID-2 will be analyzed on the treated population using an analysis of covariance (ANCOVA) model, estimated by Restricted Maximum Likelihood (REML) that includes baseline NRS value as a covariate and treatment group and stratification factor (use of daily medications / oral devices to reduce the intensity of TMD symptoms) as the main effects. The least squares mean (LS mean), standard error (SE), and 95% confidence intervals (CI) for each treatment group will be estimated and reported, as well as the LS mean, SE, and 95% CI for the difference between treatment groups (rimegepant – placebo). Descriptive summaries of PID value at each measured timepoint will be presented by treatment group to include mean, SD, median, minimum, and maximum.

The intercurrent events of non-study rescue medication and failure to log NRS pain score are treated with a composite strategy. All assessments after rescue medication administration are set to the last observation prior to the time of rescue medication use. Any missing NRS assessment(s) will be imputed to the last non-missing observation prior to the missing assessment. For clarity, in the case of intermittent missing values, missing values will be imputed based on the last non-missing observation prior to the missing value or consecutive series of missing values; any subsequent non-missing values will not be imputed unless rescue medication was administered prior to that assessment. Subjects who mistakenly dose and thus have a missing baseline NRS assessment will have the missing baseline assessment imputed as the mean of the non-missing baseline assessments across subjects.

6.3.3 Secondary Efficacy Endpoints

Secondary endpoints will be analyzed on the treated population.

6.3.3.1 Sum of Pain Intensity Difference at 24 Hours (SPID-24)

The analysis in Section 6.3.2.1 is repeated for the SPID-24 on the treated population, with SPID-24 being calculated by multiplying the PID score at each post-dose timepoint by the duration (in hours) since the preceding timepoint, then summing the values over a 24-hour period.

Each subject indicates pain using the eDiary at each of the following nominal timepoints: 0 (baseline), 15, 30, 45, 60, 90 and 120 minutes, and 4, 8, and 24 hours post-dose.

6.3.3.2 Change from Baseline of Pain on NRS at 2 Hours

Change from baseline pain on NRS score is analyzed on the treated population using a generalized linear mixed effect model that includes the baseline NRS (0-10) value as a covariate, and fixed effects for treatment group, stratification factor (use of daily medications / oral devices to reduce the intensity of TMD symptoms), scheduled time point, and time point by treatment group interaction. Time points included in the model are nominally at 15, 30, 45, 60, 90 and 120 minutes post-dose.

Repeated measures within subject are modeled using an unstructured covariance structure for within subject error. In the case the model fails to converge, a Huynh-Feldt error structure is utilized, followed by an AR(1) structure. Error degrees of freedom are calculated using the Kenward-Rogers approximation if an unstructured covariance structure fits appropriately; otherwise, a sandwich estimator is utilized to estimate the covariance structure, and the degrees of freedom are calculated using the between-within method.

Restricted maximum likelihood (REML) estimation is utilized; should the model fail to converge under REML, maximum likelihood estimation is utilized.

Least squares (LS) means, SE, and 95% CIs are reported for each treatment group at 2 hours post-dose, along with LS mean difference estimate (rimegepant - placebo) and associated SE and 95% CI.

Intercurrent events will be handled in the same way as in the primary analysis described in Section 6.3.2.1.

6.3.3.3 Pain Freedom at 2 Hours

The number and percentage of subjects in the treated population that experience pain freedom at 2 hours post-dose are analyzed after first imputing missing data at 2 hours to be failure (NC [Non-completer] = F [Failure]). Additionally, subjects who use rescue medication on or before assessment of pain at 2 hours are also assigned as failures (RM [Rescue medication use] = F). If the time of first rescue medication is missing, subjects are considered as failures if the date of rescue medication is the same as the date of dosing.

The analysis is done using Mantel-Haenszel risk estimation after imputation is done, with the stratification factor as yes/no for use of daily medications / oral devices to reduce the intensity of TMD symptoms. If one category of stratification factor has sparse data (less than 5 subjects), then the stratification factor is removed. Pain freedom is defined as an NRS score of zero at 2 hours post-dose (yes or no).

Results presented from the analysis includes the following:

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

A forest plot is produced depicting the risk difference for pain freedom at 2 hours post dose. The risk difference for each stratum will be presented, as well as the overall common risk difference.

