Statistical Analysis Plan: I5Q-MC-CGBD (Version 3.0)

A Phase 4, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Galcanezumab Versus Rimegepant in Adult Participants with Episodic Migraine

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STATISTICAL ANALYSIS PLAN

I5Q-MC-CGBD

A Phase 4, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Galcanezumab Versus Rimegepant in Adult Participants with Episodic Migraine

AUTHOR: PPD

VERSION NUMBER AND DATE: V3.0, 19May2023

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V3.0 (Dated 19May2023) for Protocol I5Q-MC-CGBD.

PPD

MODIFICATION HISTORY

SAP Version 1 is based on Protocol I5Q-MC-CGBD(d) and was approved prior to Interim Analysis and first unblinding.

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
V1.0	16Dec2022	PPD	Not Applicable – First Version
SAP Version 2.0 was approved before final data base lock. The overall changes incorporated in version 2 are summarized below:			
V2.0	24Mar2023	PPD	1) Clarified for the endpoints with acute medication use, which would use response to eDiary question #12 vs. CM_AHM (Sections 2.4, 18.2.4, 18.3.2.2, and 18.4.1). 2) Specified the listings that will be produced for the screen failures (Section 9.1). 3) Added language around the programmable deviations (Section 9.2). 4) Expanded the list of baseline characteristics that would be summarized (Section 10.0). 5) Clarified that baseline migraine headache days is derived using the diary data. 6) Provided equivalency rules for substance use. 7) Clarified how injection compliance is to be determined (Section 16.1)

			8) Noted how to manage duplicate headache dates (Section 18.1.1) 9) Change endpoint: Mean severity of remaining migraine or probable migraine headaches to Mean severity of migraine or probable migraine headaches 10) Clarified which AE summaries will be by PT vs. by SOC/PT 11) Added in the AE summaries needed for the CTR analyses
SAP Version 3.0 was approved before final data base lock. The overall changes incorporated in version 3 are summarized below:			
V3.0	19-May-2023	PPD	1. Removed the additional exploratory analysis based on daily migraine headache days (Section 2.3 (Table D); Section 18.4 (Table K) & Section 18.4.1 2. Clarified the definition of Concomitant Therapy (Section 14.2 and Appendix 2) 3. Added wording to clarify the definition for MSQ Total Score calculation (Section 18.1.4)

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
BMI	body mass index
BLQ	below the lower limit of quantification
CTMS	clinical trial management system
CTR	Clinical Trial Registry
DMC	data monitoring committee
ECG	electrocardiogram
EF	Emotional Function
eCRF	electronic case report form
ePRO	electronic patient-reported outcomes
GLIMMIX	Generalized linear mixed model procedure in SAS
IMP	Investigational medicinal product
IPD	Important protocol deviation
ITT	intent to treat
LLT	Lowest Level Term
LSMeans	Least Squares Means
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MIDAS	Migraine Disability Assessment
MMRM	Mixed-model repeated measures
MSQ	Migraine-Specific Quality of Life Questionnaire
ODT	orally disintegrating tablet
PGI-S	Patient Global Impression of Severity
PT	Preferred Term

Abbreviation	Term
QM	every month
QOD	every other day
RF-P	Role Function-Preventive
RF-R	Role Function-Restrictive
SAC	Statistical Analysis Center
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SC	subcutaneous
SOA	schedule of activities
SOC	System Organ Class
TBIL	total bilirubin
TEAE	treatment emergent adverse event
ULQ	above the upper limit of quantification
WHO	World Health Organization

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol I5Q-MC-CGBD. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol amendment D, dated 03-Nov-2022.

2. STUDY OBJECTIVES AND ESTIMANDS

2.1. PRIMARY OBJECTIVE

The primary objective is to test the hypothesis that galcanezumab is superior to rimegepant in the prevention of migraine headache in participants with episodic migraine. Superiority is defined as a greater improvement for galcanezumab compared to rimegepant, at an overall one-sided 0.025 significance level (equivalent to 2-sided 0.05 level), as measured by the percentage of participants with ≥50% reduction from baseline in monthly migraine headache days across the 3-month double-blind treatment period.

A migraine headache day is defined as any calendar day with a headache lasting longer than 30 minutes that meets the criteria for migraine or probable migraine (see endpoint definition in Section 18.1.1).

2.2. SECONDARY OBJECTIVES

2.2.1. KEY SECONDARY OBJECTIVES

If galcanezumab is statistically superior to rimegepant on the primary objective, the key secondary objectives, defined in Table A, will be tested with adjustment for multiplicity according to the methodology specified in Section 7.4.

Table A: Key Secondary Objectives and Endpoints

Objectives	Endpoints
To compare galcanezumab with rimegepant with respect to monthly migraine headache days.	The overall mean change from baseline in the number of monthly migraine headache days across the 3-month double-blind treatment period.

Objectives	Endpoints
To compare galcanezumab with rimegepant with respect to 75% response rate.	The percentage of participants with ≥75% reduction from baseline in monthly migraine headache days across the 3-month double-blind treatment period.
To compare galcanezumab with rimegepant with respect to monthly migraine headache days at: ○ Month 3 ○ Month 2 ○ Month 1	The mean change from baseline in the number of monthly migraine headache days at: ○ Month 3 ○ Month 2 ○ Month 1
To compare galcanezumab with rimegepant with respect to migraine headache days with acute (abortive) migraine treatment.	The overall mean change from baseline in the number of monthly migraine headache days requiring medication for the acute treatment of migraine or headache across the 3-month double-blind treatment period.
To compare galcanezumab with rimegepant with respect to change in functioning.	The mean change from baseline in the Role Function-Restrictive (RF-R) domain score of the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) at Month 3.
To compare galcanezumab with rimegepant with respect to 100% response rate.	The percentage of participants with 100% reduction from baseline in monthly migraine headache days across the 3-month double-blind treatment period.

2.2.2. OTHER SECONDARY OBJECTIVES

The other secondary objectives, defined in, Table B will be tested without multiplicity adjustment.

Table B: Other Secondary Objectives and Endpoints

Objectives	Endpoints
To compare galcanezumab with rimegepant with respect to changes in disability and health-related quality of life.	Changes from baseline to Month 3 on the following measures: • MSQ v2.1 total score, and Role Function-Preventive (RF-P) and Emotional Function (EF) domain scores • MIDAS (Migraine Disability Assessment) total score

Objectives	Endpoints
To describe the safety and tolerability of galcanezumab and rimegepant.	Analysis of: • treatment-emergent adverse events (TEAEs) • serious adverse events (SAEs) • discontinuation due to adverse events (AEs) • discontinuation rates • vital signs • laboratory measures

2.3. EXPLORATORY OBJECTIVES

The tertiary/exploratory objectives are listed in Table C and Table D.

Table C: Tertiary/Exploratory Objectives and Endpoints

Objectives	Endpoints
To compare galcanezumab with rimegepant with respect to change in participant global impression of the severity of migraine.	Mean change from baseline in the Patient Global Impression of Severity (PGI-S) at Month 3.
To compare galcanezumab with rimegepant with respect to change in moderate to severe headache days.	The overall mean change from baseline in the number of monthly moderate to severe headache days across the 3-month double-blind treatment period.
To compare galcanezumab with rimegepant with respect to change in Total Pain Burden.	Mean change from baseline in the Monthly Total Pain Burden across the 3-month double-blind treatment period.

Table D: Additional Exploratory Objectives and Endpoints.

Objectives	Endpoints
To assess onset of action*	
To compare galcanezumab with rimegepant with respect to weekly migraine headache days by Week 4, Week 3, Week 2, and Week 1 `	Mean change from baseline in the number of weekly migraine headache days in the months that galcanezumab was superior to rimegepant

To compare galcanezumab with rimegepant with respect to rimegepant with respect to 50% response rate at Month 3, Month 2, and Month 1	Percentage of participants with ≥50% reduction from baseline in monthly migraine headache days at Month 3, Month 2, and Month 1
To compare galcanezumab with rimegepant with respect to 50% response rate at weeks 4, Week 3, Week 2, and Week 1	Percentage of participants with ≥50% reduction in Weekly migraine headache days at weeks 4, 3, 2, 1 in the months that galcanezumab was superior to rimegepant
To assess sustained response	
To compare galcanezumab with rimegepant with respect to onset of 50% sustained response	The initial month at which galcanezumab was superior to rimegepant in the proportion of patients meeting at least a 50% reduction in monthly migraine headache days that is sustained at all subsequent months through Month 3
To assess other endpoints of interest	
To compare galcanezumab with rimegepant with respect to change in use of acute headache treatment	The overall mean change from baseline in the number of monthly days with acute headache medication use during the 3-month double-blind treatment period
To compare galcanezumab with rimegepant with respect to monthly moderate to severe migraine headache days	The overall mean change from baseline in the number of monthly moderate to severe migraine headache days across the 3-month double-blind treatment period
To compare galcanezumab with rimegepant with respect to 50% response rate in moderate to severe migraine headache days	Percentage of participants with ≥50% reduction from baseline in moderate to severe monthly migraine headache days across the 3-month double-blind treatment period

* Weekly onset was defined as the initial week at which galcanezumab was superior to rimegepant and maintained superiority at all subsequent weeks during that month..

2.4. ESTIMANDS

The primary estimand is the difference in effect for galcanezumab compared to rimegepant in participants with episodic migraine on the overall mean monthly 50% response rate (defined as participants with at least a 50% reduction from baseline in the frequency of migraine headache days) across the 3-month double-blind period (See estimand in Table E below).

All available monthly migraine headache data will contribute to analysis as long as baseline monthly migraine headache day values are available. Any migraine headache day after study

intervention discontinuation but within the double-blind period will still be used within the analysis as estimated from the model using the GLIMMIX procedure.

For all secondary endpoints, a similar estimand to the one used for the primary analysis will be employed. That is, the estimand of interest will be based on overall mean monthly estimates across/within the double-blind period and will be based on all available data during that period (even if collected after study intervention discontinuation). Additionally, baseline values must also be available.

The primary and the key secondary estimands are described in Table E:

Table E: Estimands

Objective	Estimands
Primary	
To assess whether galcanezumab is superior to rimegepant in the prevention of migraine in participants with episodic migraine	Treatment condition: Galcanezumab injections of 120 mg SC or rimegepant 75 mg ODT regardless of initiation of new preventive migraine medication, regardless the use of acute medication to treat a migraine headache and regardless of discontinuing treatment due to any reason (treatment policy strategy)
	Population: Participants who meet IHS-ICHD-3 (2018) criteria for a diagnosis of migraine with or without aura with an episodic frequency of 4 to 14 migraine headache days per month and fulfils the inclusion and exclusion criteria of the study.
	Variable (endpoint): The percentage of participants with ≥50% reduction from baseline in monthly migraine headache days across the 3-month double-blind treatment period
	Remaining intercurrent event handling: NA
	Summary measure: Difference of the overall mean monthly 50% response rate across the 3-month double-blind treatment period between treatment

Objective	Estimands
	groups
Primary Sensitivity 1	
To assess whether galcanezumab is superior to rimegepant in the prevention of migraine in participants with episodic migraine	Treatment condition: Galcanezumab injections of 120 mg SC or rimegepant 75 mg ODT regardless the use of acute medication to treat a migraine headache and regardless of discontinuing treatment due to any reason (treatment policy strategy)
	Population: Participants who meet IHS-ICHD-3 (2018) criteria for a diagnosis of migraine with or without aura with an episodic frequency of 4 to 14 migraine headache days per month and fulfils the inclusion and exclusion criteria of the study.
	Variable (endpoint): The percentage of participants with ≥50% reduction from baseline in monthly migraine headache days across the 3-month double-blind treatment period
	Remaining intercurrent event handling: The data after whichever of the following is sooner: the date of the last injection+30 days or the date of the last oral administration +1 day, will be discarded.
	Summary measure: Difference of the overall mean monthly 50% response rate across the 3-month double-blind treatment period between treatment groups
Primary Sensitivity 2	
To assess whether galcanezumab is superior to rimegepant in the prevention of migraine in participants	Treatment condition: Galcanezumab injections of 120 mg SC or rimegepant 75 mg ODT regardless of initiation of new preventive migraine medication, regardless the use of acute medication to treat an acute migraine attack and regardless of discontinuing treatment due to any reason (treatment policy strategy)

Objective	Estimands
with episodic migraine	Population: Participants who meet IHS-ICHD-3 (2018) criteria for a diagnosis of migraine with or without aura with an episodic frequency of 4 to 14 migraine headache days per month and fulfils the inclusion and exclusion criteria of the study.
	Variable (endpoint): The percentage of participants with ≥50% reduction from baseline in monthly migraine headache days across the 3-month double-blind treatment period
	Remaining intercurrent event handling: The participants that withdraw for lack of efficacy or tolerability, or participants that initiate a new preventive treatment will be considered as non-responders (composite strategy)
	Summary measure: Difference of the overall mean monthly 50% response rate across the 3-month double-blind treatment period between treatment groups
Primary Sensitivity 3	
To assess whether galcanezumab is superior to rimegepant in the prevention of migraine in participants with episodic migraine	Treatment condition: Galcanezumab injections of 120 mg SC or rimegepant 75 mg ODT regardless of initiation of new preventive migraine medication, regardless the use of acute medication to treat an acute migraine attack and regardless of discontinuing treatment due to any reason (treatment policy strategy)
	Population: Participants who meet IHS-ICHD-3 (2018) criteria for a diagnosis of migraine with or without aura with an episodic frequency of 4 to 14 migraine headache days per month and fulfils the inclusion and exclusion criteria of the study. (This population will not include participants that take acute medication and do not meet the migraine headache criteria at baseline.)
	Variable (endpoint):

