Pfizer Inc.

Protocol BHV3000-316 (C4951015)

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 Chronic Rhinosinusitis (CRS) With or Without Nasal Polyps

Statistical Analysis Plan

Version 3.0

Date: 29-Feb-2024

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 Chronic Rhinosinusitis (CRS) With or Without Nasal Polyps

Sponsor: Pfizer Inc.

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Date: 29 February 2024

Author: PPD

Rho, Inc.

PPD

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:

Edward P Whalen
Sr. Director Statistics (Group Lead),
Pfizer Inc.

PPD

Signature:_____

Date:_____

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REVISION HISTORY

Version	Description of Change
1.0	Original version based on Protocol Version 3.0 and BHV3000-3500 Core SAP v 1.0
2.0	Updated version based on BHV3000-3500 Core SAP v 2.0 and CSR TLF guidance for 3000/3500 studies
3.0	Updated version based on Protocol Version 4.0, BHV3000-3500 Core SAP v 3.0, and BHV3000-3500 Core SAP v 4.0 Updated version based on sponsor feedback. Clarified Section 2.3 regarding ineligible subjects. Clarified secondary and exploratory objectives regarding the type of objective (safety or efficacy). Updated section numbering. Clarified Section 6.2.6.2 regarding cross-tabulation. Added overall efficacy summary section and table. Updated Jump to Reference sensitivity analysis. Proposed update to definition of rescue medication in Section 6.3.4.5. Updated PGI-C analysis in Section 6.3.5.7. Added PGI-C, SNOT-22, vital signs, and ECG listing. Updated relevant protocol deviations in Section 9.1. Updated sponsor signatory to Edward P Whalen. Updated Section 4.3 for subgroup analysis by stratification factor. Updated Section 6.2.3.1 randomization to treatment disposition table to include the number and percentage of subjects who completed the study without being treated and the reason. Added treatment to completion/discontinuation table for mITT analysis set to align with mocks. Updated Section 6.2.4.1 to present relevant protocol deviation tables for full, mITT, and safety analysis sets. Updated Section 6.2.5.1 to add exception to core SAP. Also added randomization stratum frequency table for mITT analysis set, and noted a deviation from the core SAP that “COVID-19 Impacted” is not included in the demographics listing. Updated Section 6.2.6.1 to align with mock, removing rows for n(%) subjects who reported or never reported a qualifying facial pain/pressure/fullness NRS score >=6. Updated Section 6.2.6.2 to include “unknown” category for cross-tabulation if it is applicable. Added details for by-subject listing. Updated Section 6.3.3.1 to include repeating the primary analysis for the subgroup of the stratification factor. Updated Sections 6.3.4.1-6.3.4.3 to clarify that the subgroup analysis is included in the repeat analysis. Updated Section 6.3.4.4 to include headache pain listing. Updated Section 6.3.4.5 to reference the Core SAP. Updated Section 6.4.1.2 to report AE leading to study discontinuation instead of AE leading to study drug discontinuation. Updated Section 6.4.1.3 to remove local irritation AEs by intensity, add AEs leading to study discontinuation, and clarify AEs by maximum relationship. Updated Section 6.4.2.2 to note the addition of elevations of >2xULN in tabulations for ALT and AST. Also clarified how to determine evidence of hemolysis.

	Updated Section 6.4.7 to change from AE leading to discontinuation of study drug to AE leading to discontinuation of study. Added AESI column. Updated "special interest" to "significant interest". Updated Section 7.4 to add details regarding stratification factor subgroup. Updated Appendix 9.1 to remove post-baseline C-SSRS criteria and surgical history of polyps to presence of polyps in looking for discrepancies between IWRS and CRF data. Updated Section 5 for new sample size and hierarchical testing strategy. Updated Population for all estimands in Section 3. Removed baseline SNOT-22 reference from Table 5 as well as from estimand section in Table 3. Removed outdated text from Section 5. Removed stray links from Sections 6.3.4.5 and 6.3.5. Updated Section 9.1 for formatting issue, updated baseline/screening out of range criteria to remove cannabinoids, removed "9 day" criteria from systemic corticosteroid and antibiotic PDs. Updated Section 9.2 for protocol v4 and removed text regarding change from Section 9.3 of the protocol, as it no longer applies.

ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ASE	asymptotic standard error
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
CI	Confidence interval
CK	Creatine kinase
COPD	Chronic obstructive pulmonary disease
CRF	Case report form
CRS	Chronic Rhinosinusitis
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
DILI	Drug-induced liver injury
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
PGI-C	Patient Global Impression of Change
PT	Preferred term
REML	Restricted maximum likelihood

SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SI	Systeme Internationale
SNOT-22	Sino-Nasal Outcome Test – 22
SOC	System organ class
TEAE	Treatment-emergent adverse event
TBL	Total bilirubin
TLF	Table listing figure
TNSS	Total Nasal Symptom Score
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 Pfizer Inc., Protocol BHV3000-316 (C4951015): 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 chronic rhinosinusitis (CRS) with or without nasal polyps.

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/C495)/Zavegepant (BHV3500/C530) Core Statistical Analysis Plan, v4.0 (the "Core SAP") describes analysis details and methodologies common to the BHV3000 (PF-07899801) 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:

- BHV3000-316 (C4951015) is a single-dose study
- BHV3000-316 (C4951015) 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 BHV3000-316 (C4951015). COVID-19 impact will be addressed as specified in this SAP.

1.1 Research Hypothesis

Rimegepant will have efficacy superior to placebo in the acute treatment of CRS with or without polyps with a favorable safety profile.

1.2 Schedule of Analyses

During the course of 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 CRS with or without nasal polyps. The study drug will be rimegepant presented in a 75 mg ODT (placed on or under the tongue) or matching placebo.

Subjects who have consented to study participation will first participate in the screening phase (3 to 14 day period). Subjects must remain on the same dose of daily use of medications to treat CRS symptoms from screening through the duration of the study and may not start any new daily medication. Subjects meeting initial eligibility criteria will be asked to continue to a Baseline Visit. Subjects who were considered screen failures may be considered for re-screening provided the ineligibility was due to one of the eligibility criteria that may have changed due to medical intervention or one of the eligibility criteria modified in a protocol amendment. In all possible re-screening circumstances, the situation must be discussed with the sponsor prior to re-screening, with approval in writing from the sponsor prior to re-screening. If a subject is approved for re-screening, a new subject number must be obtained from the appropriate study-related system. Re-screening will only be permitted one time.

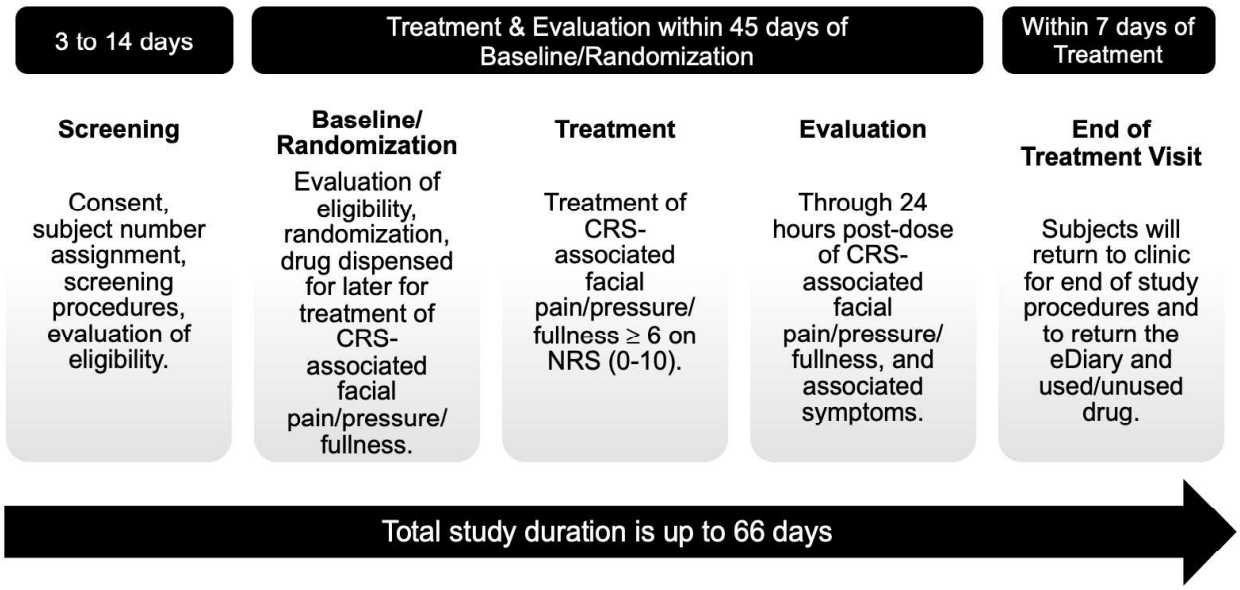
At the Baseline Visit, eligibility for continued participation in the study will be assessed before randomization occurs and before study medication is dispensed. After randomization, the subject will be dispensed a single dose of the double-blind study medication to take home for up to 45 days. The subject will be instructed to take their study medication, as an outpatient, when (if) they have a facial pain/pressure/fullness which reaches a current intensity of ≥ 6 on the Numerical Rating Scale (NRS) (0-10); they should not dose until facial pain/pressure/fullness reaches a current intensity of ≥ 6. The subject will complete questionnaires on 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. Subjects will complete Sino-Nasal Outcome Test (SNOT-22) questionnaire at the Baseline Visit (on a paper scale), and at 24 hours post-dose, subjects will complete SNOT-22 (on the eDiary). Facial pain/pressure/fullness severity, nasal congestion (obstruction) severity, and nasal discharge severity will be recorded using an NRS (0-10) just prior to taking study medication and at 15, 30, 45, 60, and 90 minutes and 2, 4, 8 and 24 hours after dosing. Total Nasal Symptom Score (TNSS) will be calculated as the sum of 3 symptom scores: (1) facial pain/pressure/fullness; (2) nasal obstruction (congestion); and (3) nasal discharge; recorded just prior to taking study medication and after dosing at time points of 15, 30, 45, 60, and 90 minutes and 2, 4, 8 and 24 hours. Subjects who experience current headache pain of moderate or severe pain intensity at the time of qualifying facial pain/pressure/fullness will record their headache pain severity using a 4-point Likert scale (0 = None; 1 = Mild; 2 = Moderate; 3 = Severe) at time of taking study medication and after dosing at time points of 15, 30, 45, 60, and 90 minutes and 2, 4, 8 and 24 hours. Subjects will complete the Patient Global Impression of Change (PGI-C) questionnaire 24 hours after dosing.