6.3.3.4 Time to Onset of Meaningful Pain Relief

Time to onset of meaningful pain relief post-dose is analyzed descriptively for the treated population using Kaplan-Meier methods. Meaningful pain relief is considered the event in these analyses and is defined as the first nominal timepoint at which a 30% reduction of pain from baseline on the NRS is achieved. For clarity, meaningful pain relief is a 2-point reduction in NRS (0-10) score for subjects with a baseline pain score of 6, 7, or 8, and a 3-point reduction in NRS (0-10) score for subjects with a baseline pain score of 9 or 10.

The survival distributions will be described at the nominal timepoints of 15, 30, 45, 60, 90, and 120 minutes, and 4, 8, and 24 hours post-dose. Subjects are considered to have an event through 24 hours if the first post-dose eDiary finding date/time where meaningful pain relief is achieved is (1) at or before the upper bound of the 24-hour analysis window in minutes (see Table 5: Analysis Visit Windows for Safety Parameters), and (2) is before the imputed rescue medication start date/time, if not missing (see Section 7.1). Subjects who do not have the event through 24 hours (even in the case of missing data) are censored at the earliest of the following: (1) upper bound of the 24-hour analysis window + 1 minute; (2) time from the study drug start date/time to the imputed rescue medication start date/time, if the time is at or before the upper bound of the 24-hour analysis window in minutes; (3) time from the study drug start date/time to the last non-missing eDiary date/time defining the endpoint, if the time was before the lower bound of the 24-hour analysis window in minutes. Likewise, subjects who take rescue medication will be censored at the time of first rescue medication use, if rescue medication is taken before meaningful pain relief is recorded.

A Kaplan-Meier (KM) plot and table using the following time intervals post-dose will be generated: using the following time intervals post-dose: 0 to 15, >15 to 30, > 30 to 45, > 45 to 60, > 60 to 90, > 90 to 120, > 120 to 180, > 180 to 240, > 240 to 360, > 360 to 495, and > 495 minutes. The KM plot displays the percentage of subjects with meaningful pain relief within 24 hours on the y-axis versus time in minutes on the x-axis. Refer to Core SAP for more details.

A time-to-event distribution table will be generated. This includes number and percentage of subjects with events; number and percentage of subjects censored in or before the last time interval; number and percentage of subjects censored in the last time interval; time-to-event median with 95% CI, first quartile, and third quartile. The 95% CI for the median is estimated using the method of Brookmeyer and Crowley.

6.3.3.5 Time to Onset of Initial Pain Relief

The analysis in Section 6.3.3.4 will be repeated with respect for the time to onset of initial pain relief. Initial pain relief will be defined as the timepoint at which a 1-point reduction of pain from baseline NRS is achieved.

6.3.3.6 Rescue Medication Use within 24 Hours

The number and percentage of subjects that use rescue medication within 24 hours post-dose are analyzed. Subjects who used rescue medication as of 24 hours post-dose are deemed failures, and subjects who did not use rescue medication as of 24 hours are deemed successes. For clarity, failure is the event being modeled (i.e. rescue medication use within 24 hours) in this analysis.

Refer to Section 6.2.6.3 for the definition of rescue medication. A rescue medication would be deemed used as of 24 hours post-dose if the date/time of first rescue medication use is strictly ≤ 24 hours after the date/time of dosing, notwithstanding Section 6.3.1 of the SAP. Subjects with a rescue medication start date on or before study drug start date/time + 24 hours and missing rescue medication start time are excluded. Subjects who report non-study medication on the Rescue Medication CRF with a missing rescue medication date, or a partial medication date that is consistent with being used within 24 hours of dosing, are also excluded. Regardless of the foregoing, if a subject has at least one rescue medication use with non-missing start time that is ≤ 24 hours after the date/time of dosing, the subject will be included in the analyses and deemed a failure.

No analysis window around the 24-hour post-dose time point is used.

The analysis follows the same methodology set forth in Section 6.3.3.3. A forest plot is produced depicting the risk difference for rescue medication use within 24 hours post dose. The risk difference for each strata will be presented, as well as the overall common risk difference.