Objective	Estimands
	The percentage of participants with ≥50% reduction from baseline in monthly migraine headache days across the 3-month double-blind treatment period
	Remaining intercurrent event handling: A migraine headache day will be considered when the participant takes acute medication regardless if the headache does not meet the criteria of migraine. This analysis will consider if a participant uses an acute medication (triptans or ergot derivatives) – as reported in the CM_AHM eCRF, regardless of whether a headache was reported. Subjects using a Triptan and/or ergot derivative will be identified by medical review of the eCRF.
	Summary measure: Difference of the overall mean monthly 50% response rate across the 3-month double-blind period between treatment groups
Primary Sensitivity 4	
To compare galcanezumab with rimegepant with respect to monthly migraine headache days	Treatment condition: Galcanezumab injections of 120 mg SC or rimegepant 75 mg ODT, regardless of initiation of new preventive migraine medication, regardless the use of acute medication to treat an acute migraine attack and regardless of discontinuing treatment due to any reason (treatment policy strategy)
	Population: Participants who meet IHS-ICHD-3 (2018) criteria for a diagnosis of migraine with or without aura with an episodic frequency of 4 to 14 migraine headache days per month and fulfils the inclusion and exclusion criteria of the study.
	Variable (endpoint): The overall mean change from baseline in the number of monthly migraine headache days across the 3-month double-blind treatment period
	Remaining intercurrent event handling: To assess the robustness of the primary analysis conclusions to

Objective	Estimands
	deviations from missing at random (MAR) assumption, this analysis will vary the assumptions of missing data for the primary analysis in a systematic way.
	Summary measure: Difference of the overall mean change from baseline in the number of monthly migraine headache days across the 3-month double-blind treatment period
Key Secondary	
To compare galcanezumab with rimegepant with respect to monthly migraine headache days	Treatment condition: Galcanezumab injections of 120 mg SC or rimegepant 75 mg ODT, regardless of initiation of new preventive migraine medication, regardless the use of acute medication to treat an acute migraine attack and regardless of discontinuing treatment due to any reason (treatment policy strategy)
	Population: Participants who meet IHS-ICHD-3 (2018) criteria for a diagnosis of migraine with or without aura with an episodic frequency of 4 to 14 migraine headache days per month and fulfils the inclusion and exclusion criteria of the study.
	Variable (endpoint): The overall mean change from baseline in the number of monthly migraine headache days across the 3-month double-blind treatment period
	Remaining intercurrent event handling: NA
	Summary measure: Difference of the overall mean change from baseline in the number of monthly migraine headache days across the 3-month double-blind treatment period
To compare galcanezumab	Treatment condition: Galcanezumab injections of 120 mg SC or rimegepant 75 mg ODT,

Objective	Estimands
with rimegepant with respect to 75% response rate	regardless of initiation of new preventive migraine medication, regardless the use of acute medication to treat an acute migraine attack and regardless of discontinuing treatment due to any reason (treatment policy strategy)
	Population: Participants who meet IHS-ICHD-3 (2018) criteria for a diagnosis of migraine with or without aura with an episodic frequency of 4 to 14 migraine headache days per month and fulfils the inclusion and exclusion criteria of the study.
	Variable (endpoint): The percentage of participants with ≥75% reduction from baseline in monthly migraine headache days across the 3-month double-blind treatment period
	Remaining intercurrent event handling: NA
	Summary measure: Difference of the overall mean monthly 75% response rate across the 3-month double-blind period between treatment groups
To compare galcanezumab with rimegepant with respect to monthly migraine headache days at each month	Treatment condition: Galcanezumab injections of 120 mg SC or rimegepant 75 mg ODT, regardless of initiation of new preventive migraine medication, regardless the use of acute medication to treat an acute migraine attack and regardless of discontinuing treatment due to any reason (treatment policy strategy)
	Population: Participants who meet IHS-ICHD-3 (2018) criteria for a diagnosis of migraine with or without aura with an episodic frequency of 4 to 14 migraine headache days per month and fulfills the inclusion and exclusion criteria of the study.
	Variable (endpoint): The mean change from baseline in the number of monthly migraine headache days at:

Objective	Estimands
	o Month 3 o Month 2 o Month 1
	Remaining intercurrent event handling: NA
	Summary measure: Difference of the mean change from baseline in the number of monthly migraine headache days at: o Month 3 o Month 2 o Month 1
To compare galcanezumab with rimegepant with respect to migraine headache days with acute (abortive) migraine treatment	Treatment condition: Galcanezumab injections of 120 mg SC or rimegepant 75 mg ODT, regardless of initiation of new preventive migraine medication, regardless the use of acute medication to treat an acute migraine attack and regardless of discontinuing treatment due to any reason (treatment policy strategy). Medication use will be based on response to question 12 of the diary.
	Population: Participants who meet IHS-ICHD-3 (2018) criteria for a diagnosis of migraine with or without aura with an episodic frequency of 4 to 14 migraine headache days per month and fulfils the inclusion and exclusion criteria of the study.
	Variable (endpoint): The overall mean change from baseline in the number of monthly migraine headache days requiring medication for the acute treatment of migraine or headache across the 3-month double-blind treatment period
	Remaining intercurrent event handling: NA
	Summary measure: Difference of the overall mean change from baseline in the number

Objective	Estimands
	of monthly migraine headache days requiring medication for the acute treatment of migraine or headache across the 3-month double-blind treatment period
To compare galcanezumab with rimegepant with respect to change in functioning	Treatment condition: Galcanezumab injections of 120 mg SC or rimegepant 75 mg ODT, regardless of initiation of new preventive migraine medication, regardless the use of acute medication to treat an acute migraine attack and regardless of discontinuing treatment due to any reason (treatment policy strategy)
	Population: Participants who meet IHS-ICHD-3 (2018) criteria for a diagnosis of migraine with or without aura with an episodic frequency of 4 to 14 migraine headache days per month and fulfils the inclusion and exclusion criteria of the study.
	Variable (endpoint): The mean change from baseline in the Role Function-Restrictive (RF-R) domain score of the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) at Month 3
	Remaining intercurrent event handling: NA
	Summary measure: Difference of the mean change from baseline in the Role Function-Restrictive (RF-R) domain score of the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) at Month 3
To compare galcanezumab with rimegepant with respect to 100% response rate	Treatment condition: Galcanezumab injections of 120 mg SC or rimegepant 75 mg ODT, regardless of initiation of new preventive migraine medication, regardless the use of acute medication to treat an acute migraine attack and regardless of discontinuing treatment due to any reason (treatment policy strategy)
	Population: Participants who meet IHS-ICHD-3 (2018) criteria for a diagnosis

Objective	Estimands
	of migraine with or without aura with an episodic frequency of 4 to 14 migraine headache days per month and fulfils the inclusion and exclusion criteria of the study.
	Variable (endpoint): The percentage of participants with 100% reduction from baseline in monthly migraine headache days across the 3-month double-blind treatment period
	Remaining intercurrent event handling: NA
	Summary measure: Difference of the overall mean monthly 100% response rate across the 3-month double-blind period between treatment groups

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

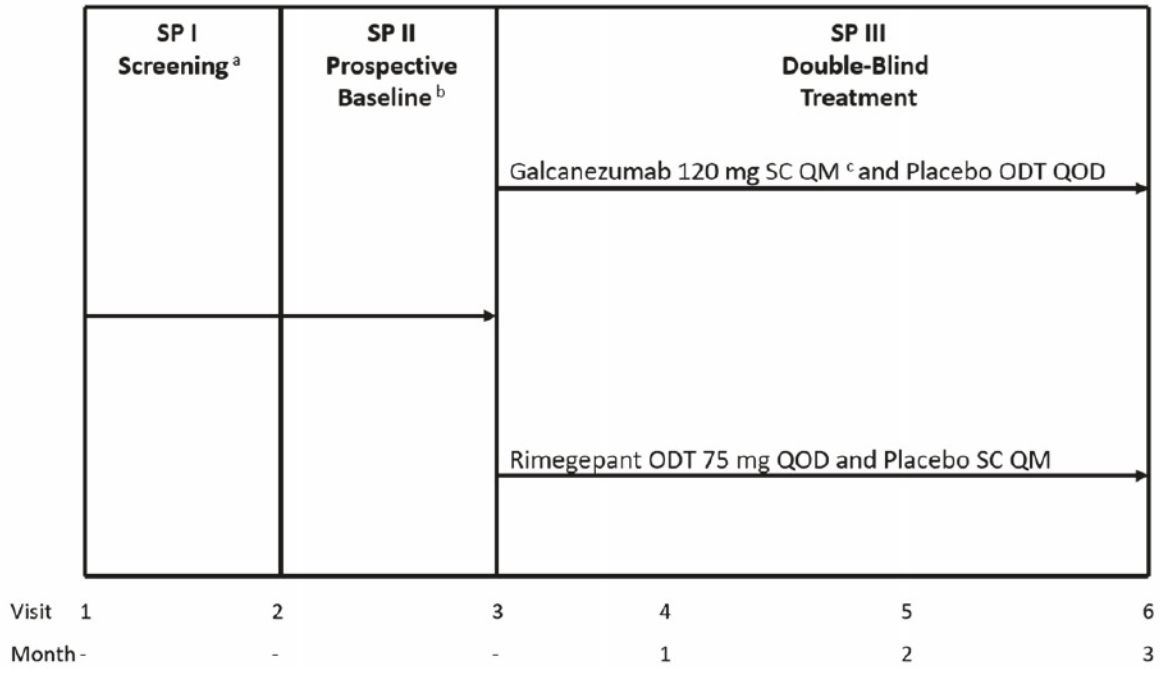
Study CGBD is a multi-site, randomized, double-blind, double-dummy, parallel-group, Phase 4 study with 3 study periods in participants who meet IHS-ICHD-3 (2018) criteria for a diagnosis of migraine with or without aura with an episodic frequency of 4 to 14 migraine headache days per month. For additional details about each study period see section 4.1 of the protocol.

Treatments:

- Galcanezumab 120 mg subcutaneous (SC) once monthly, with a 240 mg loading dose as the initial dose
- Rimegepant 75 mg orally disintegrating tablet (ODT) every other day

Participants will be given placebo in a double-dummy design. Randomization will be stratified by baseline migraine frequency (<8 migraine headache days versus ≥8 migraine headache days).

Figure A: Schema



Abbreviations: ODT = oral disintegrating tablet; QM = every month; QOD = every other day; SC = subcutaneous; SP = Study Period.

a Screening Period is 3-30 days in length.

b Eligibility is determined between a minimum of 30 days and a maximum of 40 days. Investigators have up to 5 additional days, if needed, to schedule participant's Visit 3 appointment.

c Randomization occurs at Visit 3. Participants randomized to galcanezumab will receive a loading dose of 240 mg at the first administration only.

Note: Participants will be given placebo in a double-dummy design.

3.1.1. Sample Size Determination

The study will screen an estimated 1150 potential study participants to ensure a minimum of approximately 575 randomized participants. Based on the assumption of treatment difference of 12%, the minimum sample size of approximately 575 provides more than 85% power at a two-sided significance level of 5% and a dropout rate of no more than 10%, with the opportunity to increase the final sample size at the interim analysis if indicated to maintain a well-powered

study. To preserve blinding, details of the sample size and power calculations are omitted from the protocol and are provided to the ERB in a separate document. If the interim is not performed, then the trial will enroll to a sample size as specified in the ERB document.

3.2. Schedule of Activities

Schedule of activities (SoA) can be found in Section 1.3 of the protocol.

3.3. Changes to Analysis from Protocol

In addition to the exploratory objectives and endpoints specified in the protocol, this SAP contains additional exploratory objectives and endpoints to assess onset of action, sustained response, and other endpoints of interest. See Section 2.3 for details.

4. Planned Analyses

The following analyses will be performed for this study:

- Interim Analysis
- Final Analysis

4.1. Data Monitoring Committee

There will be no DMC for this study.

4.2. Interim Analysis

One interim analysis is planned for this study. The interim analysis will occur during Study Period III (double-blind treatment); this may result in increasing the sample size or continuing with the planned sample size. Details will be documented in a separate Statistical Analysis Center (SAC) SAP and ERB supplement.

To minimize the potential bias that results from performing an interim analysis, the interim analysis for this study will be conducted by a SAC external to the study team, but internal to Lilly.

Only the SAC is authorized to evaluate unblinded interim analyses results to make an informed

decision. Study sites will receive information about interim results ONLY if they need to know for the safety of their patients.

Unblinding details will be specified in a separate unblinding plan document or in the unblinding plan section of the SAC SAP.

4.3. Final Analysis

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following Sponsor Authorization of this Statistical Analysis Plan, Database Lock, Sponsor Authorization of Analysis Sets and Unblinding of Treatment.

5. Analysis Sets

Agreement and authorization of participants included/excluded from each analysis set will be conducted prior to the unblinding of the study. Unless otherwise specified, all analyses will be conducted according to the ITT principle on the ITT population. That is, participants will be analyzed according to the treatment they were randomized, regardless of whether they actually received a different treatment.

5.1. Intention to Treat (ITT) set

The Intention to Treat (ITT) set will contain all randomized participants who receive at least 1 dose of both study interventions (injection and ODT). Participants will be included in the analyses according to their randomized treatment.

When change from baseline is assessed, the analysis will include participants in the ITT population who have a baseline and a postbaseline measurement.

5.2. Safety Analysis Set (SAF)

The safety analysis set (SAF) will contain all participants who are exposed to study intervention (either injection or ODT). Participants will be analyzed according to the treatment they actually received.

If there is any doubt whether a participant was treated or not, it will be assumed that the

participant has been treated for the purposes of analysis.

When change from baseline is assessed, the participant will be included in the analysis only if the participant has a baseline and a postbaseline measurement.

6. General Considerations

6.1. Reference Start Date and Study Day

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events. It will appear in every listing where an assessment date or event date appears. Reference start date is defined as the day of the first dose of study intervention.

Study day will be computed as follows:

> Study Day = (Date of event – Date of first dose of study treatment) + 1 if the date of the event is on or after the date of the first dose of study treatment;
> Study Day = (Date of event – Date of first dose of study treatment) if the date of the event is prior to the date of the first dose of study treatment;

where the event can be an adverse event, medical history event, start/end of concomitant medication, laboratory assessment, etc.

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings.

For participants who are randomized but do not receive study treatment, study day will be calculated using the date of randomization as the reference start date.