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 facial pain/pressure/fullness 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.

The end of the study will be defined as the date of the last visit of the last subject.

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. The randomization will be stratified by the presence of nasal polyps (yes or no) Further detail is provided in the Randomization Plan v1.0, dated 01 December 2021. Subjects will be randomized via the Interactive Web Response System (IWRS).

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 eligible subject (as per inclusion/exclusion criteria) is randomized via the IWRS randomization option. Randomization of any ineligible subjects will be a protocol deviation. Subjects maintain their subject number assigned at screening throughout the trial. The IWRS provides the double-blind treatment assignments. Further detail is provided in the BHV3000-316 (C4951015) Unblinding Plan v1.0 (as amended).

Dummy coding of treatment groups are 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 current version of the SAP is based on Version 4.0 of the protocol (14 July 2023).

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 chronic rhinosinusitis with or without polyps on mean change from baseline of facial pain/pressure/fullness on NRS (0-10) score at 2 hours post-dose.

3.1.2 Secondary Objectives

1. To evaluate rimegepant compared to placebo on change from baseline in Total Nasal Symptom Score (TNSS) at 2 hours post-dose. (Efficacy)

2. To evaluate rimegepant compared to placebo on change from baseline in nasal obstruction (congestion) score on NRS (0-10) score at 2 hours post-dose. (Efficacy)

3. To evaluate rimegepant compared to placebo on change from baseline in nasal discharge score on NRS (0-10) score at 2 hours post-dose. (Efficacy)

4. To evaluate rimegepant compared to placebo on headache pain relief on a 4-point Likert scale at 2 hours post-dose compared to baseline. (Efficacy)

5. To evaluate rimegepant compared to placebo on the probability of requiring rescue medication within 24 hours of initial treatment. (Efficacy)

3.1.3 Exploratory Objectives

1. To evaluate rimegepant compared to placebo on ≥ 30% reduction from baseline of facial pain/pressure/fullness NRS (0-10) score at 2 hours post-dose. (Efficacy)

2. To evaluate rimegepant compared to placebo on ≥ 50% reduction from baseline of facial pain/pressure/fullness NRS (0-10) score at 2 hours post-dose. (Efficacy)

3. To evaluate the effect of rimegepant compared to placebo on change from baseline of facial pain/pressure/fullness NRS (0-10) score at 15, 30, 45, 60, 90 minutes and 2, 4, 8 and 24 hours post-dose. (Efficacy)

4. To evaluate the effect of rimegepant compared to placebo on change from baseline of nasal obstruction (congestion) NRS (0-10) score at 15, 30, 45, 60, 90 minutes and 2, 4, 8 and 24 hours post-dose. (Efficacy)

5. To evaluate the effect of rimegepant compared to placebo on change from baseline of nasal discharge NRS (0-10) score at 15, 30, 45, 60, 90 minutes and 2, 4, 8 and 24 hours post-dose. (Efficacy)

6. To evaluate the effect of rimegepant compared to placebo on headache pain relief using a 4-point Likert scale at 15, 30, 45, 60, 90 minutes and 2, 4, 8 and 24 hours post-dose compared to baseline. (Efficacy)

7. To evaluate rimegepant compared to placebo on the PGI-C questionnaire at 24 hours post-dose. (Efficacy)

8. To evaluate rimegepant compared to placebo on ≥ 30% reduction from baseline of facial pain/pressure/fullness NRS (0-10) score at 24 hours post-dose. (Efficacy)

9. To evaluate rimegepant compared to placebo on ≥ 50% reduction from baseline of facial pain/pressure/fullness NRS (0-10) score at 24 hours post-dose. (Efficacy)

10. To evaluate rimegepant compared to placebo on sustained relief of facial pain/pressure/fullness, as defined by each of the following: 30% reduction from baseline on NRS (0-10), 1.5-point reduction on NRS (0-10), and a 2-point reduction on NRS (0-10) through 24 hours post-dose. (Efficacy)

11. To explore the distribution of baseline disease severity using the Sino-Nasal Outcome Test (SNOT-22). (Efficacy)

12. To evaluate rimegepant compared to placebo on the Sino-Nasal Outcome Test (SNOT-22) score at 24 hours post-dose. (Efficacy)

13. To evaluate the safety and tolerability of rimegepant in the acute treatment of chronic rhinosinusitis as measured by the frequency of adverse events of moderate or severe intensity, serious adverse events (SAEs), clinically relevant laboratory abnormalities, and nasal inspection abnormalities. (Safety)

14. To evaluate rimegepant compared to placebo for the Columbia Suicide Severity Rating Scale (C-SSRS). (Safety)

3.2 Estimands

An estimand is the target of estimation to address the scientific question of interest posed by a study objective. The five attributes of an estimand include the treatment, population of interest, variable of interest, population-level summary of the variable, 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 Table 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. The treatment for all estimands is Rimegepant formulated in a 75 mg ODT (placed on or under the tongue) or a matching placebo.

3.2.1 Primary Objective Estimand

Table 1: Primary Objective Estimand

Population	CRS with and without nasal polyps.
Variable	Change from baseline in facial pain/pressure/fullness NRS score to 2 hours post-dose.
Population-Level Summary	Difference in mean change from baseline and 95% CI in the pain/pressure/fullness NRS score between the rimegepant and placebo groups at 2 hours post-dose.
Intercurrent Events	1) Use of non-study rescue medications on or before 2 hours post-dose Hypothetical strategy: In the event a subject uses a non-study rescue medication on or before 2 hours post-dose, all data points after rescue medication was administered are set to missing. It is assumed that, had the subject not used a non-study rescue medication, their efficacy would have been similar to the efficacy of subjects from the same treatment group who did not use rescue medication. 2) 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	**Population**	CRS with and without nasal polyps.
	Variable	Change from baseline in TNSS to 2 hours post-dose.

	Population-Level Summary	Same as that of primary estimand, with respect to TNSS.
	Intercurrent Events	Same as that of primary estimand.
2	Population	CRS with and without nasal polyps.
	Variable	Change from baseline of nasal obstruction (congestion) NRS score to 2 hours post-dose.
	Population-Level Summary	Same as that of primary estimand, with respect to nasal obstruction (congestion) NRS score.
	Intercurrent Events	Same as that of primary estimand.
3	Population	CRS with and without nasal polyps.
	Variable	Change from baseline of nasal discharge NRS score to 2 hours post-dose.
	Population-Level Summary	Same as that of primary estimand, with respect to nasal discharge NRS score.
	Intercurrent Events	Same as that of primary estimand.
4	Population	CRS with and without nasal polyps.
	Variable	Percentage of subjects reporting a pain level of moderate or severe at baseline in the eDiary that experience headache pain relief at 2 hours post-dose. Headache pain relief is defined as a headache pain level of none or mild at 2 hours post-dose for subjects who reported a baseline pain level of moderate or severe at baseline.
	Population-Level Summary	The difference and 95% CI in the percentage of subjects that experience headache pain relief at 2 hours post-dose between the rimegepant and placebo groups.
	Intercurrent Events	1) Use of non-study rescue medications on or before 2 hours post-dose Composite strategy: Subjects who use rescue medication on or before assessment of pain at 2 hours are imputed as a failure. 2) Failure to report eDiary assessments at 2-hours post-dose Composite strategy: Subjects with missing data at 2 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.
5	Population	CRS with and without nasal polyps.
	Variable	Percentage of subjects that use rescue medication within 24 hours after administration of study drug. Subjects who do not report rescue medication use between 0 and 24 hours post-dose are deemed successes; subjects who report rescue medication use between 0 and 24 hours post-dose are deemed failures.
	Population-Level Summary	Same as that of secondary endpoint #4 (headache pain relief), except analysis is not limited to subjects who reported a baseline pain level of moderate or severe at baseline. Subjects who fail to include rescue medication time on all reported rescue medications are excluded from the analysis.

	Intercurrent Events	Treatment policy strategy: All available assessments on the subject are used regardless of intercurrent events.