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

- Kaplan-Meier plot and table using 2-hour time intervals (i.e., 0 to 2, > 2 to 4, … , > 24). The Kaplan-Meier plot displays the percentage of subjects taking rescue medication

within 24 hours post-dose on the y-axis versus time in hours on the x-axis. Refer to Core SAP for more details.

- Time-to-event distribution table (hours). This includes number and percentage of subjects with events; number and percentage of subjects censored in or before the last time interval; number and percentage of subjects censored in the last time interval; time-to-event median with 95% CI, first quartile, and third quartile. The 95% CI for the median is estimated using the method of Brookmeyer and Crowley.

Rescue medication use through 24 hours post-dose is considered as an event in these time-to-event analyses. See Section 7.1.5 for imputing missing rescue medication start time for purposes of time to rescue medication analyses. Subjects who do not take rescue medication within 24 hours post-dose are censored at 24 hours and 1 minute.

CCI [redacted]

6.4 Safety

Safety analyses are based on the treated analysis set by as-treated treatment group (i.e., the actual treatment received). Results for the overall treatment group are also presented in pre-treatment safety summaries.

Safety parameters include deaths, AEs, and the following findings: laboratory tests; vital signs; physical measurements; procedures and C-SSRS.

Analysis periods are pre-treatment and on-treatment (see Section 7.2). Refer to the Core SAP for slotting safety parameters into analysis periods.

Values and changes from baseline in safety findings (e.g., laboratory tests, vital signs and physical measurements) and C-SSRS endpoints are tabulated as continuous variables descriptively at baseline and the end of treatment visit. These analyses are based on observed

data without imputation and regardless of rescue medication use. In these tables of safety parameters, if a subject has multiple values in the end of treatment analysis visit window (see Section 7.3), then the last non-missing value measured in the analysis period is used. See Sections 6.3.4.1, 6.4.4.1, and 6.4.2.4 for further handling of ties on the same measurement date or time.

By-subject listings of safety parameters are described in subsections and identify on-treatment data.

6.4.1 Adverse Events

AEs are displayed in tables and listings by SOC and PT, unless specified otherwise.

Refer to the Core SAP for AE start date imputation, AE counting rules and frequency table specifications, definition of related to study drug, definition of treatment-emergent adverse events (TEAEs), definition of AEs of special interest, reporting of deaths, and AE listing contents. Exposure-adjusted multiple occurrences of unique AEs (Section 6.4.1.5 of the Core SAP) does not apply.

For purposes of applying Section 6.4.1.2 of the Core SAP (definition of TEAE), an AE with non-missing start time is considered pre-treatment if the start date/time of the AE is prior to treatment start date/time. Furthermore, the "first occurrence" of an AE means the earliest imputed start date or earliest start date/time, where an AE with non-missing start date/time is deemed prior to an AE with missing start time and an imputed start date on the same date.

A by-subject AE listing is provided for the enrolled analysis set. Notwithstanding Section 6.4.1.7 of the Core SAP, "treatment of event" is not listed.

6.4.1.1 Deaths

Deaths are identified from any the following sources:

- AE CRF with any of the following: PT of "death"; reported term containing "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 (see Section 7.1)
- Disposition CRF: subject status of "Death."

The by-subject listing of deaths is provided for the enrolled analysis set, and displays all CRF sources of death, safety analysis period, death date (see Section 7.1), study day derived from the death date, treatment day derived from the death date, and the following AE parameters: non-imputed start date and end date; SOC; PT; verbatim term; outcome; and response to the question "Fatal".

6.4.1.2 AE Overview

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

An AE overview is produced for each analysis period (pre-treatment, on-treatment) for the treated analysis set.

6.4.1.3 On-treatment AEs by SOC and PT

On-treatment AEs are tabulated by SOC and PT for the treated analysis set for the following endpoints:

- AEs by intensity
- AEs associated with study drug by intensity
- AEs by relationship to study drug (related, not related, not reported)
- SAEs
- AEs leading to study drug discontinuation
- Hepatic-related AEs by intensity *
- Cardiovascular AEs *
- Suicidality AEs *.

AEs of special interest are asterisked ("*"). AEs are displayed in descending order of rimegepant frequency within SOC and PT.

6.4.2 Laboratory Tests

Laboratory tests are analyzed using results from a central laboratory and are collected at the following visits: Screening, EOT and Unscheduled. Laboratory tests are slotted into safety analysis periods (pre-treatment and on-treatment) according to the laboratory collection date and time, as available. Some tabulations are provided for the on-treatment period only, as specified below.