6.2. Baseline and Post-Baseline

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments). If the time of the measurement is collected, both the date and time will be used to determine the baseline. For example, if assessments collected at Visit 1 to Visit 3 (prior to dosing at Visit 3, and this can be confirmed

by time of the assessment and dosing time), the last non-missing measurement at Visit 3 prior to the first dosing will be counted as baseline. In the case where the last non-missing measurement and the reference start date coincide and the time is not collected, that measurement will be considered pre-baseline if the assessment is planned per protocol to take place prior to the first dose of study medication.

Vital Parameters (Pulse, SBP, and DBP) as these are captured in triplicates. Baseline and post-baseline will be the mean of the triplicate value. If only one value available then that value is used, if 2 values are available then the 2 values are averaged and used for the value at that visit.

Adverse Events (AEs) and medications commencing on the reference start date will be considered post-baseline unless otherwise indicated based on available start date/time combination or collected eCRF information that identifies the individual event/medication as starting prior to first study medication administration.

For treatment emergent abnormal laboratory or vital signs, the baseline criterion considers all predose records, instead of the last record only. That is

- A treatment-emergent abnormal result is defined as a change from normal at all predose/baseline visits to abnormal at any time during the treatment period. Patients with all normal values at predose/baseline will be included in the analysis of treatment-emergent abnormal laboratory values
- A treatment-emergent high result is defined as a change from a value less than or equal to the high limit at all predose/baseline visits to a value greater than the high limit at any time during the treatment period. Patients with all normal or low values at predose/baseline (no high values) will be included in the analysis of treatment-emergent high laboratory values.
- A treatment-emergent low result is defined as a change from a value greater than or equal to the low limit at all predose/baseline visits to a value less than the low. Patients with all normal or high values at predose/baseline (no low values) will be included in the analysis of treatment-emergent low laboratory values.

Baseline monthly migraine headache days value for primary efficacy analysis is calculated with a time window of 30 to 40 days (normalized to 30 days).

Participant population with baseline and post-baseline definitions by type of analysis can be found in Table F:

Table F: Participant Population with Baseline and Post-Baseline Definitions by Type of Analysis

Analysis	Participant Population	Baseline Observation	Post-baseline Observation(s)
Primary/secondary/exploratory efficacy analyses (repeated measures or average of observed monthly values)	ITT Set with a baseline and at least one post-baseline observation	Visit 3	All scheduled visits 3<Visits ≤ 6
Primary/secondary/exploratory efficacy analyses	ITT Set with a baseline and at least one post-baseline observation	Visit 3	Last of Visit 3.01-6
Quality of Life analyses	ITT Set with a baseline and at least one post-baseline observation	Visit 3	All scheduled visits 3<Visits ≤ 6
TEAEs	Safety Analysis Set	All Visits 1-3	All Visits 3.01-6
Serious adverse events, discontinuations due to adverse events	Safety Analysis Set	NA	All Visits 3.01-6
Treatment emergent abnormal laboratory values	Safety Analysis Set with normal laboratory values at all non-missing baseline visits (with respect to direction being analyzed) and who have at least one post-baseline observation	Low: Minimum value from Visits 1-3 High: Maximum value from Visits 1-3	Low: Minimum value from Visits 3.01-6 High: Maximum value from Visits 3.01-6

Analysis	Participant Population	Baseline Observation	Post-baseline Observation(s)
Treatment emergent changes in temperature	Safety Analysis Set with normal temperature values at all non-missing baseline visits (with respect to direction being analyzed) and who have at least one post-baseline observation	Low: Minimum value from Visits 1-3 High: Maximum value from Visits 1-3	Low: Minimum value from Visits 3.01-6 High: Maximum value from Visits 3.01-6
Treatment emergent changes in blood pressure (average of the triplicate value)	Safety Analysis Set with normal blood pressure values at all non-missing baseline visits (with respect to direction being analyzed) and who have at least one post-baseline observation	Low: Minimum value from Visits 1-3 High: Maximum value from Visits 1-3	Low: Minimum value from Visits 3.01-6 High: Maximum value from Visits 3.01-6
Treatment emergent changes in pulse (average of the triplicate value)	Safety Analysis Set with normal pulse values at all non-missing baseline visits (with respect to direction being analyzed) and who have at least one post-baseline observation	Low: Minimum value from Visits 1-3 High: Maximum value from Visits 1-3	Low: Minimum value from Visits 3.01-6 High: Maximum value from Visits 3.01-6

- Abbreviations: ITT = intent-to-treat; forward; NA = not applicable; TEAE = treatment-emergent adverse event.
- Note: Visit 3.01 indicates the first unscheduled visit occurring after Visit 3 and prior to Visit 4.

6.3. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries but will contribute to the

hepatic lab analyses and baseline value, or best / worst case value where required (e.g. shift table).
In case of a retest (for example, a blood sample tested twice on the same day with the same analysis visit number assigned), the latest available measurement for that visit will be used for the by-visit summaries.
Listings will include scheduled, unscheduled, retest and early discontinuation data.

6.4. WINDOWING CONVENTIONS

The following describes assignment of visit windows to the following data for purposes of analysis:

- Screening lasts from 3 to 30 days, approximately.
- Eligibility is determined between a minimum of 30 days and a maximum of 40 days.
- For scheduling purposes, a month is 30 days.

See Section 18.1.1. for the derivation of diary time periods. No other assignment of visit will be done – visit as collected will be used.

6.5. STATISTICAL TESTS

The primary objective is to demonstrate that galcanezumab is superior to rimegepant in reducing migraine headaches as measured by average monthly response rate across a 3-month period (in this case, the 3-month double-blind period). If one lets π_G *and* π_R = the true 3-month average monthly 50% response rates for galcanezumab and rimegepant respectively, *the null and alternative hypotheses are as follows:*

$H_0: \pi_G \leq \pi_R$ against $H_a: \pi_G > \pi_R$

The corresponding hypotheses for secondary objectives with response rate based estimands (for example, average monthly 75% response rate) are identical as those for the primary (with corresponding changes to the true response rate of interest).

For secondary objectives that are to demonstrate the superiority of galcanezumab over rimegepant as measured by continuous measures (for example, reduction from baseline in monthly migraine headache days), the null and alternative hypotheses would be of the form:

$H_0: \mu_G \leq \mu_R$ against Ha: $\mu_G > \mu_R$

Where μ_G *and* μ_R are the true mean reductions for galcanezumab and rimegepant, respectively.

While all hypotheses given above are 1-sided, these hypotheses will operationally be evaluated via 2-sided tests.
The default significant level will be (5%); confidence intervals will be 95% (2-sided), unless otherwise specified in the description of the analyses.

6.6. Common Calculations

For quantitative measurements, change from baseline will be calculated as:

Test Value at Visit X – Baseline Value

6.7. Software Version

All analyses will be conducted using SAS version 9.4 or higher.

7. Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. Details of statistical analysis methods will be described in this SAP with the final SAP approved prior to study unblinding being the official version for this study.

Unless otherwise specified, analyses will be conducted on the ITT set for efficacy analyses and on the SAF for safety analyses (see Section 5).

7.1. Adjustments for Covariates in Analyses

For both binary (e.g. response rates) and continuous analyses (e.g. changes in headache days), continuous baseline measure will be specified in the model which will include the fixed, categorical effects of treatment, month, and treatment-by-month interaction, as well as the continuous, fixed covariate of baseline monthly migraine headache days value

If the variable to be analysed relies on migraine headache day data, then use the continuous value of baseline migraine headache days as covariate, or if the variable being analyzed does not rely on migraine headache day data, then the model will use the baseline number of migraine headache days category (<8 vs ≥8) as a covariate for the MMRM, AN(C)OVA, and GLIMMIX procedure .

7.2. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers in the US.

7.3. MISSING DATA

For the repeated measures analyses, the model parameters are simultaneously estimated using restricted likelihood estimation incorporating all of the observed data. Estimates have been shown to be unbiased when the missing data are missing at random.

Please refer to Section 18.2.2 for approach to handling missing diary data for derivation of the number of migraine headache days and other efficacy measures (with the exception of migraine attacks) derived from ePRO data per 30-day period.

7.3.1. APPROACHES TO HANDLING MISSING DIARY DATA FOR THE DERIVATION OF MIGRAINE ATTACK:

For the analysis of migraine attack, the LOCF method will be used to impute the missing ePRO diary days. In other words, if the participant was migraine headache free on the day before the missing ePRO diary day, this would be carried forward as no migraine headache day until the actual next non-missing diary day. On the other hand, if the day before the missing diary day is a migraine headache day, then it would be carried forward as migraine headache day until the next non-missing diary day. The imputation will be carried out for all the missing diary days between the first non-missing to the last day during that period.
If the compliance rate for a monthly interval is ≤50%, the number of migraine attacks during that month will be considered missing. Please refer to Section 17 for diary compliance rate calculation.

7.4. MULTIPLE COMPARISONS / MULTIPLICITY

The statistical comparisons for the primary efficacy endpoint and the key secondary endpoints will be carried out in a hierarchical order as depicted in Figure B. This means that statistically significant results for the comparison in the higher rank (primary, then ranked secondary variables) are required to initiate the testing of the next comparison in the lower rank. Since a step-down procedure is used, each comparison will be tested at a significance level of 0.05 and an overall alpha level of 0.05 will be preserved.
Type I error due to multiple comparisons for the primary and key secondary objectives will

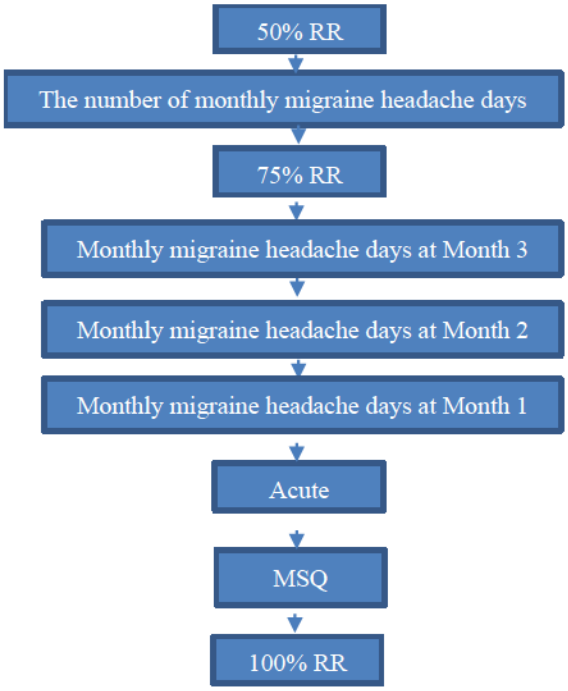
be controlled using sequential gating procedure (Kordzakhia and Dmitrienko [2013], Millen and Dmitrienko [2011], and Bretz et al. [2009]).

If galcanezumab is statistically superior to rimegepant on the primary objective, the following key secondary objectives will be tested:

- To compare galcanezumab with rimegepant with respect to monthly migraine headache days.
- To compare galcanezumab with rimegepant with respect to 75% response rate.
- To compare galcanezumab with rimegepant with respect to monthly migraine headache days at:
  - Month 3
  - Month 2
  - Month 1
- To compare galcanezumab with rimegepant with respect to migraine headache days with acute (abortive) migraine treatment.
- To compare galcanezumab with rimegepant with respect to change in functioning.
- To compare galcanezumab with rimegepant with respect to 100% response rate.

In order to provide strong control of the Type I error rate across the set of primary and key secondary hypothesis tests, we plan to implement the multiple testing procedure depicted below in Figure B. Full alpha allocation is provided to the family of primary null hypothesis (i.e. corresponding to the primary objective of the trial) at the start of the procedure; thus, testing of secondary null hypotheses (i.e. corresponding to the Key Secondary objectives of the trial) is contingent on successfully rejecting a primary null hypothesis.

Figure B: Multiple testing procedures



Abbreviations: 50% RR = 50% response rate in the number of monthly migraine headache days; 75% RR = 75% response rate in the number of monthly migraine headache days; 100% RR = 100% response rate in the number of monthly migraine headache days; Acute Meds = the number of monthly migraine headache days with the use of acute (abortive) treatment; MSQ = Role Function-Restrictive (RF-R) domain score of the Migraine-Specific Quality of Life Questionnaire.

See Section 2.4 for full definitions of endpoints.

Notations

H_{01}: the primary null hypothesis.

H_{02}: the null hypothesis associated with the number of monthly migraine headache days.

H_{03}: the null hypothesis associated with 75% response rate.

H_{04}: the null hypothesis associated with monthly migraine headache days at Month 3.

H_{05}: the null hypothesis associated with monthly migraine headache days at Month 2.

H_{06}: the null hypothesis associated with monthly migraine headache days at Month 1.

H_{07}: the null hypothesis associated with the number of monthly migraine headache days with acute medication use.

H_{08}: the null hypothesis associated with MSQ.

H_{09}: the null hypothesis associated with 100% response rate.

Let $\alpha = 0.05$ two-sided.

Sequential Algorithm and Decision Rules

The multiple testing procedure may be conducted sequentially as follows.

Step 1. Test H_{01} at level α.

If H_{01} is rejected, then

- Declare the primary objective is met
- Go to step 2

Else,

- Go to step 10.

Step 2. Test H_{02} at level α.

If H_{02} is rejected, then

- Declare the secondary objective has been met
- Go to step 3

Else,

- Go to step 10

Step 3. Test H_{03} at level α.

If H_{03} is rejected, then

- Declare the secondary objective has been met
- Go to step 4

Else,

- Go to step 10

Step 4. Test H_{04} at level α.

If H_{04} is rejected, then

- Declare the secondary objective has been met
- Go to step 5

Else,

- Go to step 10

Step 5. Test H_{05} at level α.

If H_{05} is rejected, then

- Declare the secondary objective has been met
- Go to step 6

Else,

- Go to step 10

Step 6. Test H_{06} at level α.

If H_{06} is rejected, then

- Declare the secondary objective has been met
- Go to step 7

Else,

- Go to step 10

Step 7. Test H_{07} at level α.