3.2.3 Exploratory Objective Estimands

Table 3: Exploratory Objective Estimands

1	Population	CRS with and without nasal polyps.
	Variable	The percentage of subjects with ≥ 30% reduction from baseline of facial pain/pressure/fullness NRS (0-10) score at 2 hours post-dose. Success is a ≥ 30% reduction from baseline in facial pain/pressure/fullness NRS (0-10) score at 2 hours post-dose.
	Population-Level Summary	Same methodology as secondary endpoint #4 (headache pain relief), and analysis is not limited to subjects who reported a baseline pain level of moderate or severe at baseline.
	Intercurrent Events	Same as that of secondary endpoint #4 (headache pain relief).
2	Population	CRS with and without nasal polyps.
	Variable	The percentage of subjects with ≥ 50% reduction from baseline of facial pain/pressure/fullness NRS (0-10) score at 2 hours post-dose. Success is ≥ 50% reduction from baseline in facial pain/pressure/fullness NRS (0-10) score at 2 hours post-dose
	Population-Level Summary	Same as that of secondary endpoint #4 (headache pain relief), and analysis is not limited to subjects who reported a baseline pain level of moderate or severe at baseline.
	Intercurrent Events	Same as that of secondary endpoint #4 (headache pain relief).
3	Population	CRS with and without nasal polyps.
	Variable	Change from baseline in facial pain/pressure/fullness NRS score to 15, 30, 45, 60, 90 minutes and 2, 4, 8 and 24 hours post-dose in evaluable subjects.
	Population-Level Summary	Same as that of the primary endpoint, except all scheduled time points are included in the model and reported.
	Intercurrent Events	1) Use of non-study rescue medications on or before 24 hours post-dose Hypothetical strategy: In the event a subject uses a non-study rescue medication on or before 24 hours post-dose, all data points after rescue medication was administered are set to missing. It is assumed that, had the subject not used a non-study rescue medication, their efficacy would have been similar to the efficacy of subjects from the same treatment group who did not use rescue medication. 2) All other intercurrent events: Treatment policy strategy: All available assessments on the subject are used regardless of other intercurrent events.
4	Population	CRS with and without nasal polyps.
	Variable	Change from baseline in nasal obstruction (congestion) NRS (0-10) score to 15, 30, 45, 60, 90 minutes and 2, 4, 8 and 24 hours post-dose in evaluable subjects.
	Population-Level Summary	Same as that of exploratory endpoint #3, with respect to nasal obstruction (congestion) NRS score.

	Intercurrent Events	Same as that of exploratory endpoint #3.
5	Population	CRS with and without nasal polyps.
	Variable	Change from baseline in nasal discharge NRS score to 15, 30, 45, 60, 90 minutes and 2, 4, 8 and 24 hours post-dose in evaluable subjects.
	Population-Level Summary	Same as that of exploratory endpoint #3, with respect to nasal discharge NRS score.
	Intercurrent Events	Same as that of exploratory endpoint #3.
6	Population	CRS with and without nasal polyps.
	Variable	Percentage of subjects reporting a pain level of moderate or severe at baseline in the eDiary that experience headache pain relief, at each post-dose time point.
	Population-Level Summary	The difference in the percentage of subjects that experience headache pain relief at each post-dose time point between the rimegepant and placebo groups, using Mantel-Haenszel risk estimation, for subjects with a headache pain level of moderate or severe at baseline. Headache pain relief is defined as a headache pain level of none or mild at the time point in question for evaluable subjects.
	Intercurrent Events	1) Use of non-study rescue medications on or before the time point in question: Composite strategy: Subjects who use rescue medication on or before assessment of pain at the time point in question are imputed as a failure. 2) Failure to report eDiary assessments at the time point in question: Composite strategy: Subjects with missing data at the time point in question 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.
7	Population	CRS with and without nasal polyps.
	Variable	Number and percentage of subjects in each of the 7 PGI-C improvement categories (very much improved to very much worse) relative to the baseline visit at 24 hours post-dose.
	Population-Level Summary	Frequency at 24 hours post-dose in PGI-C score by treatment group with PGI-C data, along with 2-sided exact Clopper-Pearson 95% CIs for each percentage.
	Intercurrent Events	Treatment policy strategy: All available assessments on the subject are used regardless of intercurrent events.
8	Population	CRS with and without nasal polyps.
	Variable	Same as that of exploratory endpoint #1, with respect to 24 hours post-dose.
	Population-Level Summary	Same as that of exploratory endpoint #1, with respect to 24 hours post-dose.
	Intercurrent Events	Same as exploratory endpoint #1, except subjects with missing data at 24 hours post-dose and subjects who used rescue medication prior to the assessment at 24 hours post-dose are deemed failures.
9	Population	CRS with and without nasal polyps.

	Variable	Same as that of exploratory endpoint #1, with respect to ≥ 50% reduction of facial pain/pressure/fullness on NRS (0-10) score at 24 hours post-dose.
	Population-Level Summary	Same as that of exploratory endpoint #1, with respect to ≥ 50% reduction of facial pain/pressure/fullness on NRS (0-10) score at 24 hours post-dose.
	Intercurrent Events	Same as that of exploratory endpoint #1, except subjects with missing data at 24 hours post-dose and subjects who used rescue medication prior to the assessment at 24 hours post-dose are deemed failures.
10	Population	CRS with and without nasal polyps.
	Variable	The percentage of subjects that achieve sustained relief of facial pain/pressure/fullness.
	Population-Level Summary	Same as that of exploratory endpoint #1, separately with respect to each component of sustained relief of facial pain/pressure/fullness.
	Intercurrent Events	Same as that of exploratory endpoint #1, separately with respect to each component of sustained relief of facial pain/pressure/fullness.
11	Population	CRS with and without nasal polyps.
	Variable	Change from baseline in the SNOT-22 total score and domain scores.
	Population-Level Summary	Difference in change from baseline in the SNOT-22 total score between the rimegepant and placebo treatment groups, and separately for each domain score, using an analysis of covariance (ANCOVA) model.
	Intercurrent Events	Treatment policy strategy: All available assessments on the subject are used regardless of intercurrent events.
12	Population	CRS with and without nasal polyps.
	Variable	Number and percentage of subjects with C-SSRS responses in the C-SSRS categories and sub-categories.
	Population-Level Summary	Frequency by treatment group as outlined in the Core SAP.
	Intercurrent Events	Treatment policy strategy: All available assessments on the subject are used regardless of intercurrent events.

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 and estimands:

Enrolled: Subjects who signed the informed consent form and were assigned a subject identification number by the IWRS; i.e., nonmissing 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., nonmissing IWRS randomization date. This analysis set is used mainly to assess study population.

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

Modified Intent to Treat (mITT): Randomized subjects that take study therapy, have a facial pain/pressure/fullness which reaches pain intensity of ≥ 6 on the NRS (0-10) prior to administration of treatment, and provide at least one post-baseline efficacy data point in the eDiary.

For clarity, subjects who mistakenly dose (see Section 6.2.6.1) are not included in the mITT analysis set but are included in the safety analysis set.

4.2 Treatment Groups

The two treatment groups are rimegepant 75 mg and placebo. The safety analysis set is assessed by the as-treated treatment group (i.e., actual treatment received); the full and mITT analysis sets are assessed by as-randomized treatment group; and 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 (presence of nasal polyps; yes or no), as randomized, is a subgroup of interest for the mITT analysis set. Refer to Sections 6.3.3.1 for more detail. All p-values from the subgroup analyses will be considered nominal. For the subgroup analysis by stratification factor, stratification factor will be removed as a covariate from the model as appropriate.

5 SAMPLE SIZE, POWER, AND TYPE I ERROR

If 72% of the 250 randomized (125 per treatment arm) have a facial pain/pressure/fullness which reaches pain intensity of ≥ 6 on the NRS (0-10) in the allotted time period, and complete their eDiary in the 24 hours following, we expect roughly 180 total or 90 per treatment group in the modified intent to treat (mITT) population for analysis.

Assuming rimegepant provides a 2-point reduction in NRS pain, and a 1.35-point advantage over placebo on the primary endpoint, and a common standard deviation of 3.0, then the study will have roughly 85% power on the primary endpoint. The estimates for change from baseline in NRS and common standard deviation are consistent with a modest reduction in pain over placebo and a conservative standard deviation estimate, as these varied widely in previous studies examining CRS.

Table 4: Sample Size and Power Considering Different Drop Out Rates

Drop Out Rate* (%)	Randomized Subjects	Evaluable (mITT) Subject	Power (%)
25	214	160	80.8
	228	170	83.1

	240	180	85.1
	254	190	87.0
	268	200	88.6
30	230	160	80.8
	244	170	83.1
	258	180	85.1
	272	190	87.0
	286	200	88.6

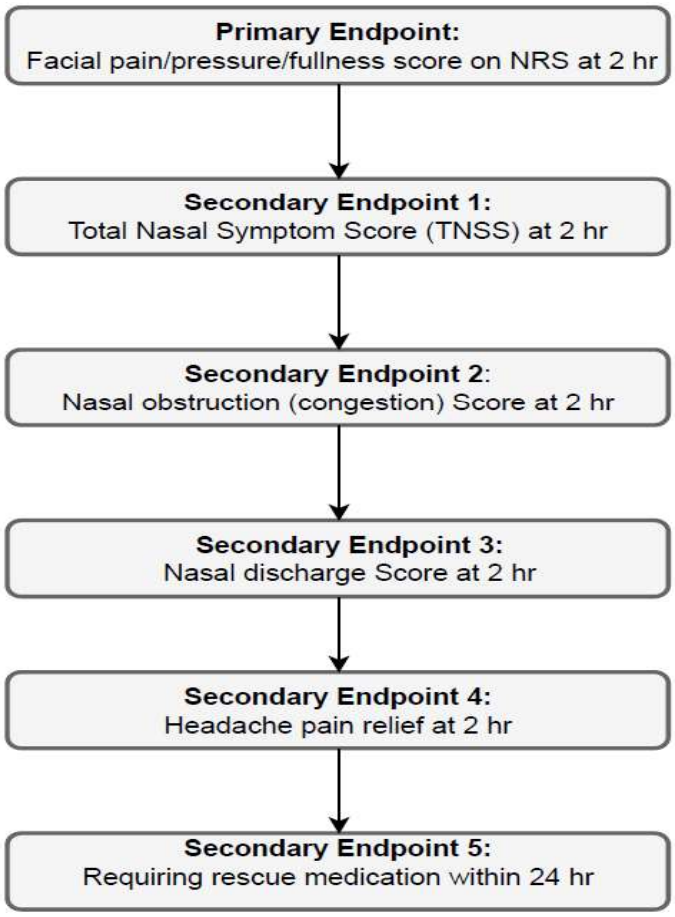
* Drop out rate: Percentage of randomized subjects who failed to move to mITT analysis set.