Fasting time is not collected; therefore, cholesterol and triglycerides are analyzed as separate laboratory test parameters according to fasting status (last 8 hours): fasting; non-fasting; overall (see Section 6.4.2 of the Core SAP).

Clinically significant laboratory abnormalities are identified as grade 3 to 4 laboratory test results. Refer to Section 6.4.2.1 of the Core SAP for laboratory tests of clinical interest for analyses, including identification of those with toxicity grades. If a toxicity grade depends on age, then age is defined as age recorded on the CRF.

Estimated glomerular filtration rate (eGFR) is derived using the modification of diet in renal disease (MDRD) formula. Notwithstanding Section 2.2 of the Core SAP, eGFR is not separately derived but is provided as reported by the central laboratory.

Laboratory test groups of clinical interest includes hematology, serum chemistry, and urinalysis.

TLFs show data in the Systeme International (SI) unit system, if applicable. Tables present results by treatment group and overall, and laboratory tests alphabetically within laboratory test group, as applicable.

6.4.2.1 Laboratory Test Abnormalities

Laboratory test abnormalities are tabulated as the number and percentage of subjects in the treated analysis set in the frequency tables specified in Section 6.4.2.2 of the Core SAP. This is provided for the on-treatment period only.

6.4.2.2 Liver Function Test Elevations

Liver function test (LFT) elevations are tabulated for laboratory tests as specified in Section 6.4.2.3 of the Core SAP (as applicable to single-dose studies).

LFT Elevations: Cumulative, Mutually Exclusive, and Composite

The number and percentage of subjects with LFT elevations are tabulated separately for each analysis period (pre-treatment, on-treatment) for the treated analysis set. LFT elevations are based on fold changes above ULN.

LFT ULN Shifts from Baseline to Worst Elevation

LFT ULN shifts from baseline to the worst (highest) on-treatment LFT elevation are tabulated as the number and percentage of subjects in the treated analysis set in pre-specified elevation categories.

6.4.2.3 LFT Plots

An evaluation of drug-induced serious hepatotoxicity (eDISH) scatter plot is produced, as specified in Section 6.4.2.4 of the Core SAP, separately for each analysis period (pre-treatment, on-treatment). By-subject longitudinal LFT plots are not produced.

6.4.2.4 Laboratory Test Changes from Baseline Table

Values and changes from baseline in laboratory tests are tabulated descriptively as continuous variables over time at baseline and EOT.

The table displays results by laboratory tests alphabetically within laboratory test group.

Multiple values in analysis visit windows are handled as set forth in Section 7.3.

6.4.2.5 Laboratory Test Listings

By-subject Listings of Laboratory Test Results

All laboratory test listings will be based on the enrolled analysis set.

A by-subject listing of the following select laboratory tests is provided for subjects with at least one laboratory assessment of grade 3 or 4 abnormality or a positive pregnancy test result: hematology results, serum chemistry results, and urinalysis results. 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.

Refer to Section 6.4.2.6 of the Core SAP for listing contents as applicable to this study.

By-subject Listing of LFT Values and Ratios to ULN

Liver function test (LFT) values and ratios to upper limit of normal (ULN) (i.e., alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin [TBL] and alkaline phosphatase [ALP]) are displayed for SI units. The listing displays all LFT results over time for subjects with select LFT elevations (ALT or AST > 3x ULN; ALP or TBL > 2x ULN) at any time point. Refer to Section 6.4.2.6 of the Core SAP for listing contents as applicable to this study.

6.4.3 Vital Signs and Physical Measurements

Vital signs include systolic blood pressure, diastolic blood pressure, heart rate, and temperature. These parameters are measured at Screening, Baseline, and EOT. Vital signs are slotted into safety analysis periods (pre-treatment, on-treatment) according to the measurement date. Vital signs are tabulated for the on-treatment analysis period (see Section 7.2) for the treated analysis set.

Physical measurements include height, weight, and body mass index (where height and weight are measured at Screening only). Physical measurements are slotted into safety analysis periods (pre-treatment, on-treatment) according to the measurement date.