If H_{07} is rejected, then

- Declare the secondary objective has been met
- Go to step 8

Else,

- Go to step 10

Step 8. Test H_{08} at level α.

If H_{08} is rejected, then

- Declare the secondary objective has been met
- Go to step 9

Else,

- Go to step 10

Step 9. Test H_{09} at level α.

If H_{09} is rejected, then

- Declare the secondary objective has been met
- Go to step 10

Step 10. retain all non-rejected null hypotheses and discontinue testing

If the sample size is increased based on the interim analysis results, an appropriate methodology will be utilized at the completion of the study to control the Type-I error and the details of the final analysis will be outlined in the SAP before the final database lock. If the sample size is not increased based on the interim results, there will be no adjustments to the test statistic at the completion of the study to control the Type-I error and a conventional final analysis will be utilized.

7.5. Active-Control Studies Intended to Show Non-inferiority or Equivalence

Not applicable.

7.6. Examination of Subgroups

No subgroup analyses will be performed for this study.

8. Output Presentations

APPENDIX 1 shows conventions for presentation of data in outputs.
The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by IQVIA Biostatistics.

9. Disposition and Withdrawals

All participants who provide informed consent will be accounted for in this study.

9.1. Disposition

The number and percentage of all ITT participants who complete the study, or discontinue early, or who discontinue treatment but stay in the study to complete all study assessments will be tabulated for all treatment groups for both overall and by visit and by type of discontinuation (i.e. discontinuation from treatment or study). Reasons for discontinuation will be compared between treatment groups using Fisher's exact test with the ITT population. Subcategories of discontinuation from treatment or study due to subject decision will be summarized too. Listings of screen failures and subjects in post-study hepatic follow-up and

the reasons for discontinuation will be presented.
Participant allocation by investigator will be summarized and listed for all ITT participants.

9.2. PROTOCOL DEVIATIONS

Throughout the clinical conduct of the study, protocol deviations will be reported by site via Clinical Trial Management System (CTMS) according to the protocol deviation management plan. Protocol deviations identified in CTMS may be imported into the database if determined to be important and cross-checked with the programmable important protocol deviations. For the programmable deviations of excluded medications, input from the clinical team will be used to properly identify these medications.
The categories in CTMS that may result in important protocol deviations include but are not limited to the following:

Informed Consent and Process
Inclusion Criteria
Exclusion Criteria
Concomitant Medication
Laboratory Assessment
Study Procedures
Safety
Randomization
IP compliance
Blinding
Subject Discontinuation
Other Criteria

During the review of all reported protocol deviations, important deviations that potentially compromise the data integrity and participants' safety will be identified. Additional important protocol deviations (IPDs), such as Data Quality Criteria, will be identified via programming APPENDIX 3 contains a table that lists the categories, subcategories, and study-specific terms of programmable important protocol deviations source of identification, and the method to identify each deviation. Per study team's discretion, for non-programmable protocol deviations, additional categories, and subcategories other than the ones in Appendix 3, Table 1 can always be added into the final non-programmable protocol deviations list, as deemed necessary.

A table and listing of IPDs for the ITT set during baseline, double-blind treatment phase, will be provided by each randomized treatment arm and overall.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the ITT set. Comparisons between treatment groups will be performed using Fisher's exact test for categorical data and ANOVA with treatment as independent variables in the model for continuous data.

The following demographic and other baseline characteristics will be reported for this study:

- Age (years) - calculated relative to date of consent
- Sex (Male, Female)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Applicable, Not Reported)
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- Time since migraine diagnosis (years)
- Participants reporting aura
- Prior migraine preventative treatment
- Patient Global Impression of Severity
- MIDAS Total Score
- MSQ Total Score
- Role Function-Preventive Score
- Role Function-Restrictive Score
- Emotional Function Score

10.1. DERIVATIONS

BMI (kg/m^2) = weight (kg) / height $(m)^2$

11. DISEASE HISTORY

The following disease history characteristics will be summarized overall and by treatment group based on the ITT:

- Duration of migraine illness (years) – calculated relative to date of first dose of study treatment.
- Migraine and/or headache measures per 30-day baseline period.
  - number of migraine headache days
  - number of migraine headache days with acute (abortive) medication use
  - number of migraine headache hours
  - number of migraine attacks
  - number of headache days
  - number of moderate-severe headache days
  - number of headache hours
  - mean severity of migraine headaches
  - number of migraine headache days with aura
  - number of migraine headache days with nausea and/or vomiting
  - number of migraine headache days with photophobia and phonophobia
  - number of migraine headache days with prodromal symptoms other than aura
  - Prior migraine preventive treatment:
    - Without prior migraine preventive treatment
    - With prior migraine preventive treatment and did not fail
    - With prior migraine preventive treatment and failed at least 1 medication
    - With prior migraine preventive treatment and failed at least 2 medications.
    - Number of prior migraine treatment failed: 1, 2, 3, …
- Baseline number of migraine headache day category (<8 versus ≥8, based on patient diary)
- PGI-S
- Alcohol, tobacco, caffeine, and nicotine use

Comparisons between treatment groups will be performed using Fisher's exact test for categorical data and ANOVA with treatment as independent variables in the model for continuous data.
All disease history characteristics will be listed.

11.1. DERIVATIONS

Time since migraine diagnosis (days) is calculated as (Date of first dose of study treatment – Date of migraine diagnosis)
Number of migraine headache days with aura is calculated as the total number of migraine headache days with an answer of "yes" to Question 10 from ePRO diary data in a 30-day period.
Number of migraine headache days with nausea and/or vomiting is calculated as the total number of migraine headache days with an answer of "yes" to Question 8 in a 30-day period
Number of migraine headache days with photophobia and phonophobia is calculated as the total number of migraine headache days with an answer of "yes" to Question 7 in a 30-day period.
Number of migraine headache days with prodromal symptoms other than aura is calculated as the total number of migraine headache days with an answer of "yes" to Question 11 in a 30-day period.

Please refer to Section 14 for derivations for prior migraine preventive treatment and failures.
Please refer to Section 18.1.1 for derivations for migraine and/or headache measures.

Conversion of each substance to equivalent units was done as follows:
If SUBSTANCE = 'BEER', 'COFFEE', or 'SODA', set to '12oz'.
If SUBSTANCE = 'WINE', set to '5oz'.
If SUBSTANCE = 'SPIRITS' or 'EXPRESSO', set to '1.5oz'.
If SUBSTANCE = 'TEA', set to '6oz or 180mL'.
If SUBSTANCE = 'ENERGY DRINK', set to '16oz'.
If SUBSTANCE = 'ENERGY SHOT', set to '2oz'.
All of substance units were left as is.
Conversion of substance use to weekly use is as follows:
If daily use is reported, the amount is multiplied by 7;

If monthly use is reported, the amount is divided by 4.33;
If yearly use is reported, the amount is divided by 52;
If weekly use is reported, the amount is left as is.

12. PRE-EXISTING CONDITIONS AND MEDICAL HISTORY

Pre-existing conditions and medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary version 24.0 or higher and summarized via System Organ Class (SOC) and Preferred Term (PT).

Pre-existing conditions and medical history will be summarized by SOC and PT overall and by randomized treatment group based on the ITT set, and comparison between treatment groups will be performed using Fisher's exact test. All pre-existing conditions and medical history data will be listed.

13. CONCOMITANT ILLNESSES

Not applicable.

14. THERAPIES/MEDICATIONS

14.1. PREVIOUS MIGRAINE PREVENTION THERAPY

The proportion of participants who received previous migraine prevention therapy (as reported on the CM_PTH CRF page), and the proportion of participants with response to the previous migraine prevention therapy within each of the 6 categories (to enter this trial, medical history event, adequate response, inadequate response, no response, and treatment availability) will be summarized for all ITT participants. Treatment group comparisons will be done using Fisher's exact test. Previous migraine prevention therapies are those therapies that started prior to the date of the first dose and stopped prior to or at the date of first dose and indication is "primary study condition" or corresponding medical history event preferred term that includes "migraine".

Reasons for Discontinuation of Previous Migraine Prevention Therapy will be summarized by medication. If a participant failed the same medication multiple times with different reasons, the

most recent reason will be included in the summary table.

14.2. CONCOMITANT THERAPY

The proportion of participants who received concomitant medication collected from eCRF (CM) as well as acute headache/migraine medications (CM_AHM) will be summarized for all ITT participants. Concomitant therapies are those which started, stopped or continued during the double blind treatment period (SPII). If medication started and stopped on the same day of first dose, it will still be considered as concomitant medication. If a medication started before the first day of injection but stopped on the same day of injection, then it will not be counted as concomitant medication.

Treatment group comparisons will be done using Fisher's exact test with ITT population.

Medications will be coded using World Health Organization (WHO) Drug Global dictionary, version September 2021 B3 or later.

See APPENDIX 2 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior or concomitant, the medication will be classified by the worst case, i.e. concomitant.

14.3. ACUTE MEDICATIONS

Acute medications as collected in eCRF will be summarized.

15. STUDY MEDICATION EXPOSURE

Patients will receive the investigational medicinal product (IMP) at the following planned time points:
Beginning of Month 1 (Visit 3)
Beginning of Month 2 (Visit 4)
Beginning of Month 3 (Visit 5)

The number of Injections planned at each time point are as follows:

- Month 1 (Visit 3), two injections, count as 1 dose injected

- Month 2 (Visit 4), one injection, count as 1 dose injected
- Month 3 (Visit 5), one injection, count as 1 dose injected

The following information will be recorded on the eCRF for each dose:

- Confirmation that the patient received the IMP (including reason if the IMP was not given)
- Date and time of administration

A summary and listing will be produced, for treatment phase (SP III), of the number and percentage of patients with 1 dose, 2 doses, or 3 doses injected. Comparisons between treatments for duration of IMP exposure will be performed using an ANOVA with treatment in the model. Number of patients with 1 dose, 2 dose, or 3 doses injected will be compared between treatment groups with Fisher's exact test. In addition, injections not administered will be listed.

15.1. DERIVATIONS

The following will be derived from the information recorded on the eCRF:

For treatment phase (SP III), duration of exposure in days is calculated as treatment phase disposition date (i.e. study disposition date) – first date IMP administered +1 for subjects or one of the below if it is earlier:

For ODT:
Duration of exposure (days) = date of last study medication administration – date of first study medication administration + 1.

For Injection:
Duration of exposure (days) = date of last study medication administration – date of first study medication administration + 30.

16. STUDY MEDICATION COMPLIANCE

Compliance to study medication will be presented for the SAF.

Comparisons between treatments for treatment compliance will be performed using an ANOVA with treatment in the model.

16.1. DERIVATIONS

Treatment compliance for injection is based on the eCRF data will be calculated as:

$$\frac{\text{number of doses received} * 100}{\text{number of intended doses}}$$

The intended number of injections is 2 injections loading dose and 1 injection monthly for the next 2 months, resulting in a total of 3 monthly doses (4 syringes for injection). Thus, for participants in Safety analysis set who discontinued the study after less than 1 month treatment, the number of intended injections is 2.
The intended ODT dose is 1 tablet every other day starting on Day 1, thus the expected total number of tablets is the integer part of (the treatment duration in days plus 1 and divided by 2).

For participants in Safety analysis set who stayed on treatment for 1 month or longer, the number of intended injections is 2 plus the integer part of the treatment duration in months. Note for injections, if subject is compliant, no unused injections should be returned.

Compliance for ODT, based on the drug accountability data, will be calculated as the number of tablets taken (total dispensed – total returned) divided by the prescribed number of tablets expressed as a percentage, see calculations below.
Compliance (%) = (Actual total number of tablets / Expected total number of tablets) x 100
For ODT, it is possible depending on the length of the treatment phase, some unused ODT may be returned. If the date of last dose is available, then the date of last dose of ODT should be used for determining the expected number of tablets.

For subjects without a date of last dose and no study drug returned and subjects report taking their study medication: it will be assumed that subjects took the medication as prescribed.

Comparisons between treatments for treatment compliance will be performed using an ANOVA with treatment in the model. For this analysis, partial dose (for example, a patient only got 1 injection instead of 2) will be considered as no dose received.

17. ELECTRONIC PATIENT REPORTED OUTCOMES DIARY COMPLIANCE

Electronic patient reported outcomes diary compliance at each 1-month period (including baseline, Month 1, 2, 3) as well as for treatment period overall (Month 1 through Month 3) will be calculated.
Treatment comparisons for diary compliance for each period will be performed separately using an ANOVA with treatment in the model.
Electronic patient reported outcomes diary compliance will be presented for the SAF.

17.1. DERIVATIONS

Diary compliance at each period is calculated as:

$$\frac{\text{Actual number of diary days in the period} * 100}{\text{Expected number of diary days in the period}}$$

Expected number of Diary days is calculated as date of injection at the end of interval minus date of injection at the beginning of the interval +1.

18. EFFICACY OUTCOMES

18.1. EFFICACY MEASURES

18.1.1. MIGRAINE AND HEADACHE MEASURES

Headache information will be collected via an ePRO diary. Patients will need to enter ePRO diary data daily beginning from V2 and continuing until V6. Should there be duplicate headache dates, the date with the later study date/time should be used. A summary table and a listing of the responses to each diary question will be presented.

Information recorded in the ePRO diary, the possible responses, and the assignment to the type of headache is presented in Table G:

Table G: ePRO Diary Questions, Responses, and Assignment to Headache Type

QUESTION	RESPONSE	HEADACHE ASSIGNMENT
Q1. Yesterday, did you have a headache that lasted for thirty minutes or more?	Yes	
	No[a]	
Q2. Enter the total number of hours you had a headache yesterday.	Range 1 to 24	If ≥1 the headache will be counted as a headache day.
Q3. Yesterday, what was the worst headache pain?	Mild	
	Moderate	Migraine Criteria A
	Severe	Migraine Criteria A
Q4. Yesterday, was the headache throbbing or pounding?	Yes	Migraine Criteria A
	No	
Q5. Yesterday, was the headache just on the right or left side of your head?	Yes	Migraine Criteria A
	No	
Q6. Yesterday, was the headache made worse by your usual daily activity?	Yes	Migraine Criteria A
	No	
Q7. Yesterday, did the headache come with sensitivity to light and sound?	Yes	Migraine Criteria B
	No	
Q8. Yesterday, did you feel sick to the stomach or throw-up with the headache?	Yes	Migraine Criteria B
	No	
Q9. Yesterday, did you have your menstrual period (if female)?	Yes	
	No	
Q10. Yesterday, did you experience aura?	Yes	
	No	
Q11. Yesterday, did you experience any warning symptoms (prodrome symptoms) that a migraine was coming other than aura?	Yes	
	No	
Q12. Yesterday, did you take any medicine for your headache?	Yes	Medication will only count as headache medication on a day a headache occurred.
	No	

[a] If "No" is answered for Q1, then the patients will skip Q2 - Q6, only answer questions Q7 - Q12 by removing reference to headache.