5.1 Hierarchical Testing Strategy

If the primary endpoint test is significant, then secondary endpoints are evaluated using a hierarchical gate keeping procedure, with each test in the hierarchy conducted at 5% level (or one sided 2.5% level). For hierarchical testing, the p-value of 'rimegepant vs placebo' derived over entire population for each objective will be used (i.e., p-value from sub-groups will not be considered). All analyses will be conducted on the mITT population.

The order of the endpoints in the hierarchy is shown below through a schematic diagram:

Figure 2: Hierarchical Gate Keeping Procedure



Thus, a secondary endpoint is tested only if the preceding secondary endpoint in the hierarchy is determined to be significant. Descriptive p-values are provided for any non-significant secondary endpoints and comparative exploratory endpoints.

No attempt is made to adjust for multiplicity when testing the exploratory endpoints. Any exploratory endpoints subjected to significance testing are evaluated at an unadjusted two-sided alpha level of 5% (or one sided 2.5%).

6 STATISTICAL ANALYSES

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

6.1 General

6.1.1 Programmed Output

A list of TLFs and corresponding templates, 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. 26.1 and World Health Organization-Drug Dictionary (WHO-DD) version September 2023 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.

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 Pharmaceuticals Holding Company Limited Biostatistics Global TLF Standards, 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).

The number and percentage of subjects in the mITT analysis set with missing efficacy data at each relevant time point will be tabulated for the following endpoints: facial pain/pressure/fullness NRS, nasal obstruction (congestion) NRS, nasal discharge NRS, TNSS, headache pain relief, SNOT-22 total score, and PGI-C.

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 and mITT analysis sets; as-treated for the safety 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 the full analysis set. 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 separate subject disposition table is provided for study milestones and analysis sets, as specified below:

- Enrollment to randomization for the enrolled analysis set. This includes the number and percentage of enrolled subjects randomized, not randomized (i.e. screen failures) with reasons for screen failure, and re-screened (including randomized following re-screening and screen failures following re-screening). For subjects whose reason is screen failure due to inclusion/exclusion criteria, the reason(s) for screen failure from the Inclusion/Exclusion Criteria CRF are also included as subcategories, and for this display, subjects may be counted in more than one category of inclusion/exclusion criteria. Subjects who have re-screened and were later randomized are included in the number of randomized subjects and are not counted under the number of screen failures.

- Randomization to treatment for the full analysis set. This includes the number and percentage of subjects who took study drug and did not take study drug with reasons for discontinuation. In addition, the number and percentage of subjects who completed the study without being treated, and the derived reason, are summarized.

- Treatment to completion/discontinuation for the safety and mITT analysis sets. 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), an indication whether the subject was re-screened, previous subject ID, 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, disposition listings 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

- 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, mITT, and safety analysis sets. 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 enrolled analysis set. This includes deviation type, category, and subcategories, which are additional sorting variables. Footnotes describe the medical dictionary and the drug dictionary as applicable.

6.2.4.2 Significant Protocol Deviations

Significant protocol deviations are those with major severity reported by sites in the clinical trial management system.

The by-subject listing of significant protocol deviations is provided for the enrolled analysis set. This includes the date of deviation, date identified, whether the deviation is IRB reportable, date reported to IRB, study day, treatment day, category, subcategory, description, and resolution.

6.2.5 Baseline Characteristics

Baseline characteristics include (1) demographics and other relevant baseline characteristics, (2) baseline disease characteristics (i.e., CRS History, CRS/Nasal Polyp surgical history), (3) medical history, and (4) prior non-study medications. These are tabulated for the safety and mITT analysis sets.

By-subject listings are provided for the enrolled analysis set for the following: demographics, medical history, CRS history, and CRS/Nasal Polyp surgical history. Alcohol use and smoking history will be listed for the enrolled analysis set.

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:

- "Experiences menstrual periods, if female" is not tabulated, as this data is not collected.
- 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.
- Previous study participation is not tabulated, as this does not apply to these study subjects.

Randomization Stratum Frequency Table

A frequency table of randomization stratum displays the number and percentage of subjects in each randomization stratum for the full and mITT analysis sets 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, with the following adjustment:

- "COVID-19 Impacted" is not included in the 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.

CRS/Nasal Polyp Surgical History

Results are based on the Chronic Rhinosinusitis/Nasal Polyp Surgical History CRF.

CRS/nasal polyp surgical history is 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 category, the denominator is the number of subjects in the relevant population.

- History of functional endoscopic sinus surgery (FESS)
    - Number of FESS's for subjects with a history of at least one (categorical)
- History of nasal polyp surgery

  - Number of nasal polyp surgeries for subjects with a history of at least one (categorical)

- History of prior steroid eluting sinus stent placement

- History of nasal septum surgery

  - Number of nasal septum surgeries for subjects with a history of at least one (categorical)

- History of rhinoplasty surgery
  - Number of rhinoplasty surgeries for subjects with a history of at least one (categorical)

A by-subject listing of CRS/nasal polyp surgical history is provided for enrolled subjects and includes the date of most recent surgery for the applicable surgeries.

CRS History

Results are based on the Chronic Rhinosinusitis (CRS) History CRF.

CRS history is 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 listed below (e.g. the denominator for history of aspirin-exacerbated respiratory disease), the denominator is the number of subjects in the population. For each low-level category listed below, the denominator is the number of subjects with a value of "yes" to the corresponding high-level category. (For example, the denominator for each subtype of aspirin-exacerbated respiratory disease is the number of subjects with "yes" to a history of aspirin-exacerbated respiratory disease).

- History of aspirin-exacerbated respiratory disease

  - Subtype of aspirin-exacerbated respiratory disease (Class 1, Class 2, Class 3, Class 4, unknown)

  - Prior desensitization therapy

- History of asthma (yes/no)

  - Active or inactive asthma

  - Severity (intermittent, mild, moderate, severe)

- Prior history (not current) of invasive fungal sinusitis

- Current allergic rhinitis

- Inadequate response to vaccines
- Sinus CT scan in the past 12 months
    - Most recent Lund-MacKay CT score (if available)
    - Most recent Lund-MacKay score not available
- Nasal endoscopy in the past 12 months
    - Nasal endoscopic polyp score (if applicable):
    - Nasal endoscopic polyp score is not applicable
- Treated with systemic corticosteroid courses in the past 12 months for treatment of CRS-associated symptoms
    - Number of courses of treatment in the past 12 months (categorical)
- CRS diagnosis met (yes/no)
    - Facial pain/pressure/fullness – 3 month history
    - Nasal obstruction (congestion) – 3 month history
    - Nasal discharge (anterior, posterior, or both) – 3 month history
    - Decreased sense of smell– 3 month history
    - Endoscopic findings of mucopurulent drainage (not clear) or edema in the middle or superior meatus, or anterior ethmoid region – within 12 months
    - Polyps in nasal cavity or the middle or superior meatus– within 12 months
    - Radiographic imaging showing inflammation of the paranasal sinuses with partial opacification of at least two sinuses or complete opacification of at least one sinus– within 12 months
- Number of instances CRS-associated facial pain/pressure/fullness reached moderate or severe intensity on a 4-point rating scale (0 = None, 1 = Mild, 2 = Moderate, 3 = Severe) in the past 30 days.

A by-subject listing of CRS history is provided for enrolled subjects and includes date(s) of applicable procedures if available; CRS diagnostic criteria are separately listed.

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 for the safety analysis set:

- Previous medications
- Current medications
- Stable CRS medications through completion or discontinuation of the study

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 CRS medications through Screening are defined as CRS medications taken > 1 month 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 > 30 days, and (2) completion or discontinuation ≤ imputed medication stop date, with no change in dose amount or frequency. For purposes of this analysis, CRS medications is defined as follows:

- Saline and other non-medicated spray/rinse (additives such as detergents, moisturizers, and mucolytics)
- Topical nasal corticosteroids (spray or rinse)
- Topical nasal antibiotics and antifungal medications (spray or rinse)
- Topical nasal antihistamines (non-sedating)
- Topical nasal cromolyn
- Leukotriene modifiers
- Cromolyn (oral or inhalation)
- Methylxantines (e.g., theophylline, aminophyllines)
- Mucoactive agents (e.g., guaifenesin, acetylcysteine)
- Any medication indicated for asthma or chronic obstructive pulmonary disease (COPD)

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 subjects in the full analysis set and includes:

- The number (and percentage) of subjects in the full analysis set 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 facial pain/pressure/fullness" 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 facial pain/pressure/fullness NRS score (≥ 6) (i.e. the subject responded "Yes" to the question "Please confirm you took your Study Medication" in the "Initial facial pain/pressure/fullness" eDiary.
- The number and percentage of subjects in the full analysis set who never reported taking study medication

Subjects who mistakenly take drug are included in safety analyses but excluded from efficacy analyses.

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 subjects in the full analysis set 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 cross-tabulation of exposure and accountability data is prepared. This is done overall for subjects in the full analysis set and separately for subjects in the mITT analysis set who had a qualifying facial pain/pressure/fullness NRS score. For the accountability data, the categories are: took IP, did not take IP, and unknown (if applicable); for the exposure data, the categories are: took IP, did not take IP, and unknown (if applicable).