6.4.3.1 Vital Sign Changes from Baseline

Values and changes from baseline in vital signs are tabulated descriptively as continuous variables at baseline and EOT. Physical measurements (i.e. weight, height, and BMI) are not included in this display.

Multiple values in analysis visit windows are handled as set forth in Section 7.3.

6.4.3.2 Vital Signs Abnormalities

Vital sign abnormalities are tabulated as the number and percentage of subjects in the treated analysis set meeting categories specified in Section 6.4.3.2 of the Core SAP during the on-

treatment analysis period, except weight change from baseline is not calculated. Analyses are based on the subset of subjects with non-missing data in the on-treatment analysis period for a given parameter.

6.4.3.3 Vital Signs and Physical Measurements Listing

Refer to Section 6.4.3.3 of the Core SAP for details on the by-subject vital signs and physical measurement listing, as applicable to this study. All vital signs and physical measurements listings will be based on the enrolled analysis set.

6.4.4 Procedures

Procedures are listed for the enrolled analysis set using the Concomitant Procedures CRF. The listing includes the name of the procedure/surgery, SOC and PT, the date of the procedure/surgery, and analysis periods. See Section 6.4.5 of the Core SAP for further details. Procedures are slotted into safety analysis periods according to the procedure date. Note that procedures are slotted like AEs, but without date imputation (see Section 7.2).

6.4.5 Suicidality

The C-SSRS is a clinician administered questionnaire used for suicide assessment. The C-SSRS Screening version is used at the Screening Visit and the Since Last Visit version is used at subsequent visits. C-SSRS is measured at Screening, Baseline and EOT. The C-SSRS Assessment is intended to help establish a person's immediate risk of suicide.

At the Screening Visit, the recall period for completing the C-SSRS is past 12 months for ideation, and 10 years for attempt and behavior; at all other visits, the recall period for completing the C-SSRS is since the last visit.

Refer to the Core SAP for the definitions of C-SSRS parameters and specifications for tabulation. However, notwithstanding Section 6.4.6.2 of the Core SAP, C-SSRS results are not separately tabulated by analysis periods but instead tabulated by visit (Screening, Baseline, and EOT). Unscheduled or early termination visits following treatment are reassigned as specified in Section 7.3; unscheduled or early termination visits prior to treatment are not reassigned or tabulated.

6.4.6 Safety Narrative Subject Identifiers Listing

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

- All deaths on-treatment or during follow-up, regardless of treatment
- SAEs on-treatment or during follow-up for rimegepant-treated subjects, regardless of relationship to study drug

- Any AE leading to discontinuation of study drug for rimegepant-treated subjects, regardless of relationship to study drug

- On-treatment events of special interest for rimegepant-treated subjects:

    - ALT or AST > 3x ULN

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

    - TBL or ALP > 2x ULN

    - Select hepatic-related AE, i.e., PT containing cirrhosis, hepatic failure, hepatitis, jaundice, or liver failure

    - Cardiovascular AE

    - Suicidality AE

Refer to the Core SAP for additional details. The listing flags subjects with select events.

Should the criteria stated in the Biohaven Rimegepant Safety Narrative Scope conflict with the criteria above, the Biohaven Rimegepant Safety Narrative Scope will take precedence.

7 CONVENTIONS

7.1 Derived Dates

Refer to Section 7.1 of the Core SAP for the definition of complete dates, partially complete dates, and the term “date/time.”

7.1.1 Analysis Period Reference Dates

Analyses periods are determined by analysis period reference date/times. The analysis period reference date/time for the pre-treatment and on-treatment analysis periods are the date of informed consent and the study drug date/time (see Section 7.2).

Derived dates (or date/time values) are defined as follows.

7.1.1.1 Study Drug Dates

- Study drug date/time:

    - For subjects who indicated that they took study medication (not mistakenly) on the “Initial Pain Diary,” the date/time that the “Initial Pain Diary” is saved.

    - For subjects who indicated that they mistakenly took study medication on the “Initial Pain Diary,” the date/time that the subject entered on the “Initial Pain Diary” in

response to the question "When did you take the Study Medication?" (Note that if the subject indicated that they dosed on the same day, only time is manually entered.)

- For subjects who reported to the site that they took study medication without interacting with eDiary, the date/time recorded by the site and transmitted to the electronic patient-reported outcome vendor.