Migraine and Headache Endpoint Definitions are provided in Table H:

Table H: Migraine and Headache Endpoint Definitions

Diagnosis	Definition/Criteria

Migraine headache	A headache, with or without aura, of ≥30 minutes duration, with both of the following required features (A and B): A. At least 2 of the following headache characteristics: • Unilateral location • Pulsating quality • Moderate or severe pain intensity • Aggravation by or causing avoidance of routine physical activity AND B. During headache at least 1 of the following: • Nausea and/or vomiting • Photophobia and phonophobia (Definition adapted from the standard IHS ICHD-3 definition)
Probable migraine headache	A headache of ≥30 minutes duration, with or without aura, but missing one of the migraine features in the IHS ICHD-3 definition. To be exact, it meets either at least two A criteria and zero B criteria, or one A criteria and at least one B criteria.
Migraine headache day (primary objective)	A calendar day on which a migraine headache or probable migraine headache occurs.
Migraine headache attack	Beginning on any day a migraine headache or probable migraine headache is recorded and ends when a migraine-free day occurs.
Non-migraine headache	All headaches of ≥30 minutes duration not fulfilling the definition of migraine or probable migraine.
Non-migraine headache day	A calendar day on which a non-migraine headache occurs.
Headache day	A calendar day on which any type of headache occurs (including migraine, probable migraine, and non-migraine headache).

Primary Measure: >=50% Percent Reduction in migraine headache days

The primary measure is the percent reduction from baseline in migraine headache days (per 30-day period). A migraine headache day is defined as a calendar day on which a **migraine or probable migraine** occurs.

The percent change from baseline in the number of migraine headache days will be calculated for any post-baseline 30-day period as:

$$-1 * \frac{100 \times (\#\text{ of MHD in Month Y} - \#\text{ of MHD in baseline period})}{\#\text{ of MHD in baseline period}}$$

A 50% responder (Participant with ≥50% reduction from baseline in migraine headache days): is defined as Yes, if any participant who has a ≥50% reduction in the total number of migraine headache days in a 30-day period relative to baseline period, as No if otherwise. Therefore, if the percent change from baseline in the number of migraine headache days is ≥50%, the participant will be counted as an 50% responder.

Change from baseline in the number of monthly migraine headache days in each 30-day period will be summarized from daily data for each patient in that period (including approximately 30 days of daily data from the baseline period prior to randomization, 3 months of daily data during double-blind treatment period).

The daily ePRO data will reflect whether the patients meet the migraine / probable migraine criteria; those data will be aggregated, and the number of migraine headache days will be provided for each of the 30-day periods.

18.1.2. ADJUSTING FOR THE NUMBER OF DAYS WITH NON-MISSING DIARY DATA IN THE PERIOD:

In calculating the number of migraine headache days for each period, if the period is not equal to 30 days, the number of migraine headache days will be adjusted by multiplying the number of migraine headache days by (30/x) where "x" is the total number of non-missing diary days in the period.

This approach to missing ePRO diary data assumes that the rate of migraine headaches per day is the same with missing and non-missing ePRO diary days, and it is missing at random. The same approach will also be applied to secondary and exploratory measures that are derived from the ePRO data.

Additionally, if the ePRO compliance rate (please refer to Section 17) for a monthly interval is ≤50%, then all endpoints to be derived from the ePRO diary data for that one-month period will be considered missing. For a participant who discontinued early in the double-blind treatment

phase, compliance rate for the last month of that study period will be calculated with the denominator of the maximum of 30 and the total number of calendar days in that month.

Secondary and Exploratory Migraine and Headache Measures

Number of migraine headache days with acute (abortive) medication use is calculated as the number of calendar days in a 30-day period on which migraine or probable migraine occurs and acute (abortive) medication is used (based on the response to question 12 in the daily diary questions, Table G).

Weekly migraine headache days is defined as is calculated as the number of migraine headache days in a 7-day period on which a migraine headache occurs. For each month, the first 7 calendar days will be counted as week 1, the second 7 calendar days will be counted as week 2, the third 7 calendar days will be counted as week 3, and the rest of days will be counted as week 4.

Number of migraine headache hours is calculated as the total number of headache hours in a 30-day period on days when a migraine or probable migraine occurs.

Number days with acute (abortive) medication use is calculated as the number of calendar days in a 30-day period on which an acute (abortive) medication is used (based on the response question 12 in the in the daily diary questions, Table G.

Number of headache days is calculated as the number of calendar days in a 30-day period on which a headache occurs (includes migraine, probable migraine, and non-migraine).

Number of moderate to severe headache days is calculated as the number of calendar days in a 30-day period on which a headache occurs with a moderate or severe severity (based on Q3 response, Table G.)

Number of migraine attacks per 30-day period is calculated as the number of sets of consecutive days with migraine or probable migraine separated by at least one migraine-free day. For example, a migraine or probable migraine starting on 5JAN and ending on 6JAN will result in a migraine/probable migraine-free day on 7JAN (assuming that there is no migraine/probable migraine on 7JAN). This will count as 1 migraine attack that started on 5JAN and ended on

6JAN. For a migraine attack that begins in one 30-day period but ends in another, only 1 migraine attack will be counted in the first of the 2 periods. For example, in the case of 7 days of consecutive migraine/probable migraine headache with 3 days in the baseline period and 4 days in Month 1, only 1 migraine attack will be counted in the baseline period; the 4 days of migraine/probable headache in Month 1 will not be counted as a migraine attack in Month 1.

Mean severity of migraine or probable migraine headaches on migraine headache days will be calculated at each period (including baseline and any post-baseline periods). For the calculation of mean severity, for days with migraine or probable migraine, severity varies from 1 to 3 with 1=mild, 2=moderate, and 3=severe. The mean severity for each period will be calculated as:

$$\frac{\text{Sum of Severity of migraine headache days in the period}}{\text{\# of migraine headache days in the period}}$$

For periods with zero migraine headache days, the mean severity is considered not applicable hence missing in the analysis data set.

An X% responder is defined as Yes, if any patient who has a ≥X% reduction in the total number of migraine headache days in a 30-day period relative to baseline period, as No if otherwise. Therefore, if the percent change from baseline in the number of migraine headache days is ≥X%, the patient will be counted as an X% responder. In other words, if the response rate defined above in a month is ≥X%, then the patient will be an X% responder in that month. In addition to the primary response endpoint with X=50, indicators of X% responders will be derived for X= 75, and 100. The same calculation that was used for percent change from baseline in the number of migraine headache days for the primary endpoint will be used for these endpoints as well.

18.1.3. MIDAS (Migraine Disability Assessment) Questionnaire

The Migraine Disability Assessment questionnaire (MIDAS) consists of 5 questions (Q1-Q5) and 2 additional questions (A and B). The questionnaire measures the impact that migraine headaches have on migraineurs' life, including days of work or school missed, days with productivity at work or school reduced to half or more, days with household work missed, days with productivity in household work reduced to half or more, and days missed family / social / leisure activities. Each question is answered as a numeric number of days during the past 3

months of assessment, ranging from 0 to 90. The answers to all 5 questions will be added up to a total MIDAS score. No imputation is needed when calculating the total score as participants are not allowed to send partial data. The answers to all 5 questions will be added up to a total MIDAS score. The total MIDAS score and item scores will be analyzed.

18.1.4. Migraine Specific Quality of Life (MSQ) v2.1

Migraine Specific Quality of Life (MSQ) v2.1 consists of 14 questions. The questions measure the impact of migraine on health-related quality of life across 3 domains: 1) Role Function-Restrictive (7 questions), examines the degree to which performance of daily activities is limited by migraine; 2) Role Function-Preventive (4 questions), examines the degree to which performance of daily activities is prevented by migraine; 3) Emotional Function (3 questions), examines feelings of frustration and helplessness due to migraine.

Precoded item values and final item values for each MSQ item response are shown in Table I. All item values range from 1 to 6. Final item value will be used as for analysis with higher score reflecting better quality of life.

Table I: Item Values for Migraine Specific Quality of Life (MSQ) Item Responses

Response Categories	Precoded Item Value	Final Item Value
None of the time	1	6
A little bit of the time	2	5
Some of the time	3	4
A good bit of the time	4	3
Most of the time	5	2
All of the time	6	1

Questions 1 to 7 of the questionnaire will be grouped together as Role Function-Restrictive domain, questions 8 to 11 as Role Function-Preventive domain and questions 12 to 14 as the Emotional Function domain. In general, no imputation for missing values is necessary because the MSQ was collected using participant direct data entry on an electronic device which did not allow participants to skip items. Participant either completed the scale in its entirety or not at all.

The raw score of each domain will be calculated as the sum of the raw scores of each question in that domain. The total score will be calculated as the sum of raw scores of Role Function-Restrictive, Role Function-Preventive, and Emotional Function domain scores.

. If any of the 3 domain scores is missing, then total score will be missing.

In addition, the raw scores of each domain and the total score will be transformed to a 0 to 100 scale using the following formulae:

- Role Function-Restrictive (range of 7 to 42):

$$\frac{(\text{raw score} - 7)\text{x}100}{35}$$

- Role Function-Preventive (range of 4 to 24):

$$\frac{(\text{raw score} - 4)\text{x}100}{20}$$

- Emotional Function (range of 3 to 18):

$$\frac{(\text{raw score} - 3)\text{x}100}{15}$$

- Total Score (range of 14 to 84):

$$\frac{(\text{raw total score} - 14)\text{x}100}{70}$$

18.1.5. Total Pain Burden

Total pain burden: The total pain burden for a given month (severity-weighted duration) was calculated by multiplying duration (hours) of migraine headache and maximum pain severity (0 = none, 1 = mild, 2 = moderate, 3 = severe) for each migraine headache day and summing these over the days in a month. Total pain burden for a given month to be adjusted for 30 day period for a month as defined section 18.1.2.

18.1.6. Patient Global Impression

The Patient Global Impression of Severity (PGI-S): In this single-item scale, participants rate the severity of their migraine condition on a scale ranging from “not at all ill” (coded as 1) to “extremely ill” (coded as 7).
Change from baseline in PGI-S scores will be analyzed.

18.2. PRIMARY EFFICACY

18.2.1. PRIMARY EFFICACY VARIABLE(S) & DERIVATION(S)

The primary endpoint is the percentage of participants with ≥50% reduction from baseline in monthly migraine headache days across the 3-month double-blind treatment period. Please refer to Section 18.1.1 for derivations.

18.2.2. MISSING DATA METHODS FOR PRIMARY EFFICACY VARIABLE(S)

For the repeated measures analyses, the model parameters are simultaneously estimated using restricted likelihood estimation incorporating all of the observed data. Estimates have been shown to be unbiased when the missing data are missing at random.
Please refer to Section 18.1.2 for approach of handling missing diary data for derivation of the number of migraine headache days and other efficacy measures derived from ePRO data per 30-day period.

18.2.3. PRIMARY ANALYSIS OF PRIMARY EFFICACY VARIABLE(S)

The primary objective of this study is to assess whether galcanezumab is superior to rimegepant in the prevention of migraine in participants with episodic migraine. The primary estimand of interest is the overall mean monthly 50% response rate across the 3-month double-blind period attributable to the randomized treatment based on all available data as estimated from the model based on GLIMMIX-procedure. All available monthly migraine headache data will contribute to analysis as long as baseline monthly migraine headache day values are available. Any migraine headache day data collected after study intervention discontinuation but within the double-blind period will still be used within the analysis.

The primary efficacy analysis will be performed for the ITT. This endpoint (50% responder) is binary variable with repeated measures and will be analyzed using a GLIMMIX procedure as pseudo-likelihood-based mixed effects repeated measures analysis. The GLIMMIX procedure will include the fixed, categorical effects of treatment, month, and treatment-by-month interaction, as well as the continuous, fixed covariate of baseline monthly migraine headache days value. Binary distribution and logit link will be used.

An unstructured covariance structure will be used to model the within-participant errors (denoted by TYPE=CHOL in the RANDOM statement). The Newton-Raphson method with ridging will

be used for nonlinear optimization (denoted by including NLOPTIONS TECH=NRRIDG). The Kenward-Roger (Kenward and Roger 1997) approximation will be used to estimate denominator degrees of freedom. If the model does not converge, the Fisher scoring algorithm will be utilized by the SCORING option in SAS.

If the model still fails to converge, the model will be fit using covariance matrices in the following order specified by a decreasing number of covariance parameters until convergence is met:

- Heterogeneous Toeplitz,
- Heterogeneous autoregressive,
- Toeplitz, and
- Autoregressive.

If necessary, both fitting algorithms will be used in the pre-specified order before proceeding to the next covariance structure in the sequence.

For models where the unstructured covariance matrix is not utilized, the sandwich estimator (Diggle et al. 1994) will be used to estimate the standard errors of the fixed effects parameters. The sandwich estimator is utilized by the EMPIRICAL option in SAS. When the sandwich estimator is utilized, the Kenward-Roger approximation for denominator degrees of freedom cannot be used. Instead, the denominator degrees of freedom will be partitioned into between-subject and within-subject portions by the DDFM=BETWITHIN option in SAS.

For the repeated binary efficacy measure where the objective is to assess the proportion of patients with 50% response during the 3-month double-blind treatment phase, the endpoint for comparing galcanezumab with rimegepant will be estimated as the treatment main effect from the categorical MMRM analysis assessing the response rate across Months 1, Month 2 and Month 3.