A by-subject listing is prepared that indicates the study drug exposure and accountability status for the full analysis set; this listing includes study drug start date/time and study day, whether or not the exposure was recorded in the eDiary or drug was mistakenly taken, drug accountability kit dispensed date, kit returned date, kit ID, and IP used status (IP taken, IP not taken), and number of tablets dispensed and returned. 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 safety 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.

A by-subject listing of non-study concomitant medications is provided for the enrolled analysis set.

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 and times are not imputed. Rescue medications are separately tabulated and displayed in descending order of overall frequency within therapeutic class and preferred name for the safety analysis set and separately for the mITT 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 rescue medications is provided 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 (September 2023).

6.3 Efficacy

Unless otherwise noted, all efficacy analyses are conducted using the mITT analysis set as outlined below. Efficacy tabulations present results by as-randomized treatment group only (excluding overall), unless specified otherwise. All 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 (i.e. NRS scores, SNOT-22 scores, and PGI-C scores) at each time point, along with change from baseline, as applicable.

6.3.1 Overall Efficacy Summary

Table 5 provides a summary of the statistical methods used for the primary, secondary, and exploratory endpoints.

Unless otherwise noted, all efficacy analyses will be conducted using the mITT population.

A by-subject listing of eDiary NRS results is provided for the full analysis set.

Table 5: Efficacy Endpoints and Analysis Methods

Efficacy Endpoints	Linear model	Mantel-Haenszel	Cumulative logit model	Descriptive only
Primary				
Change from baseline in facial pain/pressure/fullness NRS score to 2 hours post-dose.	X			
Secondary				
Change from baseline in TNSS to 2 hours post-dose	X			
Change from baseline of nasal obstruction (congestion) NRS score to 2 hours post-dose	X			
Change from baseline of nasal discharge NRS score to 2 hours post-dose.	X			
Percentage of subjects reporting a pain level of moderate or severe at baseline in the eDiary that experience headache pain relief at 2 hours post-dose		X		
Percentage of subjects that use rescue medication within 24 hours after administration of study drug.		X		
Exploratory				
The percentage of subjects with ≥ 30% reduction from baseline of facial pain/pressure/fullness NRS (0-10) score at 2 hours post-dose.		X		
The percentage of subjects with ≥ 50% reduction from baseline of facial pain/pressure/fullness NRS (0-10) score at 2 hours post-dose.		X		

Change from baseline in facial pain/pressure/fullness NRS score to 15, 30, 45, 60, 90 minutes and 2, 4, 8 and 24 hours post-dose in evaluable subjects.	X			
Change from baseline in nasal obstruction (congestion) NRS (0-10) score to 15, 30, 45, 60, 90 minutes and 2, 4, 8 and 24 hours post-dose in evaluable subjects.	X			
Change from baseline in nasal discharge NRS score to 15, 30, 45, 60, 90 minutes and 2, 4, 8 and 24 hours post-dose in evaluable subjects.	X			
Percentage of subjects reporting a pain level of moderate or severe at baseline in the eDiary that experience headache pain relief, at each post-dose time point.		X		
Number and percentage of subjects in each of the 7 PGI-C improvement categories (very much improved to very much worse) relative to the baseline visit at 24 hours post-dose.			X	
The percentage of subjects with ≥ 30% reduction from baseline of facial pain/pressure/fullness NRS (0-10) score at 24 hours post-dose.		X		
The percentage of subjects with ≥ 50% reduction from baseline of facial pain/pressure/fullness NRS (0-10) score at 24 hours post-dose.		X		
The percentage of mITT subjects that achieve sustained relief of facial pain/pressure/fullness.		X		
Change from baseline in the SNOT-22 total score and domain scores.	X ANCOVA			
Number and percentage of subjects with C-SSRS responses in the C-SSRS categories and sub-categories.				X

6.3.2 Rescue Medication

Rescue medications are defined in Section 6.2.6.3. For efficacy evaluations (except for the analysis set forth in Section 6.3.4.5), 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 the efficacy evaluation or, if the eDiary assessment is missing at that time point, if the date/time of first rescue medication use is ≤ the upper limit of the window for that assessment as specified in Table 7. For instance, if a subject receives rescue medication 2 hours and 5 minutes post-dose and the "2 hour" efficacy assessment is conducted at the 2 hours and 10 minute time point (within the protocol window), the subject is treated as having used rescue medication prior to the "2 hours post-dose" efficacy time point. Similarly, if the eDiary assessment at 2 hours is missing, the subject is treated as having used rescue medication prior to the "2 hours post-dose" efficacy time point if the date/time of first rescue medication use is ≤ 135 minutes (end of protocol window for 2 hour post-dose time point). 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 the efficacy evaluation.

For efficacy evaluations, 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, as specified in Sections 6.3.3, 6.3.4, or 6.3.5.

6.3.3 Primary Efficacy Endpoint

6.3.3.1 Primary Analysis

Facial pain/pressure/fullness is assessed using an NRS score ranging in integers from 0 to 10, with 0 being "no facial pain/pressure/fullness" and 10 being "worst imaginable facial pain/pressure/fullness."

Change from baseline in facial pain/pressure/fullness NRS score is analyzed on the mITT population using a linear model that includes the baseline NRS (0-10) value for facial pain/pressure/fullness as a covariate, and fixed effects for treatment group, stratification factor (presence of nasal polyps; yes or no), 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 the 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 autoregressive (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.

The model will be repeated for the subgroup of the stratification factor, presence of nasal polyps (yes/no), excluding the stratification factor from the model. Only the overall p-value will be considered in hierarchical testing.

Least squares (LS) means, standard errors (SE), 95% confidence interval (CI) are reported for each treatment group at 2 hours post-dose, along with LS mean difference estimate (rimegepant - placebo) and associated SE, 95% CI and p-value. The LS mean change from baseline is also plotted over time.

In the event a subject uses a non-study rescue medication prior to or at 2 hours post-dose, all assessments after rescue medication administration are set to missing (RM = M: Rescue medication use = Missing). If the time of first rescue medication is missing but the date of rescue medication is the same as the date of dosing, all data points after baseline are set to missing (i.e. the subject is excluded from the analysis as they will not have evaluable post-baseline data available).

Likewise, if a subject fails to log their pain score after study drug is administered, through 2 hours post-dose, this data is considered missing (NC = M: Non-completers = Missing).

6.3.3.2 Sensitivity Analyses

The primary analysis of the primary endpoint assumes data are missing at random (MAR). It further assumes that had the subjects not used a rescue medication, their efficacy would have been similar to the efficacy of subjects from the same treatment group who did. The purpose of these sensitivity analyses is to investigate departures from these assumptions.

The following sensitivity analyses are planned:

- Jump to reference
- Tipping Point

Sensitivity analyses are not repeated by subgroup. All sensitivity analyses are conducted on the mITT population.

6.3.3.2.1 Jump to Reference

The purpose of this sensitivity analysis is to investigate the departure from the MAR assumption for the treatment group. A reference-based multiple imputation (MI) approach is applied to missing data. It assumes the treatment effect observed in rimegepant subjects with missing data, including subjects with missing data due to use of rescue medication, immediately trends towards the estimated mean in the placebo group.

Missing values in the placebo group and intermittent missing values in the rimegepant group (ie, due to subjects failing to log their pain score at one or more timepoints but resuming entering scores at a later timepoint) are assumed to be MAR, while terminal missing values in the rimegepant group (ie, due to subjects who ceased entering pain scores entirely, or who used rescue medication prior to 2 hours and have scores set to missing through 2 hours as described in Section 6.3.3.1) are assumed to be missing not at random (MNAR). Specifically, it is assumed that subjects in the rimegepant group with terminal missing scores, including those who took rescue medication prior to 2 hours post-dose, would have had similar subsequent NRS scores to those in the placebo arm. Terminal missing values in the rimegepant group are multiply imputed based on a distribution with estimated mean values at missing time points similar to that of subjects in the placebo group.

The MI procedure includes the following steps:

- Intermittent missing values are first imputed using the Markov Chain Monte Carlo (MCMC) method with the SAS MI procedure, which is appropriate for non-monotonic missing data.
- For rimegepant subjects, monotone missing values are then multiply imputed with the SAS MI procedure using the monotone regression method. The MNAR option in PROC MI is used and references the placebo group for informing the imputation. The placebo arm subjects use the profile under MAR.
- For each stage, MI is performed with covariates baseline NRS score, stratification factor, and non-missing NRS scores. MI is performed within treatment group for the first stage.
- Twenty imputations are performed.
- The primary analysis described in Section 6.3.3.1 is implemented for each imputed dataset.
- Results are combined to generate an overall estimate and associated variance using Rubin's rules (Rubin 1987).

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

6.3.3.2.2 Tipping Point

The purpose of this sensitivity analysis is to investigate the departure from the MAR assumption.

Missing data in the placebo group and all intermittent missing data are assumed to be MAR, while terminal missing data from the rimegepant group are multiply imputed assuming that subjects with missing data have missing data that are worse by a Δ value compared to similar subjects with observed data. Missing values are multiply imputed via this method with increasing Δ values. The primary efficacy outcome analysis methodology is applied to the

imputed datasets, combined via Rubin's rules (Rubin, 1987), and repeated until statistical significance no longer holds.