7.1.2 Imputed Dates

Refer to Section 7.1.2 of the Core SAP for the imputation of non-study medication start dates (except rescue medications), non-study medication end dates, AE start dates, and AE end dates, with the following adjustment: with respect to the use of birth date in the imputation logic, the complete birth date is assumed to be January 1st of the birth year if the birth year is non-missing.

7.1.3 Last Contact Date

The last contact date is used to determine select parameters (i.e., time on study, imputed non-study medication end dates, and death date), and is typically defined using non-imputed dates as follows:

1. Earliest complete death date from all sources that collect death dates (e.g., AE CRF), if it exists.
2. Otherwise, the maximum complete date of the following CRF or external data sources, as applicable: AE start or end; COVID-19 visit where the COVID-19 visit impact type is not a missed visit; ECG; efficacy assessment; informed consent; IWRS randomization; laboratory test collection; non-study medication start or end; physical exam; physical measurement; protocol deviation; questionnaire; study drug start; subject disposition completion/discontinuation; visit; vital sign.
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.

7.1.4 COVID-19 Visit Date

COVID-19 visit dates are not derived and are not displayed on listings.

7.1.5 Other Derived/Imputed Dates

Additional derived dates include.

- Date/time of eDiary assessments: The date/time of a given assessment collected in the eDiary is the datetime the diary for that time point is saved (e.g., the date/time of all assessments collected on the 15 minute diary is the datetime the 15 minute diary is saved).

- Rescue medication start date/time: Earliest rescue medication date/time. Missing time is considered to be earlier than non-missing time on the same date. Refer to Section 6.2.6.3.

- Imputed rescue medication start date/time: This is used **only** for time-to-event efficacy analyses in Section 6.3.3.5.
    - If the rescue medication start date and time are both not missing, then the imputed rescue medication start date/time is set to the rescue medication start date/time.
    - If the rescue medication start time is missing and the rescue medication start date is equal to the study drug dose date, then the imputed rescue medication start date/time is set to the study drug dose date/time.
    - Otherwise, if the rescue medication start time is missing and the rescue medication start date is equal to a post-dose eDiary finding date with non-missing efficacy data on that date (i.e., the day after dosing), then the imputed rescue medication start date/time is set to the first eDiary finding date/time on that date corresponding to non-missing efficacy data.
    - Otherwise, if the rescue medication start time is missing and rescue medication start date is equal to the study drug dose date + 1 day, with no eDiary efficacy data recorded the day after dosing, then the imputed rescue medication start date/time is set to the study drug start date/time + upper bound of the *2*4-hour analysis window (see Table 6).

- Death date: Last contact date (see Section 7.1.3), derived only for subjects who died (see Section 6.4.1.1).

No imputations are performed on these derived dates, except as specifically mentioned in this Section 7.1.5. Complete dates are those with valid, non-missing day, month, and year.

7.2 Analysis Periods

Measurements are slotted into analysis periods by comparing both measurement date and time to analysis period reference date and time (i.e., study drug start date and time; see Section 7.1.1). Otherwise, if (1) time is missing or not available for either the measurement or the analysis period reference, or (2) time is not required for slotting, then only the measurement date is compared to the analysis period reference date.

Note that the measurement date must be complete for the measurement to be slotted into an analysis period (see Section 7.1). Exceptions are noted for the pre-treatment analysis period for subjects in the enrolled analysis set who are not in the safety analysis set and for AEs, where imputed start dates are used if start date is incomplete.

Analysis periods are defined as follows.

- Pre-treatment: measurement date/time at or before the study drug dose date/time. This period is used to derive baseline values and to assess pre-treatment endpoints. Note that all measurements are pre-treatment for subjects in the enrolled analysis set with missing study drug dose date and that AEs with imputed start date prior to study drug dose date are included in this analysis period (or start date/time < study drug dose date/time if AE start time is non-missing).

- On-treatment: measurement date/time after the study drug dose date/time. This period is used to assess safety endpoints on treatment. Note that AEs with imputed start date equal to study drug dose date are included in this analysis period, unless start time is non-missing and start date/time is < study drug dose date/time. Baseline assessments are not count as "on treatment" but are included in "on treatment" tables that report change from baseline.

See Section 7.1 for derived dates for determining analysis periods.