18.2.4. Sensitivity Analysis of Primary Efficacy Variable(s)

The following sensitivity analyses are of the primary efficacy variable are planned:

I) To consider the case where to discard the data of the participants that discontinue treatment and may have different expectations regarding efficacy of the two treatments such as the onset of effect given the different dosing and mode of administration of the comparators. For such analyses, the data after whichever of the following is sooner will be discarded: the date of the last injection+30 days or the

date of the last oral administration +1 day.

II) To consider participants that withdraw for lack of efficacy or tolerability, or participants that switch preventive treatment as no responders (composite strategy).

III) To consider a migraine headache day when the participant takes acute medication regardless of the headache does not meet the criteria of migraine. This analysis will consider if a participant uses an acute medication (triptans or ergot derivatives) – as reported in the CRF (CM_AHM), regardless of whether a headache was reported. For this analysis baseline and post-bassline 'migraine headache days' need to be defined using the reporting of medications in CM_AHM CRF. Input from clinical will be used to help identify the classes of acute medication used.

IV) To assess the robustness of the primary analysis conclusions to deviations from missing at random (MAR) assumption. The approach for these analyses is to vary the assumptions of missing data for the primary analysis in a systematic way. Basically, the method will be to predict the missing outcomes and then add values (Δ_{120},Δ_{75}) to the predictions in the Galcanezumab 120 mg and rimegepant 75 mg treatment groups respectively, regardless of the reason the data are missing. This approach is consistent with the sensitivity approach suggested in Permutt (2015). This procedure will be repeated multiple times for different values of (Δ_{120},Δ_{75}) using the following steps:

1) Predict the missing outcomes for each treatment via multiple imputation based on observed primary endpoint and baseline values. Such imputation will be carried out using a Markov Chain Monte Carlo method with a Jeffreys prior via SAS® PROC MI. Thirty (30) such imputations will be created.
2) Add the corresponding Δ value (i.e. Δ_{120},Δ_{75}) to the imputed values based on the patient treatment group.
3) Conduct the primary analysis separately for each of the 30 imputations.
4) Combine the results of these analyses using Rubin's combining rules, as implemented in SAS® PROC MI ANALYZE.

The above steps will be repeated multiple times for different values of (Δ_{120}, Δ_{75}) with Δ_{75} ranging from 0 to twice the absolute value of the mean value seen for rimegepant in the primary analysis, Δ_{120} ranging from Δ^{75} to Δ_{75} + absolute value of the biggest mean treatment difference seen within the primary analysis. For example, if the overall mean change from

baseline for rimegepant is -3.6 and the maximum overall treatment difference is -1.5, then Δ_{75} would range from 0 to7.2 and Δ_{120} would range from Δ_{75} to Δ_{75} + 1.5.

18.3. SECONDARY EFFICACY

The secondary efficacy analyses, as defined in Table J, will be performed for the ITT. For all secondary endpoints, a similar estimand to the one used for the primary analysis will be employed. That is, the estimand of interest will be based on overall mean monthly estimates across/within the double-blind period and will be based on all available data during that period (even if collected after study intervention discontinuation). Additionally, baseline values must also be available.

Table J: Secondary Efficacy Variables and Analysis Methods

Efficacy Endpoint/Variable	Analysis
Overall mean change from baseline in the number of monthly migraine headache days across the 3-month double-blind treatment period	MMRM
The percentage of participants with X% reduction from baseline in monthly migraine headache days across the 3- month double-blind treatment period. (X=75 or 100)	GLIMMIX
The mean change from baseline in the number of monthly migraine headache days at Months 3, 2, and 1	MMRM
The overall mean change from baseline in the number of monthly migraine headache days requiring medication for the acute treatment of migraine or headache across the 3-month double-blind treatment period	MMRM
The mean change from baseline in the Role Function-Restrictive (RF-R) domain score of the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) at Month 3	ANCOVA
Changes from baseline to Month 3 in MSQ v2.1 total score, and Role Function-Preventive (RF-P) and Emotional Function (EF) domain scores	ANCOVA
Changes from baseline to Month 3 in MIDAS (Migraine Disability Assessment) total score	ANCOVA

Abbreviations: G.LIMMIX = Generalized linear mixed model (for binary variables); MMRM = Mixed models repeated measures; ANCOVA= Analysis of Covariance

18.3.1. Missing Data Methods for Secondary Efficacy Variable(s)

For the repeated measures analyses, the model parameters are simultaneously estimated using restricted likelihood estimation incorporating all of the observed data. Estimates have been shown to be unbiased when the missing data are missing at random.

Please refer to Section 18.1.1 for approach of handling missing diary data for derivation of the number of migraine headache days and other efficacy measures (with the exception of migraine attacks) derived from ePRO data per 30-day period.

18.3.2. Analysis of Secondary Efficacy Variables

18.3.2.1. Analysis of Key Binary Secondary Efficacy Endpoints

Dichotomous outcomes will be analyzed using a the same GLIMMIX as pseudo- likelihood-based mixed effects repeated measures analysis used for the primary endpoint. The GLIMMIX procedure will include the fixed, categorical effects of treatment, month, and treatment-by-month interaction, as well as the continuous, fixed covariate of baseline for the variable of interest. Please refer to Section 18.2.3 for details.

For the repeated binary efficacy measure where the objective is to assess the proportion of patients with X% response during the 3-month double-blind treatment phase, the endpoint for comparing galcanezumab with rimegepant will be estimated as the treatment main effect from the categorical MMRM analysis assessing the average response rate across Months 1, Month 2 and Month 3.

18.3.2.2. Continuous Efficacy Measures

Continuous efficacy variables with repeated measures will be analyzed using a restricted maximum likelihood (REML)-based mixed models repeated measures (MMRM) technique and will include the fixed, categorical effects of treatment, month, and treatment-by-month interaction, well as the continuous fixed covariates of baseline number of migraine headache days and baseline-by-month interaction. This model is referred to as the MMRM model throughout this document.

The Kenward-Roger (Kenward and Roger 1997) approximation will be used to estimate denominator degrees of freedom. Wherever possible an unstructured covariance matrix will be used to model the correlation structure among repeated measures. If the model does not converge with both the Hessian and the G matrix being positive definite under the default fitting algorithm used by PROC MIXED, the Fisher scoring algorithm will be implemented by specifying the SCORING option in SAS. If the model still fails to converge, the model will be fit using covariance matrices of the following order specified by a decreasing number of covariance parameters until convergence is met:

- Heterogeneous Toeplitz
- Heterogeneous First-order autoregressive
- Toeplitz
- First-order autoregressive

When the unstructured covariance matrix is not utilized, the sandwich estimator (Diggle and Kenward 1994) will be used to estimate the standard errors of the fixed effects parameters. The sandwich estimator is implemented by specifying the EMPIRICAL option in SAS®. When the sandwich estimator is utilized, the Kenward-Roger approximation for denominator degrees of freedom cannot be used. Instead, the denominator degrees of freedom will be partitioned into between-subject and within-subject portions by the DDFM=BETWITHIN option in SAS®. SAS® PROC MIXED will be used to perform the analysis.

For continuous efficacy variables without repeated measures, an analysis of covariance (ANCOVA) which contains the main effects of treatment, and the continuous fixed covariate of baseline. Type III sum-of-squares for the LSMeans will be used for the statistical comparisons.

For continuous secondary efficacy measures where the objective is to assess overall mean change during the 3-month double-blind treatment period, the endpoint for galcanezumab compared with rimegepant will be estimated as the treatment main effect from the MMRM analysis assessing the average treatment effect across Months 1, 2, and 3.

The statistical comparisons for the primary efficacy endpoint and the key secondary endpoints will be carried out in the hierarchical order. This means that statistically significant results for the comparison in the higher rank (primary, then ranked secondary variables) are

required to initiate the testing of the next comparison in the lower rank. Since a step-down procedure is used, each comparison will be tested at a significance level of 0.05 and an overall alpha level of 0.05 will be preserved.
The order of objectives/comparisons may change (with the exception of the primary objective). Should such a change take place, the final hierarchical order used/multiplicity adjustment approach employed to ensure overall 0.05 alpha-level control will be documented within an approved final SAP prior to study unblinding.

If galcanezumab is statistically superior to rimegepant on the primary objective, the following key secondary endpoints will be tested with adjustment for multiplicity:

- The overall mean change from baseline in the number of monthly migraine headache days across the 3-month double-blind treatment period. (Using MMRM method)

  From above model, the mean change from baseline in the number of monthly migraine headache days can be obtained at:

  - Month 3
  - Month 2
  - Month 1

- The percentage of participants with ≥75% reduction from baseline in monthly migraine headache days across the 3-month double-blind treatment period. (Using GLIMMIX procedure)
- The overall mean change from baseline in the number of monthly migraine headache days requiring medication for the acute treatment of migraine or headache across the 3-month double-blind treatment period. (Using MMRM method). For this analysis, medication use will be based on the response to question 12 in the diary.

Other key secondary endpoints will be analyzed using corresponding analysis methods as specified:

- The mean change from baseline in the Role Function-Restrictive (RF-R) domain score of the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) at Month 3. (Using ANCOVA method)
- The percentage of participants with 100% reduction from baseline in monthly migraine

headache days across the 3-month double-blind treatment period. (Using GLIMMIX procedure)

18.3.2.3. Analysis of Changes from Baseline to Month 3 on Disability and Health-related Quality of Life

There are two changes from baseline to Month 3 on disability and health-related quality of life to be analyzed:

- MSQ v2.1 total score, and Role Function-Preventive (RF-P) and Emotional Function (EF) domain scores
- MIDAS (Migraine Disability Assessment) total score

For the above continuous efficacy variable without repeated measures, an ANCOVA model which contains the main effects of treatment, and the continuous fixed covariate of baseline. Type III sum-of-squares for the LS Means will be used for the statistical comparisons.

18.4. EXPLORATORY EFFICACY

The exploratory efficacy analyses will be performed for the ITT. Table K summarizes all the planned secondary efficacy analyses.

Table K: Exploratory Efficacy Variables and Analysis Methods

Efficacy Variables	Analysis
Change from baseline in the Patient Global Impression of Severity (PGI-S) at Month 3	ANCOVA
Change from baseline in the number of monthly moderate to severe headache days across the 3-month double-blind treatment period	MMRM
Change from baseline in the Monthly Total Pain Burden across the 3-month double-blind treatment period	MMRM
50% response rate: • Percentage of participants with ≥50% reduction from baseline in monthly migraine headache days at Month 3, Month 2, and Month 1 • Percentage of participants with ≥50% reduction in Weekly migraine headache days at weeks 4, 3, 2, 1 in the months that galcanezumab was superior to rimegepant • The initial month at which galcanezumab was superior to rimegepant in the proportion of patients meeting at least a 50% reduction in monthly migraine headache days that is sustained at all subsequent months through Month 3 • Percentage of participants with ≥50% reduction from baseline in moderate to severe monthly migraine headache days across the 3-month double-blind treatment period	GLIMMIX
Change from baseline in the number of weekly migraine headache days in the months that galcanezumab was superior to rimegepant	MMRM
Change from baseline in the number of monthly days with acute headache medication use during the 3-month double-blind treatment phase	MMRM
Change from baseline in the number of monthly moderate to severe migraine headache days across the 3-month double-blind treatment period	MMRM

Abbreviations: ANCOVA = analysis of covariance; GLIMMIX = Generalized linear mixed model (for binary variables); MMRM = Mixed models repeated measures.

18.4.1. Exploratory Efficacy Variables & Derivations

- Mean change from baseline in the Patient Global Impression of Severity (PGI-S) at Month 3
- The overall mean change from baseline in the number of monthly moderate to severe

headache days across the 3-month double-blind treatment period
- Mean change from baseline in the Monthly Total Pain Burden across the 3-month double-blind treatment period

Additional exploratory endpoints to assess onset of action:

- Mean change from baseline in the number of weekly migraine headache days in the months that galcanezumab was superior to rimegepant
- Percentage of participants with ≥50% reduction from baseline in monthly migraine headache days at Month 3, Month 2, and Month 1
- Percentage of participants with ≥50% reduction in Weekly migraine headache days at weeks 4, 3, 2, 1, in the months that galcanezumab was superior to rimegepant

Additional exploratory endpoint to assess sustained response:

The initial month at which galcanezumab was superior to rimegepant in the proportion of patients meeting at least a 50% reduction in monthly migraine headache days that is sustained at all subsequent months through Month 3

Other exploratory endpoints of interest:

- The overall mean change from baseline in the number of monthly days with acute headache medication use during the 3-month double-blind treatment phase (this is based on any day). Medication use will be based on response to question 12 in the diary.
- The overall mean change from baseline in the number of monthly moderate to severe migraine headache days across the 3-month double-blind treatment period (– Only includes Migraine Headache day)
- Percentage of participants with ≥50% reduction from baseline in moderate to severe monthly migraine headache days across the 3-month double-blind treatment period

18.4.2. Missing Data Methods for Exploratory Efficacy Variable(s)

Two statistical approaches to handling missing data will be used as appropriate: repeated

measures analyses and ANCOVA model using change from baseline Month 3 of treatment period.
For the repeated measures analyses, the model parameters are simultaneously estimated using restricted likelihood estimation incorporating all of the observed data. Estimates have been shown to be unbiased when the missing data are missing at random.

18.4.3. Analysis of Exploratory Efficacy Variables

18.4.3.1. Analysis of Mean Change from Baseline in the Patient Global Impression of Severity (PGI-S) at Month 3

For this continuous efficacy variable without repeated measures, an ANCOVA model with contains the main effects of treatment, and the continuous fixed covariate of baseline. Type III sum-of-squares for the LSMeans will be used for the statistical comparisons.

18.4.3.2. Analysis of the Overall Mean Change from Baseline in the Number of Monthly Moderate to Severe Headache Days Across the 3-month Double-blind Treatment Period

This endpoint with repeated measures will be analyzed using MMRM methods. The MMRM will include the fixed categorical effects of treatment, month, and treatment-by- month interaction, as well as the continuous fixed covariates of baseline and baseline-by-month interaction. Wherever possible an unstructured covariance matrix will be used to model the correlation structure among repeated measures.