The same MI methods in Section 6.3.3.2.1 are applied, except at the second stage, rather than implementing the MNAR option in PROC MI for the rimegepant group, monotone missing values are multiply imputed separately by treatment group under MAR. However, a shift parameter is progressively added to imputed rimegepant scores to decrease the treatment difference until the p-value is >0.05. The shift parameter starts at 0 and increases in increments of an absolute value of 0.25 points. The increment(s) may be determined at the time of analysis, with the intent to refine the grid around the tipping points.

The tipping point analysis is only performed if statistical significance is achieved in the primary analysis, in favor of rimegepant. If the p-value is >0.05 with a shift parameter of 0, the analysis stops there.

LS means, SEs, 95% CI are reported for each treatment group at 2 hours post-dose, along with LS mean difference estimate (rimegepant - placebo) and associated SE, 95% CI and p-value. Values are reported for each shift parameter until the p-value is >0.05.

6.3.4 Secondary Efficacy Endpoints

If the primary endpoint test is significant, then the secondary endpoints are evaluated using a hierarchical gate-keeping procedure, with each test in the hierarchy conducted at p=0.05. These secondary endpoints are tested in the following order.

1. Change from baseline of TNSS at 2 hours post-dose
2. Change from baseline of nasal obstruction (congestion) at 2 hours post-dose
3. Change from baseline of nasal discharge at 2 hours post-dose
4. Headache pain relief at 2 hours post-dose
5. The probability of requiring rescue medication within 24 hours after administration of study medication

Should any test in the hierarchy fail to achieve statistical significance, nominal p-values are reported for any subsequent tests.

No sensitivity analyses are performed for secondary endpoints.

6.3.4.1 Total Nasal Symptom Score (TNSS)

TNSS is calculated at each time point as the sum of 3 symptom scores: (1) facial pain/pressure/fullness; (2) nasal obstruction (congestion); and (3) nasal discharge, at the applicable time point.

The analysis in Section 6.3.3.1, including the subgroup analysis, is repeated for TNSS, except baseline TNSS value is included as covariate instead of baseline NRS score (facial pain/pressure/fullness).

6.3.4.2 Nasal Obstruction (Congestion)

The analysis in Section 6.3.3.1, including the subgroup analysis, is repeated for the nasal obstruction (congestion) NRS score, except baseline nasal obstruction (congestion) NRS score is included as covariate instead of baseline facial pain/pressure/fullness NRS score.

6.3.4.3 Nasal Discharge

The analysis in Section 6.3.3.1, including the subgroup analysis, is repeated for the nasal discharge NRS score, except baseline nasal discharge NRS score is included as covariate instead of baseline facial pain/pressure/fullness NRS score.

6.3.4.4 Headache Pain Relief

The number and percentage of subjects that experience headache pain relief at 2 hours post-dose are analyzed after first imputing missing data at 2 hours to be failure (i.e., NC = F: Non-Completers = Failure). Additionally, subjects who use rescue medication on or before assessment of pain at 2 hours are also assigned as failures (RM = F: Rescue medication use = Failure). 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 stratification by presence of nasal polyps (yes or no). If one category of stratification factor has sparse data (less than 5 subjects), then the stratification factor is removed from the analysis.

Headache pain is defined using a 4-point scale (0 = None; 1 = Mild; 2 = Moderate; 3 = Severe). Headache pain relief is defined as a headache pain level of none or mild at 2 hours post-dose, with a headache pain level of moderate or severe at baseline. Note that only subjects with a headache pain level of moderate or severe at baseline are included in this analysis.

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, 95% CI, and p-value by randomization stratum
- Stratified percentage difference between treatment groups (rimegepant – placebo), ASE, 95% CI, and p-value*

* P-value for comparison of stratified percentage difference between treatment groups will be used in hierarchical testing procedure.

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

A by-subject listing of headache pain is provided for the randomized analysis set.

6.3.4.5 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. The p-value for comparison of stratified percentage difference between treatment groups will be used in hierarchical testing procedure.

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 6.3.2 of the SAP. If time of first rescue medication use is missing, a rescue medication would be deemed used as of 24 hours post-dose if the date of first rescue medication use is ≤ (treatment start date + one day). This is handled analogously to Section 8.7 of the Core SAP.

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

The analysis follows the same methodology set forth in Section 6.3.4.4. 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.

6.3.5 Exploratory Efficacy Endpoints

The following efficacy-related exploratory endpoints are planned. Any p-values reported for exploratory endpoints are nominal.

1. To evaluate rimegepant compared to placebo on ≥ 30% reduction from baseline of facial pain/pressure/fullness NRS (0-10) score at 2 hours.

2. To evaluate rimegepant compared to placebo on ≥ 50% reduction from baseline of facial pain/pressure/fullness NRS (0-10) score at 2 hours.

3. To evaluate the effect of rimegepant compared to placebo on change from baseline of facial pain/pressure/fullness NRS (0-10) score at 15, 30, 45, 60, 90 minutes and 2, 4, 8 and 24 hours post-dose.

4. To evaluate the effect of rimegepant compared to placebo on change from baseline of nasal obstruction (congestion) NRS (0-10) score at 15, 30, 45, 60, 90 minutes and 2, 4, 8 and 24 hours post-dose.

5. To evaluate the effect of rimegepant compared to placebo on change from baseline of nasal discharge NRS (0-10) score at 15, 30, 45, 60, 90 minutes and 2, 4, 8 and 24 hours post-dose.

6. To evaluate the effect of rimegepant compared to placebo on headache pain relief using a 4-point Likert scale at 15, 30, 45, 60, 90 minutes and 2, 4, 8 and 24 hours post-dose compared to baseline.

7. To evaluate rimegepant compared to placebo on the PGI-C questionnaire at 24 hours post-dose.

8. To evaluate rimegepant compared to placebo on ≥ 30% reduction from baseline of facial pain/pressure/fullness NRS (0-10) score at 24 hours.

9. To evaluate rimegepant compared to placebo on ≥ 50% reduction from baseline of facial pain/pressure/fullness NRS (0-10) score at 24 hours.

10. To evaluate rimegepant compared to placebo on sustained relief of facial pain/pressure/fullness, as defined by each of the following: 30% reduction from baseline on NRS (0-10), 1.5-point reduction on NRS (0-10), and a 2-point reduction on NRS (0-10) through 24 hours post-dose.

11. To explore the distribution of baseline disease severity using the Sino-Nasal Outcome Test (SNOT-22).

12. To evaluate rimegepant compared to placebo on the Sino-Nasal Outcome Test (SNOT-22) score at 24 hours post-dose.

The following exploratory endpoints are discussed in Section 6.4.

1. To evaluate the safety and tolerability of rimegepant in the acute treatment of chronic rhinosinusitis as measured by the frequency of adverse events of moderate or severe intensity, serious adverse events (SAEs), clinically relevant laboratory abnormalities, and nasal inspection abnormalities.

2. To evaluate rimegepant compared to placebo for the Columbia Suicide Severity Rating Scale (C-SSRS).

6.3.5.1 ≥ 30% Reduction from Baseline of Facial Pain/Pressure/Fullness NRS (0-10) Score at 2 Hours

The percentage of subjects with ≥ 30% reduction from baseline of facial pain/pressure/fullness NRS score at 2 hours is analyzed using the methodology set forth in Section 6.3.4.4, with the following adjustments. Subjects with ≥ 30% reduction from baseline in facial

pain/pressure/fullness NRS (0-10) score at 2 hours post-dose are deemed successes. Subjects with < 30% reduction from baseline in facial pain/pressure/fullness NRS (0-10) score at 2 hours post-dose are deemed failures. Subjects with missing data at 2 hours post-dose and subjects who use rescue medication prior to the assessment at 2 hours post-dose are deemed failures as well. Figures will not be produced.

6.3.5.2 ≥ 50% Reduction from Baseline of Facial Pain/Pressure/Fullness NRS (0-10) Score at 2 Hours

The percentage of subjects with ≥ 50% reduction from baseline of facial pain/pressure/fullness NRS score at 2 hours is analyzed and tabulated using the methodology set forth in Section 6.3.5.1, with respect to ≥ 50% reduction from baseline.

6.3.5.3 Change from baseline of facial pain/pressure/fullness NRS (0-10) score at 15, 30, 45, 60, 90 minutes and 2, 4, 8 and 24 hours post-dose

Change from baseline in facial pain/pressure/fullness NRS (0-10) score is analyzed using the methodology set forth in Section 6.3.3.1, except time points 15, 30, 45, 60, 90 minutes and 2, 4, 8 and 24 hours post-dose are included in the model. Estimates from the model are reported for each time point.

If a subject uses a rescue medication, all data points after rescue medication use is set to missing.

A line graph is produced depicting the LS mean change from baseline in facial pain/pressure/fullness NRS score with 95% CI bars by planned timepoint .

6.3.5.4 Change from baseline of nasal obstruction (congestion) NRS (0-10) score at 15, 30, 45, 60, 90 minutes and 2, 4, 8 and 24 hours post-dose

Change from baseline in nasal obstruction (congestion) NRS (0-10) score at 15, 30, 45, 60, 90 minutes and 2, 4, 8 and 24 hours post-dose is analyzed using the same methodology set forth in Section 6.3.5.3.

A line graph is produced depicting the LS mean change from baseline in nasal obstruction (congestion) NRS score with 95% CI bars by planned timepoint .

6.3.5.5 Change from baseline of nasal discharge NRS (0-10) score at 15, 30, 45, 60, 90 minutes and 2, 4, 8 and 24 hours post-dose

Change from baseline in nasal discharge NRS (0-10) score at 15, 30, 45, 60, 90 minutes and 2, 4, 8 and 24 hours post-dose is analyzed using the same methodology set forth in Section 6.3.5.3.