7.3 Analysis Visit Windows

Refer to Protocol Section 4.2 for the schedule of assessments.

Study days are calculated from the randomization date as follows:

- Measurement date – randomization date + 1, if measurement date ;: randomization date
- Measurement date – randomization date, if measurement date < randomization date.

Treatment days are calculated from the study drug dose date as follows:

- Measurement date – study drug dose date + 1, if measurement date ;: study drug dose date
- Measurement date – study drug dose date, if measurement date < study drug dose date.

Analysis visit windows for safety parameters are presented in Table 4.

Table 4: Analysis Visit Windows for Safety Parameters

Analysis Visit	Analysis-Specified Interval
Screening	• ⟩ Study day – 1 or both study day and treatment day missing • ⟩ Treatment day – 1 *
Baseline	Study day 1
End of treatment	• ;: Study day 2 • ;: Treatment day *

*Applies only to subjects who took study drug but were not randomized

Notwithstanding Sections 6.4.3.1 of the Core SAP, multiple values in analysis visit windows are handled as follows:

- The scheduled visit takes priority over unscheduled or early termination visits.
- If a subject does not have a scheduled visit, the unscheduled or early termination visit closest to the target date takes priority.

- If there are still multiple values on the same measurement date, then the last value collected timewise takes priority (if time is collected); if ties remain, the value with the highest ECG reference identifier, vital signs identifier, or laboratory barcode is used, as applicable.

For clarity, displays that tabulate baseline values tabulate the baseline value as defined in Section 7.5, rather than the value that maps to the Baseline Visit, unless otherwise explicitly noted (see Section 6.4.6).

For efficacy assessments collected on the eDiary, windows are imposed by the eDiary, as shown in Table 5. No additional analysis windows are imposed. The anchor point for the windows is the date/time of exposure, as defined in Section 7.1.

Table 5: Evaluation Intervals for Efficacy Analyses

Post-dose Evaluation	Analysis-Specified Interval	Target Time
15 min diary	10-20 min	Study medication start time + 15 min
30 min diary	25-35 min	Study medication start time + 30 min
45 min diary	40-50 min	Study medication start time + 45 min
60 min diary	55-65 min	Study medication start time + 60 min
90 min diary	85-95 min (1hr 25 min – 1 hr 35 min)	Study medication start time + 90 min
2 hr diary	115-135 min (1hr 55 min – 2 hr 15 min)	Study medication start time + 2 hr
4 hr diary	225-255 min (3hr 45 min – 4 hr 15 min)	Study medication start time + 4 hr
8 hr diary	465-495 min (7 hr 45 min – 8 hr 15 min)	Study medication start time + 8 hr
24 hr diary	1380-1500 min (23 hr – 25 hr)	Study medication start time + 24 hr

7.4 Subgroups

Section 7.4 of the Core SAP does not apply in its entirety.

7.5 Baseline Value

The baseline value for a safety parameter collected with a measurement date/time (e.g., weight) is defined according to analysis set as follows:

- Enrolled analysis set but not in the randomized analysis set: Last non-missing value

- Full analysis set but not in the treated analysis set: Last non-missing value at or before the IWRS randomization date
- Treated analysis set: Last non-missing value in the pre-treatment analysis period

"Last" is determined by the last complete measurement date/time. See Section 7.1 for complete dates, Section 7.2 for analysis periods, and Sections 6.4.2.4 and 6.4.3.1 for handling multiple values on the same measurement date.

The baseline NRS pain score is the value collected on the "Initial pain" eDiary where the subject confirmed having dosed (not mistakenly). The date/time of the associated baseline value is the date and time that the "Initial pain" eDiary is saved. For subjects who mistakenly took drug and thus are missing baseline NRS pain scores (see Section 6.2.6), baseline NRS pain scores are imputed as the mean of the non-missing baseline NRS pain scores across subjects.

8 CONTENT OF REPORTS

The final CSR is produced after the final database lock, which occurs after last subject last visit. All TLFs described in this SAP are produced for the final CSR. No interim analyses are planned.