18.4.3.3. Analysis of Mean Change from Baseline in the Monthly Total Pain Burden Across the 3-month Double-blind Treatment Period

This endpoint with repeated measures will be analyzed using MMRM methods. The MMRM will include the fixed categorical effects of treatment, month, and treatment-by-month interaction, as well as the continuous fixed covariates of baseline and baseline-by-month interaction. Wherever possible an unstructured covariance matrix will be used to model the correlation structure among repeated measures.

18.4.3.4. Analysis of Additional Exploratory Endpoints

The additional change from baseline exploratory endpoints with repeated measures will be analyzed using MMRM methods. The MMRM will include the fixed categorical effects of treatment, month, and treatment-by-month interaction, as well as the continuous fixed covariates

of baseline and baseline-by-month interaction. Wherever possible an unstructured covariance matrix will be used to model the correlation structure among repeated measures.
The additional binary exploratory variables with repeated measures will be analyzed using a GLIMMIX as pseudo- likelihood-based mixed effects repeated measures analysis. The GLIMMIX procedure will include the fixed, categorical effects of treatment, month, and treatment-by-month interaction, as well as the continuous, fixed covariate of baseline value.

19. QUALITY OF LIFE ANALYSIS

Quality of Life (QoL) will be analyzed under efficacy analyses.

20. SAFETY OUTCOMES

Safety endpoints consist of incidences of treatment emergent adverse events (TEAEs), serious adverse events (SAEs) and adverse events (AEs) in general and leading to discontinuation, vital signs (blood pressure, pulse, and body temperature), weight and laboratory measures (chemistry, hematology, and urinalysis). All outputs for safety outcomes will be based on the Safety Analysis Set.

For categorical safety variables (such as AEs and other categorical changes of interest), comparisons between treatment groups will be performed using Fisher's exact test.

20.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using MedDRA central coding dictionary, Version 24.1 or higher. Treatment-emergent adverse events are defined as the reported AEs that first occurred or worsened during the post-baseline phase compared with baseline phase. Adverse events (AE) that occurred on the visit date of Visit 3 will be determined to be pre-dose or after dose based on AE start time and the injection time: pre-dose if AE start time is before the injection time; post dose if AE start time is after the injection time.

For each TEAE, the severity level of the event (mild, moderate, or severe) will be determined by participant or physician opinion. The MedDRA Lowest Level Term (LLT) will be used in the treatment emergent computation. For each LLT, the maximum severity at baseline will be used

as the baseline severity. If the maximum severity during post-baseline is greater than the maximum baseline severity, the event is considered to be treatment emergent for post-baseline period. For each participant and TEAE, the maximum severity for the MedDRA level being displayed (PT) is the maximum post-baseline severity observed from all associated LLTs mapping to that MedDRA level. Summary tables will present events by PT by decreasing frequency of PT or by SOC/PT and by decreasing frequency of PT within SOC.

See APPENDIX 2 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case; i.e. treatment emergent.

An overall summary of number of participants within each of the categories described in the sub-section below, will be provided as specified in the templates. Listings will include TEAEs and Non-TEAEs.

20.1.1. ALL AEs

Incidence of TEAEs will be presented by both by Preferred Term (PT) and by System Organ Class (SOC) and Preferred Term (PT) by decreasing percentages of PT.

20.1.1.1. Severity

Severity is classed as mild / moderate / severe (increasing severity). TEAEs starting after the first dose of study medication with a missing severity will be classified as severe. If a participant reports a TEAE more than once within that SOC / PT, the AE with the worst-case severity will be used in the corresponding severity summaries. TEAE by maximum severity will be summarized by decreasing percentages of PT.

20.1.1.2. Relationship to Study Medication

Relationship, as indicated by the Investigator, is classed as No, Yes. A ”related” TEAE is defined as a TEAE with a relationship to study medication as ‘Yes’. TEAEs with a missing relationship to study medication will be regarded as Yes related to study medication. If a participant reports the same AE more than once within that SOC / PT, the AE with the worst-case relationship (i.e. Yes) to study medication will be used in the corresponding relationship summaries and will be presented by decreasing percentages of PT. A listing of TEAE related to

non-study drug treatment will be presented as well.

20.1.1.1. Adverse Events by Outcome

A summary of TEAE by outcome and PT will be presented.

20.1.1.2. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as ”Serious” on the Adverse Events page of the electronic case report form (eCRF). A summary of all SAEs and serious TEAEs by PT will be prepared and will present the following will be provided:

- the number of participants at risk of an event
- the number of participants who experienced each event term
- the number of events experienced.

20.1.1.3. Other Adverse Events

An AE is considered in the “Other” category if it is both a TEAE and is not serious. For “Other” AE, for each term and treatment group, the following will be provided:

- the number of participants at risk of an event
- the number of participants who experienced each event term
- the number of events experienced.

20.1.1.4. TEAEs Leading to Discontinuation of Study Intervention

TEAEs leading to permanent discontinuation of study medication will be identified by using AE action as “Drug Withdrawn”. Summaries of incidence rates (frequencies and percentages) by PT will be prepared.

20.1.1.5. Adverse Events Leading to Study Discontinuation

All AEs leading to discontinuation from the study (from any of the following Study Disposition forms: DS_HEP, DS_SDWOV, DS_SF, DS_STUDY) will be summarized.

20.1.1.1. Adverse Events Leading to Death

All TEAEs leading to death will be summarized and listed.

20.1.1.2. Adverse Events Related to Injection Sites

TEAEs related to injection sites will be defined using terms from the MedDRA High Level Term "Injection Site Reactions".

The number and percentage of participants with TEAEs related to injection sites, SAEs related to injection sites, and AEs related to injection sites resulting in study drug discontinuation will be summarized using MedDRA PT. Events will be ordered by decreasing frequency within PT.

The number and percentage of participants with TEAEs related to injection sites by maximum severity will be summarized by treatment groups using MedDRA PT. For each participant and AEs related to injection sites, the maximum severity for the MedDRA level being displayed (PT) is the maximum post-baseline severity observed from all associated LLTs mapping to that MedDRA level.

The number and percentage of participants with TEAEs related to injection sites by timing will be summarized using MedDRA preferred terms ordered by decreasing frequency. Note the timing of AEs related to injection sites is collected through eCRF and categorized into the following categories:

- Occurs DURING study drug administration
- within 30 minutes of end of study drug administration
- >30 minutes and up to 6 hours from end of study drug administration
- >6 Hours and up to 24 Hours from end of study drug administration
- >24 Hours and Up to 14 Days from end of study drug administration
- >14 Days from end of study drug administration
- Unknown

20.1.1. Adverse Events Of Special Interest

Not applicable.

20.1.2. CTC Grading for Adverse Events

Not applicable.

20.2. Laboratory Evaluations

Results from the central laboratory will be included in the reporting of this study for Hematology, Clinical Chemistry and Urinalysis. A list of laboratory assessments to be included in the outputs is included in the protocol, Sections 10.4 and 10.5. Presentations will use SI Units. The incidence rates of participants with treatment emergent abnormal, high, or low laboratory values based on the reference ranges at any time post-baseline will be assessed using Fisher's exact test for each laboratory test.

Participants will be defined as having a treatment emergent low value if they have normal or high values at all predose/baseline visits, followed by a value below the lower reference limit at any post-baseline visit. Participants with normal or high values at all predose/baseline visits (no low values) will be included in the analysis of treatment emergent low laboratory values. Participants will be defined as having a treatment emergent high value if they have normal or low values all predose/baseline visits, followed by a value above the upper reference limit at any post-baseline visit. Participants with normal or low values all predose/baseline visits (no high values) will be included in the analysis of treatment emergent high laboratory values. For analyses simply classified as normal or abnormal, participants will be defined as having a treatment emergent abnormal value if they have normal values all predose/baseline visits, followed by an abnormal value at any post-baseline visit. Participants with normal values all predose/baseline visits will be included in the analysis of treatment emergent abnormal laboratory values.

The incidence of participants with the following elevations in hepatic laboratory tests at any time post-baseline will also be summarized and compared between treatment groups using Fisher's exact test. A listing of participants with any of these elevations will be produced and will include all LFT parameters and visits.

- The number and percentage of participants with an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) measurement greater than or equal to 1 time (1X), 3 times (3x), 5 times (5x), 10 times (10x), and 20 times (20x) the performing lab upper limit of normal (ULN) during the treatment period will be summarized for all participants with a post-baseline value.

- The number and percentage of participants with an alkaline phosphatase (ALP) measurement greater than or equal to 2 times (2x) and 3 times (3x), the performing lab ULN during the treatment period will be summarized for all participants with a post-baseline value.
- The number and percentage of participants with a total bilirubin (TBIL) measurement greater than or equal to 2 times (2x), 5 times (5x), and 8 times (8x) the performing lab ULN during the treatment period will be summarized for all participants with a post-baseline value.
- The number and percentage of participants with a direct bilirubin (BILDIR) measurement greater than or equal to 2 times (2x) and 5 times (5x) the performing lab ULN during the treatment period will be summarized for all participants with a post-baseline value.
- The number and percentage of participants with an international normalized ratio (INR) measurement greater than or equal to 1.5 times (1.5x), 3 times (3x), and 5 times (5x) the performing lab ULN during the treatment period will be summarized for all participants with a post-baseline value.
- The number and percentage of participants with gamma glutamyl transferase (GGT) measurement greater than or equal to 2 times (2x) the performing lab ULN during the treatment period will be summarized for all participants with a post-baseline value.

Additional Analyses:

Treatment-Emergent Potentially Drug-Related Hepatic Disorders	Potentially drug-related hepatic disorders are defined using a custom query based on the following SMQs: • Broad and narrow terms in the Liver-related investigations, signs and symptoms SMQ (20000008) • Broad and narrow terms in the Cholestasis and jaundice of hepatic origin SMQ (20000009) • Broad and narrow terms in the Hepatitis non-infections SMQ (20000010) • Broad and narrow terms in the Hepatic failure, fibrosis and cirrhosis and other liver damage SMQ (20000013) • Narrow terms in the Liver-related coagulation and bleeding disturbances SMQ (20000015) These SMQs are a subset of the sub-SMQs comprising the full Hepatic Disorders SMQ. Only the sub-SMQs considered applicable to capturing potentially **drug**-related hepatic disorders are included. The percentage of study participants with any one of the MedDRA preferred teams from any of the SMQs will be summarized in addition to the percentages for each MedDRA preferred term.
Potentially Drug-Related Hepatic Disorders That Led to Permanent Study Treatment Discontinuation	The percentages of study participants with potentially drug-related hepatic disorders that led to permanent discontinuation of study drug will be summarized only if there is a sufficient number to warrant a summary.
Hepatocellular Drug-Induced Liver Injury Screening Plot (TBL vs ALT or AST)	Each participant's data is plotted based on their maximum postbaseline TBL (y-axis) and transaminase (ALT or AST, whichever is higher), regardless of the time between the two maximum values. Dashed lines represent TBL and transaminase cut-offs of 2X ULN and 3X ULN, respectively. A potential Hy's law case is circled and is defined as having a maximum postbaseline TBL equal to or exceeding 2X ULN within 30 days after maximum postbaseline ALT or AST equal to or exceeding 3X ULN, without cholestasis (defined as ALP less than 2X ULN).
Hepatocellular Drug-Induced Liver Injury Screening Table	The percentages of study participants falling in each of the three relevant quadrants of the plot (right upper, left upper, right lower) will be summarized in a table.
Cholestatic Drug-Induced Liver Injury Screening Plot (TBL vs ALP)	Each participant's data is plotted based on their maximum postbaseline TBL (y-axis) and ALP (x-axis), regardless of the time between the two maximum values. Dashed lines represent TBL and ALP cut-offs of 2X ULN and 3X ULN, respectively. A potential cholestatic liver injury case is circled and is defined as having a maximum postbaseline TBL equal to or exceeding 2X ULN within 30 days after maximum postbaseline ALP equal to or exceeding 3X ULN.

Cholestatic Drug-Induced Liver Injury Screening Table	The percentages of study participants falling in each of the three relevant quadrants of the plot (right upper, left upper, right lower) will be summarized in a table.
List of Participants With Potential Hepatocellular Drug-Induced Liver Injury	Includes participants falling in the right upper quadrant in the Hepatocellular Drug-Induced Liver Injury Screening plot Variables to include are unique subject ID, age, sex, race, actual treatment (at first ALT/AST elevation), max AST, max ALT, max ALP, max TBL
List of Participants With Potential Cholestatic Drug-Induced Liver Injury	Includes participants falling in the right upper quadrant in the Cholestatic Drug-Induced Liver Injury Screening plot Variables to include are unique subject ID, age, sex, race, actual treatment (at first ALP elevation), max AST, max ALT, max ALP, max TBL
Participant profiles	Participant profiles will be created for participants meeting criteria for a comprehensive hepatic evaluation (as defined in the protocol). Participant profiles will include demographics, disposition, information collected on the hepatic safety CRFs (where applicable) and a display of study drug exposure, adverse events, medications, blood pressure, heart rate, and the liver -related measurements over time. The review for these study participants include which treatment the participant was taking over time, the changes in hepatic labs over time, and the temporal association with potential causes. The review of participant profiles will also include the identification of any potential Hy's law case or potential cholestatic liver injury case that could have been missed by focusing only on the maximum values when determining 30-day time associations.

All laboratory data will be listed.

20.2.1. Laboratory Specific Derivations

Quantitative laboratory measurements reported as "<X", i.e. below the lower limit of quantification (BLQ), or ">X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "<X" or ">X" in the listings.

20.3. Vital Signs

Vital signs include body temperature, blood pressure, and pulse. Blood pressure and pulse will be measured in triplicate in the sitting position after the participant has rested for at least 5

minutes, and before collection of blood samples and dosing (if dosing is on the same day), according to the SoA, and following the study-specific recommendations included in the Reference Manual for the study.