A line graph is produced depicting the LS mean change from baseline in nasal discharge NRS score with 95% CI bars by planned timepoint .

6.3.5.6 Headache pain relief at 15, 30, 45, 60, 90 minutes and 2, 4, 8 and 24 hours post-dose

The percentage of subjects achieving headache pain relief is separately evaluated at 15, 30, 45, 60, 90 minutes and 2, 4, 8 and 24 hours post-dose, following the same methodology set forth in Section 6.3.4.4 separately for each time point. Figures will not be produced.

The number of subjects that experience headache pain relief at each specified time point is analyzed after first imputing missing data at that time point to be failure (i.e., NC = F: Non-Completers = Failure). Additionally, subjects who use rescue medication on or before assessment of pain at that time point are also assigned as failures (RM = F: Rescue medication use = Failure). If the time of first rescue medication is missing, subjects are considered as failures 1) if the date of rescue medication is the same as the date of dosing or 2) only with respect to the 24 hours post-dose analysis, if the date of rescue medication is the same as or one day after the date of dosing.

Headache pain level at each time point will also be summarized for mITT subjects with a headache pain level of moderate or severe at baseline.

6.3.5.7 PGI-C at 24 hours post-dose

The PGI-C is a patient-rated scale which assesses how the subject's current illness state has changed relative to the baseline visit. The subject is asked to rate a change in their overall disease condition on a 7-point Likert scale, with the following response options: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. The PGI-C is a global index scale that may be used to rate the response of a condition to a therapy. The eDiary is used to evaluate the PGI-C Questionnaire at 24 hours post-dose.

PGI-C score at 24 hours post-dose is tabulated as the number and percentage of subjects in each category by treatment group, with response options 1-3 combined into a single "improved" category, response option 4 as "no change" and response options 5-7 combined into a single "worsening" category. Percentages are based on subjects with non-missing PGI-C data at the 24 hour time point. A cumulative logit model will be used to investigate the effect of treatment on PGI-C score. The number of observations (i.e. frequency) in each category will be modelled with treatment group and nasal polyps (yes or no) as covariates. Analysis will consider "placebo" group as reference. Odds ratio (Treatment vs Placebo), 95% Wald CI, and predicted probabilities in each response group for treatment and placebo group will be reported. A by-subject listing of PGI-C results is provided for the full analysis set.

6.3.5.8 ≥ 30% Reduction from Baseline of Facial Pain/Pressure/Fullness NRS (0-10) Score at 24 Hours

The percentage of subjects ≥ 30% reduction from baseline of facial pain/pressure/fullness NRS score at 24 hours post dose is analyzed using the methodology set forth in Section 6.3.5.1, with respect to ≥ 30% reduction from baseline at 24 hours. Subjects with missing data at 24 hours

post-dose and subjects who use rescue medication prior to the assessment at 24 hours post-dose are deemed failures.

6.3.5.9 ≥ 50% Reduction from Baseline of Facial Pain/Pressure/Fullness NRS (0-10) Score at 24 Hours

The percentage of subjects ≥ 50% reduction from baseline of facial pain/pressure/fullness NRS score at 24 hours post dose is analyzed using the methodology set forth in Section 6.3.5.1, with respect to ≥ 50% reduction from baseline at 24 hours. Subjects with missing data at 24 hours post-dose and subjects who use rescue medication prior to the assessment at 24 hours post-dose are deemed failures.

6.3.5.10 Sustained Relief of Facial Pain/Pressure/Fullness

Sustained relief of facial pain/pressure/fullness is assessed separately for each of the following criterion:

1) 30% reduction from baseline on NRS (0-10), achieved for each time point from 2 hours to 24 hours post-dose

2) 1.5-point reduction on NRS (0-10), achieved for each time point from 2 hours to 24 hours post-dose

3) 2-point reduction on NRS (0-10) through 24 hours post-dose, achieved for each time point from 2 hours to 24 hours post-dose

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

- Achieving pain relief as defined in (1), (2), or (3) above at all time points from 2 to 24 hours post-dose, respectively for each of the 3 criteria
- Missing facial pain/pressure/fullness at ≤ 1 timepoint from 4 to 8 hours post-dose
- No rescue medication taken at or before 24 hours post-dose

Subjects who have any of the following are classified as failures:

- Rescue medication taken at or before 24 hours post-dose (RM=F)
- Did not achieve pain relief as defined in (1), (2), or (3) above for at least one time point from 2 to 24 hours post-dose, respectively for each of the 3 criteria
- Missing facial pain/pressure/fullness at 2 or 24 hours post-dose
- Missing facial pain/pressure/fullness at > 1 time point from 4 to 8 hours post-dose

Sustained relief (separately for each of the above 3 criteria) is analyzed following the same methodology set forth in Section 6.3.4.4. Figures will not be produced.

6.3.5.11 Sino-Nasal Outcome Test (SNOT-22)

SNOT-22 is a validated symptom-based outcome measure to assess the burden of CRS symptomatology. It is a 22-item instrument that includes both nasal and extra-nasal symptoms such as poor sleep and mood disturbance. The questionnaire consists of 22 items across 5 domains: Nasal, Ear/Facial, Sleep, Function, and Emotional. Items are categorized as specified by Khan et. al. (2022). A scale ranging from 0 (no problem) to 5 (problem as bad as it can be) is used to respond to each item in the questionnaire. The total scores range from 0 to 110 with higher total scores implying greater impact on quality of life. The SNOT-22 is collected on paper at the Baseline Visit and on the eDiary at 24 hours post-dose.

Total and domain scores are derived by taking the sum of the non-missing item responses at each assessment (baseline and 24 hours post-dose). Any missing responses are imputed with the mean value of non-missing answers; however, if at least half of the answers were missing for each domain or the entire questionnaire, the given domain or entire questionnaire, respectively, is set to missing.

Summary statistics are reported for the total score and separately for each domain.

Change from baseline in the total SNOT-22 score, and separately for each domain score, are evaluated using an analysis of covariance (ANCOVA) model with baseline SNOT-22 score as a covariate and fixed effects for treatment group and stratification factor (presence of nasal polyps; yes or no).

LS means, SE, 95% CI are reported for each treatment group, and LS mean difference estimate (rimegepant - placebo), SE, 95% CI and p-value are reported.

A by-subject listing of SNOT-22 results is provided for the full analysis set.

6.4 Safety

Safety analyses are based on the safety 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; electrocardiograms (ECGs); 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, ECGs) and C-SSRS endpoints are tabulated as continuous variables descriptively at baseline and the EOT 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 EOT 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 system organ class (SOC) and preferred term (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 significant 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 pretreatment 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 discontinuation; hepatic-related AE; cardiovascular AE; and suicidality AE.

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

6.4.1.3 On-treatment AEs by SOC and PT

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

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

AEs of significant 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 by the central laboratory using the modification of diet in renal disease (MDRD) formula. 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 Internationale (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 safety 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). Elevations of >2 x ULN are also tabulated for ALT and AST. In addition, LFT elevations which are potential cases of drug-induced liver injury (DILI) per Section 8.5 of the protocol will be tabulated. Potential DILI cases will be defined as the following:

- Subjects with aspartate aminotransferase (AST)/alanine aminotransferase (ALT) and total bilirubin (TBL) baseline values within the normal range who subsequently present with AST OR ALT values ≥3 × upper limit of normal (ULN) AND a TBL value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase (ALP) value <2 × ULN or not available. Evidence of hemolysis will be determined by the presence of the text string "hemolysis" in the comments field of the laboratory record, including any variations in capitalization or spelling/typos which are clearly intended to represent hemolysis. Hemolysis records will also be confirmed by the medical advisor.

- For subjects with baseline AST OR ALT OR TBL values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values AND ≥3 × ULN; or ≥8 × ULN (whichever is smaller).

    - Preexisting values of TBL above the normal range: TBL level increased from baseline value by an amount of ≥1 × ULN or if the value reaches ≥3 × ULN (whichever is smaller).

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 safety 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 safety 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

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

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

LFT values and ratios to ULN (i.e., ALT, AST, TBL and ALP) for SI units. The listing displays all LFT results over time for subjects with select LFT elevations (ALT or AST > 3x ULN; ALP or TBL > 2x ULN) at any time point. 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 safety 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.

A by-subject listing of vital signs and physical measurements is provided for the enrolled analysis set.

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 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 safety 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.

6.4.4 Electrocardiogram

ECG parameters include RR, QRS, PR, QT, QTcF, and ventricular heart rate. ECGs are measured at the following visits: Screening and EOT. ECG parameters are slotted into safety analysis periods (pre-treatment, on-treatment) according to the measurement date and time, as available. ECGs are tabulated for the on-treatment analysis period (see Section 7.2) for the safety analysis set. A by-subject listing of ECG results is provided for the enrolled analysis set.

6.4.4.1 ECG Changes from Baseline

Values and changes from baseline in ECG parameters are tabulated descriptively as continuous variables at baseline and EOT in the on-treatment analysis period for the safety analysis set.

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

6.4.4.2 ECG Abnormalities

On-treatment ECG abnormalities are tabulated as the number and percentage of subjects with on-treatment ECG abnormalities in the categories specified in Section 6.4.4.2 of the Core SAP. Analyses are based on the subset of subjects with non-missing data in the on-treatment analysis period.

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

6.4.5 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).

6.4.6 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 Visit, 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.