9 APPENDICES

9.1 Relevant Protocol Deviations

Relevant eligibility protocol deviations include the following categories:

- TMD history not aligned with eligibility requirements as any of the following:
    - TMD onset less than 3 months prior to Screening OR longer than 5 years
    - Qualifying TMD Pain Disorder not selected (myalgia AND Right arthralgia AND Left arthralgia not selected)
- Finding out of range at Screening (or at Baseline, as applicable), defined as any of the following:
    - ALT/AST/Direct Bilirubin/Indirect Bilirubin/Total Bilirubin > ULN
    - 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 2: 150 msec
        - Intraventricular Conduction Defect with a QRS duration 2: 150 msec
    - Neutrophil count :S 1000/μL (or equivalent)
    - HbA1c 2: 6.5%
    - Diastolic blood pressure > 100 mmHg after 10 mins of rest
    - 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, cannabinoids, or PCPs at any visit
    - Females with a positive pregnancy test at Screening or Baseline
    - C-SSRS suicidal ideation with active intent or plan to act, or suicidal behavior present during screening. Defined as having a “yes” response to any of the following C-SSRS questions at Screening Visit or Baseline Visit:
        - 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).

Relevant subject management protocol deviations include the following:

- Prohibited non-study medications, procedures, or therapies defined as any of the following:
    - Daily medications with dose change or with start date < 3 months
    - Daily oral devices without consistent use or with start date < 3 months
    - Excluded current or recent treatments (Section 5.3.6 of the protocol) prior to the Screening Visit or throughout the study as follows:
        - history of active dental orthodontic use within the 3 months prior to the Screening Visit, or new or recently modified use of non-active dental orthodontics.
        - history of dental restorative care (e.g., crowns, bridges) within the 3 months prior to the Screening Visit.
        - new or recently modified physical therapy treatment in the head and/or neck area within the 3 months prior to the Screening Visit.
        - has a history of Transcutaneous Electrical Nerve Stimulation (TENS) within the 3 months prior to the Screening Visit.
        - history of injection therapy other than botulinum therapy (e.g., lidocaine, corticosteroids, hyaluronic acid) within the 30 days prior to the Screening Visit.
    - Non-narcotic analgesic taken on 2: 15 days per month for greater 2: 3 month prior to the Screening Visit
    - Acetaminophen or acetaminophen containing products taken within 2 days before randomization.
    - Use of acetaminophen during the screening phase (3 to 14 days) or throughout the study at daily dosing levels of greater than 1000 mg/day
    - Muscle relaxants taken up to 14 days prior to randomization or afterward (except cyclobenzaprine)
    - Systemic corticosteroids taken up to 30 days prior to the Screening Visit or afterward
    - Narcotic medication, such as opioids, taken up to 30 days prior to the Screening Visit or afterward
    - Strong CYP3A4 inhibitors taken up to 14 days prior to the Baseline Visit or afterward
    - Moderate or strong CYP3A4 inducers taken up to 14 days prior to the Screening Visit or afterward
    - Atypical antipsychotics such as Abilify (aripiprazole), Zyprexa (olanzapine), Seroquel (quetiapine), Geodon (ziprasidone), or Risperdal (risperidone) or Depakote/Depakene (valproic acid/valproate) taken up to 90 days prior to the Baseline Visit or afterward

      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.
- Finding out of range during the study, defined as any of the following:

  - C-SSRS suicidal ideation with active intent or plan to act, or suicidal behavior present during screening. Defined as having a "yes" response to any of the following C-SSRS questions at the Baseline Visit and the subject is randomized:
    - 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).
  - Females with a positive pregnancy test at Baseline Visit and the subject is randomized
  - Positive for cocaine, cannabinoids or PCPs at any post-baseline visit, including End of Treatment visit

- Medical history, defined as any of the following subcategories:
  - History of trigeminal neuralgia or postherpetic neuralgia
  - Trauma in the craniocervical area, including joint sprain/strain, within the 3 months prior to the Screening Visit
  - History of TMJ surgery (e.g., arthrocentesis, arthroscopy, TMJ implants) or ear surgery

- Prescence of concomitant medications/devices discrepant between IWRS and CRF data, defined as any of the following subcategories:
  - IWRS randomization stratum of yes, but no concomitant oral medications reported AND no concomitant devices reported
  - IWRS randomization stratum of no, but concomitant oral medications reported OR concomitant devices reported
- End of treatment visit outside of 9 days after treatment administered

10 REFERENCES

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