The baseline criteria for determining treatment-emergent vital sign abnormalities are:

- Participants will be defined as having a treatment-emergent low value if they have all normal or high values at all predose/baseline visits, followed by a value below the lower reference limit at any post-baseline visit. Participants with all normal or high values at all predose/baseline visits (no low values) will be included in the analysis of treatment-emergent low values.
- Participants will be defined as having a treatment-emergent high value if they have all normal or low values at all predose/baseline visits, followed by a value above the upper reference limit at any post-baseline visit. Participants with all normal or low values at baseline (no high values) will be included in the analysis of treatment-emergent high values.

The number and percent of participants meeting criteria for treatment-emergent abnormalities in vital signs at any time during study will be summarized. Treatment group comparisons will be performed using Fisher's exact test.

Table L displays the criteria used to define treatment emergent changes in vital signs and weight. The last column of the table displays the participant populations defined by baseline categories, the treatment-emergent categorical changes will be analyzed for each of those participant populations. The criteria generally consist of 2 parts, an absolute threshold and a change from baseline amount. The baseline and post-baseline definitions for vital signs analyses are in Table F

Table L displays the criteria for categorical changes of interest in vital signs. The last column of the table displays the participant populations defined by baseline categories. All vital signs data will be listed.

Table L: Criteria for Categorical Changes of Interest in Vital Signs

Parameter	Direction	Criteria	Participants Population defined by Baseline Categories
Systolic BP (mm Hg) (sitting)	Low	≤90 and decrease ≥20	Low Population
	High	≥140 and increase ≥20	High Population
Diastolic BP (mm Hg) (sitting)	Low	≤50 and decrease ≥10	Low Population
	High	≥90 and increase ≥10	High Population
Pulse (bpm) (sitting)	Low	<50 and decrease ≥15	Low Population
	High	>100 and increase ≥15	High Population
Temperature (° F)	Low	<96° F and decrease ≥2° F	≥96°F
	High	≥101° F and increase ≥2° F	<101°F

Low Population definition: All participants who have values less than or equal to the low limit at all pre-baseline and baseline visits and at least one nonmissing postbaseline value.
High population definition: All participants who have values less than or equal to the high limit at all pre-baseline and baseline visits and at least one nonmissing postbaseline value.
Abbreviations: BP = blood pressure; bpm = beats per minute; F = degrees Fahrenheit; kg = kilograms; mm Hg = millimeters of mercury; PCS= Potentially Clinically Significant

20.4. PHYSICAL EXAMINATION

Weight and height are collected on eCRF.
Weight, height, and BMI will be summarized in demographics.

20.5. PREGNANCY TESTING

Pregnancy testing data (serum) will be collected for all woman of childbearing potential according to SoA. All pregnancy testing data will be listed.

20.6. OTHER SAFETY ASSESSMENTS

20.6.1. CLINICAL TRIAL REGISTRY ANALYSES

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements. These analyses will be the responsibility of the Sponsor.
Analyses provided for the CTR requirements include the following:

A summary of AEs will be provided as a dataset which will be converted to an XML file. Both SAEs and "Other" AEs are summarized: by treatment group, by MedDRA Preferred Term.

21. GENETIC ANALYSIS

Not applicable.

22. REFERENCES

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APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

Output Conventions

Outputs will be presented as shown in the Output shells.
If the original data has N decimal places, then the summary statistics should have the following decimal places:
– Minimum and maximum: N
– Mean (and LS Means), median: N + 1
– SD or SE: N + 2
Percentages will be reported to one decimal place. Where counts are zero, percentages will not appear in the output.
P-values will be reported to three decimal places, except values <1.000 but >0.999 will be presented as ">0.999" (eg, 0.9998 is presented as >0.999). P-values <0.001 will be presented as "<0.001" (eg, 0.0009 is presented as <0.001). Rounding will be applied after the <0.001 and >0.999 rule.

Dates & Times

Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:PPD

Spelling Format

English US.

Presentation of Treatment Groups

For outputs, treatment groups will be represented as follows and in the given order:

Treatment Group	For Tables and Graphs	For Listings (include if different to tables)
Galcanezumab 120 mg SC once monthly	Galcanezumab	Galcanezumab
Rimegepant 75 mg ODT every other day	Rimegepant	Rimegepant
Not Randomized		Not Randomized

Presentation of Visits

For outputs, visits will be represented as follows and in that order:

Long Name (default)	Short Name
Screening (Visit 1)	Scr (V1)
Baseline (Visit 2)	BL (V2)
Randomization (Visit 3)	RND (V3)
Month 1 (Visit 4)	M1 (V4)
Month 2 (Visit 5)	M2 (V5)
Month 3 (Visit 6)	M3 (V6)

Listings

All listings will be ordered by the following (unless otherwise indicated in the template):
Randomized treatment group (or treatment received if it's a safety output), first by Galcanezumab and then Rimegepant,
Center-subject ID,
Date (where applicable),
For listings where non-randomized participants are included, these will appear in a category after the randomized treatment groups labeled "Not Randomized".

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

AE START DATE	AE STOP DATE	ACTION
Known	Known/Partial/ Missing	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known/Partial/ Missing	Not TEAE
Partial, could be on or after study med start date OR Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

AE START DATE	AE STOP DATE	ACTION

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:

CM START DATE	CM STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of double-blind treatment period, assign as concomitant
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of double-blind treatment period, assign as concomitant
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of double-blind treatment period, assign as concomitant
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of double-blind treatment period, assign as concomitant

CM START DATE	CM STOP DATE	ACTION
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of double-blind treatment period, assign as concomitant
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= end of double-blind treatment period, assign as concomitant
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant
	Missing	Assign as concomitant

APPENDIX 3. DESCRIPTION OF IMPORTANT PROTOCOL DEVIATIONS

Category	Subcategory	Study-specific	Source	Comments
ICF	ICF not obtained	Initial ICF date is missing or is after (Visit 1 date or Visit 1 lab date)	Programmable - Stats	
	Improper ICF	ICF not signed prior to initiation of protocol procedures	Non-programmable - Monitor identified	
	Improper ICF	Patient not provided ICF in language appropriate for this study and their language proficiency (English or US Spanish)	Non-programmable - Monitor identified	
Eligibility	Inclusion/ Exclusion	Age <18 or >65 years old at study entry (if enrolled under Amendment A)	Non-programmable- Monitor identified	
		Age <18 or >75 years old at study entry (if enrolled under Amendment B or later)	Non-programmable- Monitor identified	
		Number of migraine headache days <4 or >14 per 30-day period at baseline	Programmable - Stats	Based on normalized number of migraine headache days.
		Number of migraine attack <2 per 30-day period at baseline	Programmable - Stats	Based on normalized number of migraine headache days.
		Baseline ePRO compliance <80%	Programmable - Stats	
		Female patients have a positive serum pregnancy test prior to randomization visit	Programmable - Stats	

Category	Subcategory	Study-specific	Source	Comments
Eligibility	Inclusion/ Exclusion	Patient is pregnant at time of randomization	Non-programmable-Monitor identified	
		Insufficient washout of prohibited migraine preventive medication for at least 5 days prior to Visit 2	Programmable - Stats	Patients must have discontinued such treatment at least 5 days prior to Visit 2.
		Insufficient Washout of Botulinum toxin A and B at least 3 months prior to Visit 2 if for therapeutic use	Non-Programmable-Study Team identified	1) Stats will create the list of patients who meet this IPD criteria. 2) Among those, the true IPDs will be manually added into non-programmable Excel spreadsheet. 3) A month may be defined as 4 weeks.
		Insufficient Washout of Nerve Block or Device Use in the head or neck area or for migraine prevention at least 30 days prior to Visit 2	Non-Programmable-Study Team identified	1) Stats will create the list of patients who meet this IPD criteria. 2) Among those, the true IPDs will be manually added into non-programmable Excel spreadsheet.
		Current or prior exposure to a CGRP antagonist	Non-Programmable-Study Team identified	1) Stats will create the list of patients who meet this IPD criteria. 2) Among those, the true IPDs will be manually added into non-programmable Excel spreadsheet.
		BMI ≥40 at baseline	Programmable - Stats	
		Positive or No urine drug screen prior to randomization	Programmable - Stats	For randomized patients if prior to Visit 3, a patient has a positive UDS result and a repeated UDS not done or last repeat UDS is positive or UDS never collected.
		Other inadvertent enrollment which is deemed clinically important by Lilly Medical	Non-Programmable-Study Team identified	Not all inadvertent enrollments will necessarily be considered clinically important.

Category	Subcategory	Study-specific	Source	Comments
Data Quality	Missing Data	Diary compliance <=50% for half or more of patient's double-blind treatment phase participation	Programmable – Stats	With <=50% ePRO compliance rate for half or more months of double-blind treatment phase, where "month" refers to a dosing interval. For example, • if patient remained in the study for 3 months (i.e., dose intervals), and >=2 months have epro compliance <=50%. • if patient remained in the study for 1 or 2 months (i.e., dose intervals), and >=1 months have epro compliance <=50%. Lost to follow-up patients' last month interval should not be included in the consideration above. If a patient discontinued before Visit 4 or if total time in double-blind period was less than 2 weeks, the patient should not be counted here.
		Missing safety measurement: vital signs (Blood pressure, body temperature, pulse) at baseline or in SP III		For randomized patients, if blood pressure, body temperature, or pulse are missing all baseline measures or missing all post-baseline measures during the double-blind treatment period. For patients who discontinued due to "lost to follow up", if all postbaseline measures are missing, it is not an important protocol deviation
		Missing safety measurement: Chemistry or Hematology at baseline or in SP III	Programmable – Stats	For randomized patients, if calcium and hemoglobin are missing all baseline measures, or if there is non-missing Visit 6 or early termination data and missing the post-baseline measures in the double-blind treatment period. For patients who discontinued due to "lost to follow up", if all post-baseline measures are missing, it is not an important protocol deviation.

Category	Subcategory	Study-specific	Source	Comments
Data Quality	Missing Date	Missing safety measurement: ECGs at baseline and in SP III	Non-programmable-Monitor identified	Same rule as for "Missing safety measurement: Chemistry or hematology at baseline or in SP III".
		Missing hepatic follow-up labs	Non-Programmable-Study Team identified	
	Treatment Assignment/ Randomization Error	IWRS data entry errors that impact patient stratification	Programmable – Stats	If migraine headache day categories (<8 vs ≥8) from IWRS was different from derived from ePRO.
Study Procedures	Discontinuation	Participant met at least one criterion for Study intervention discontinuation, but continued with dosing	Non-programmable-Monitor identified	
		Participant met at least one criterion for Study discontinuation, but continued in the study with dosing	Non-programmable-Monitor identified	
	Excluded Conmeds	Taking prohibited migraine preventive medication for primary study indication for >7 consecutive days during SP II or III	Programmable - Stats	Prior therapy should be excluded in the consideration.
		Taking prohibited migraine preventive medication for any indication for >7 consecutive days during SP II or III	Programmable - Stats	Prior therapy should be excluded in the consideration.

Category	Subcategory	Study-specific	Source	Comments
Study Procedures	Excluded Conmeds	Taking Botulinum toxin A and B in the head or neck for therapeutic indication during SP II or III	Non-Programmable- Study Team identified	1) Stats will create the list of patients meet this IPD criteria. 2) Among those, the true IPDs will be manually added into non-programmable excel sheet.
		Opioid, barbiturate, or steroid use >7 consecutive days during SP II or III	Programmable - Stats	Prior therapy should be excluded in the consideration.
		Any use of NURTEC (rimegepant) during SPII or III as a concomitant medication	Non-Programmable- Study Team identified	1) Stats will create the list of patients meet this IPD criteria. 2) Among those, the true IPDs will be manually added into non-programmable excel sheet.
		Taking prohibited CGRP antagonist (oral; except rimegepant) for >7 consecutive days during SPII or III	Non-Programmable- Study Team identified	1) Stats will create the list of patients meet this IPD criteria. 2) Among those, the true IPDs will be manually added into non-programmable excel sheet.
		Any use of a CGRP antagonist (monoclonal antibody) during SPII or III as a concomitant medication	Non-Programmable- Study Team identified	1) Stats will create the list of patients meet this IPD criteria. 2) Among those, the true IPDs will be manually added into non-programmable excel sheet.
Investigational Product	Medication not fit for use	Patient received drug that was declared "Not Fit for Use"	Non-programmable - Monitor identified	
	Dosing Error	Significant violations of study drug dosing	Non-programmable - Monitor identified and Study Team identified	1) Stats will create the list of patients who have incorrect dosing (not including skipped dose). 2) Monitors will identify other events not able to be captured by programming (such as switched IP packages) 3) Medical will review both lists and identify IPDs to be manually added into non-programmable Excel sheet.
	Injection Schedule	Skipped dose of study drug	Programmable - Stats	Will not be a protocol deviation if the patient's study intervention was withheld by the investigator for safety reasons

Category	Subcategory	Study-specific	Source	Comments
Investigational Product	ODT schedule	Taking <80% or >120% of prescribed ODT doses	Programmable - Stats	Will not be a protocol deviation if the patient's study intervention was withheld by the investigator for safety reasons
	Unblinding	Unjustified un-blinding of patient treatment assignment	Non-programmable - Monitor identified	
Administrative/ Oversight	Suspected misconduct	Suspected Fraud	Non-programmable - Monitor identified	
	Patient privacy violation	Privacy Breach	Non-programmable - Monitor identified	This will only include those events which result in a full de-identification of the patient.
Safety	Other	Site did not appropriately report SAE	Non-programmable - Monitor identified	Failure to report an SAE within a reasonable timeframe relative to the requirement of within 24 hours of the investigator being made aware of the SAE (for example 28 hours would not be an important deviation); Failure to respond to SAE queries.
		Dosed female has positive pregnancy test during the treatment phase and not discontinued from treatment	Non-programmable - Monitor identified	

Abbreviations: BMI = body mass index; Conmeds = concomitant medications; ICF = informed consent form; IPD=important protocol deviations; ePRO= electronic patient reported outcome; SAE = serious adverse event.