6.4.7 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 for rimegepant-treated subjects, regardless of relationship to study drug
- On-treatment events of significant interest for rimegepant-treated subjects:
    - ALT or AST > 3x ULN
    - ALT or AST > 3x ULN concurrent with TBL > 2x ULN
    - TBL > 2x ULN
    - Select hepatic-related AE, i.e., PT containing cirrhosis, hepatic failure, hepatitis, jaundice, or liver failure
    - Suicidality AE
- Any event of significant interest

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

Should the criteria in the study Safety Narrative Plan conflict with the criteria above, the Safety Narrative Plan 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

Analysis 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 facial pain/pressure/fullness Diary," the date/time that the "Initial facial pain/pressure/fullness Diary" is saved.
    - For subjects who indicated that they mistakenly took study medication on the "Initial facial pain/pressure/fullness Diary," the date/time that the subject entered on the

"Initial facial pain/pressure/fullness 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.

- 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 counted 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 6.

Table 6: 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 Section 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 7. The anchor point for the windows is the date/time of exposure, as defined in Section 7.1.

Table 7: 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 (1 hr 25 min – 1 hr 35 min)	Study medication start time + 90 min
2 hr diary	115-135 min (1 hr 55 min – 2 hr 15 min)	Study medication start time + 2 hr
4 hr diary	225-255 min (3 hr 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. The stratification factor subgroup is as noted in Section 4.3. The hierarchical testing strategy will always follow the overall p-values rather than the subgroup p-values.

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 full analysis set: Last nonmissing value

Full analysis set but not in the safety analysis set: Last nonmissing value at or before the IWRS randomization date

mITT and safety analysis sets: Last nonmissing value in the pre-treatment analysis period

The baseline value for SNOT-22 is defined as the last nonmissing 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, 6.4.3.1, and 6.4.4.1 for handling multiple values on the same measurement date.

For NRS and headache pain scores, the baseline value is the value collected on the "Initial facial pain/pressure/fullness" eDiary in the same session where the subject confirmed having dosed (not mistakenly), and the date/time of the associated baseline values is the date/time the "Initial

facial pain/pressure/fullness" eDiary is saved. For subjects who mistakenly took drug (see Section 6.2.6), baseline NRS and headache pain scores are missing.

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:

- CRS history not aligned with eligibility requirements as any of the following:
  - Subject has been treated with systemic corticosteroids within 30 days prior to Screening
  - CRS onset less than 3 months prior to Screening
- Inflammation documentation older than 12 months
- Finding out of range at Screening (or at Baseline, as applicable), defined as any of the following:
  - ALT/AST/Direct Bilirubin/Indirect Bilirubin/TBL > ULN if originally consented to protocol version 3 or lower
  - TBL > 1.5 x ULN if originally consented to protocol version 4 or higher
  - For subjects consented to protocol version 4 or higher with a history of Gilbert's syndrome, Direct Bilirubin > 1 x ULN
  - AST or ALT > 2 x ULN if originally consented to protocol version 4 or higher
  - ECG abnormalities as follows if originally consented to protocol version 3 or lower:
    - 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 ≥ 6.5% if originally consented to protocol version 3 or lower
  - HbA1c > 7.5% if originally consented to protocol version 4 or higher
  - Systolic blood pressure > 150 mmHg after 10 mins of rest if originally consented to protocol version 3 or higher
  - Diastolic blood pressure > 100 mmHg after 10 mins of rest if originally consented to protocol version 3 or higher

- eGFR according to the MDRD Study equation ≤ 40 mL/min/1.73m^2 if originally consented to protocol version 3 or lower
- eGFR according to the MDRD Study equation ≤ 30 mL/min/1.73m^2 if originally consented to protocol version 4 or higher
- BMI ≥ 33 kg/m^2 if originally consented to protocol version 3 or lower
- BMI > 35 kg/m^2 if originally consented to protocol version 4 or higher
- Positive for cocaine or PCPs
- Females with a positive pregnancy test at Screening or Baseline
- CSSRS suicidal ideation with active intent or plan to act, or suicidal behavior present during screening through baseline. Defined as having a "yes" response to any of the following CSSRS 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:

- eDiary assessment compliance
  - Subject has missed a 2-hour endpoint assessment.
  - Subject has mistakenly taken dose
- Prohibited non-study medications, procedures, or therapies defined as any of the following:
  - Daily CRS medications with dose change (see Section 6.2.5.4 for the definition of CRS medication)
  - Excluded current or recent treatments (Section 5.3.6 of the protocol) prior to the Screening Visit or throughout the study as follows:
    - Non-steroid immunosuppressants (i.e., calcineurin inhibitors, interleukin inhibitors, selective immunosuppressants, TNF-α inhibitors, other immunosuppressants) use within the 60 days prior to Screening Visit or throughout the study.
    - New or recently modified allergen immunotherapy within the 3 months prior to Screening Visit or throughout the study.
    - Monoclonal antibody therapy (e.g., dupilumab, mepolizumab, omalizumab, benralizumab, reslizumab) within the 6 months prior to Screening Visit or throughout the study (Protocol version 3 or lower).
    - Monoclonal antibody therapy (e.g., dupilumab, mepolizumab, omalizumab, benralizumab, reslizumab) within the 3 months prior to Screening Visit or throughout the study (Protocol version 4 or higher).

  - New or recently modified leukotriene modifiers therapy within the 3 months prior to Screening Visit or throughout the study (Protocol version 2 or lower).
  - New or recently modified leukotriene modifiers therapy within the 1 month prior to Screening Visit or throughout the study (Protocol version 3 or higher).
  - New or recently modified β-adrenoceptor agonists therapy within the 3 months prior to Screening Visit or throughout the study (Protocol version 2 or lower).
  - New or recently modified β-adrenoceptor agonists therapy within the 1 month prior to Screening Visit or throughout the study (Protocol version 3 or higher).
- Non-narcotic analgesic taken on ≥ 15 days per month for greater ≥ 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
- Systemic corticosteroids taken up to 30 days prior to the Screening Visit or afterward (specifically, 1) if the subject dosed after taking systemic corticosteroid or 2) if the subject did not discontinue the study).
- Antibiotics, other than topical nasal antibiotics, taken up to 14 days prior to the Screening Visit or afterward (specifically, 1) if the subject dosed after taking the antibiotics or 2) if the subject did not discontinue the study).
- Monoclonal antibody therapy taken during the study.
- Barbiturate-containing products taken up to 14 days prior to the Baseline Visit or afterward
- Narcotic medication, such as opioids, taken up to 2 days prior to the Baseline 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 Baseline 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:

  - Positive for cocaine, cannabinoids or PCPs at any post-baseline visit, including EOT visit

- Medical history, defined as any of the following subcategories:
  - Ongoing rhinitis medicamentosa*
  - Nasal or upper respiratory infection starting/ending less than or equal to 2 weeks prior to Screening Visit**
  - Acute bacterial/viral rhinosinusitis starting/ending less than or equal to 2 weeks prior to Screening Visit**
- Presence of polyps discrepant between IWRS and CRF data, for the following subcategories:
  - IWRS randomization stratum of no, but presence of polyps or prior history of nasal polyp surgery

* In the case of partial start and/or end dates, rhinitis medicamentosa is considered 'ongoing' if 1) the month and year of the partial start date is on or before the month and year of the Screening Visit AND 2) the month and year of the end date is after the month and year of the Screening Visit. It is not considered ongoing if the start and end date are both completely missing.
** In the case of partial start and/or end dates, the medical history is considered having started/ended than or equal to 2 weeks prior to Screening Visit if:

1) If the date of the Screening Visit is less than the 14th of the month, the month and year of the partial start date is on or before the month and year of the Screening Visit AND (the month and year of the partial end date is on or before the month and year of the Screening Visit, the complete date of the end date is less than 14 days before the Screening Visit, OR the end date is missing)
2) If the date of the Screening Visit is greater than the 14th of the month, the month and year of the partial start date is before the month and year of the Screening Visit AND (the month and year of the partial end date is before the month and year of the Screening Visit, the complete date of the end date is less than 14 days before the Screening Visit, OR the end date is missing)

In the case of repeat Screening assessments, for purposes of identifying whether a medication was used or medical history occurred prior to the Screening Visit, the first Screening visit is used. For "finding out of range," the most recent assessment prior to randomization is used.

9.2 Changes to Planned Analyses in the Protocol

The following changes to v4.0 of the Protocol are made in this SAP:

- Section 3.1 of the protocol states that "[c]hange from baseline facial pain/pressure/fullness will be assessed using the number of evaluable subjects that report

facial pain/pressure/fullness ≥ 6 on NRS (0-10) at baseline and who also report pain level at 2 hours post-dose recorded in the eDiary." The analysis is not limited to subjects who report pain level at 2 hours post-dose.

- Section 4.2.2.1 of the protocol states, "Subjects will record the date and time of dosing…in their eDiary." Since subjects only directly record their date/time of dosing if they mistakenly dosed, the date/time of dosing in general will be imputed as the date/time the applicable eDiary is saved (see Section 7.1).
- Section 9.4.3 of the protocol states, "The number of subjects that use rescue medication at 24 post-dose will be analyzed after first imputing missing data at 24 hours to be failure (NC = F)." Since rescue medication use is recorded on paper form and not recorded on the eDiary, subjects with missing eDiary data at 24 hours are not imputed as failures for purposes of analyzing rescue medication use within 24 hours (see Section 6.3.4.5)

10 REFERENCES

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Envelope Summary Events	Status	Timestamps
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Certified Delivered	Security Checked	2/29/2024 2:37:06 PM
Signing Complete	Security Checked	2/29/2024 2:37:23 PM
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Document Title:	A Phase 2/3, Double Blind, Randomized, Placebo-Controlled, Safety and Efficacy Trial of BHV3000 (rimegepant) Orally Disintegrating Tablet for Acute Treatment of Chronic Rhinosinusitis With or Without Polyps

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