Protocol: I5Q-MC-CGBD(d)

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

NCT05127486

Approval Date: 02-Nov-2022

Title Page

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Protocol Number: I5Q-MC-CGBD

Amendment Number: d

Compound: Galcanezumab (LY2951742)

Brief Title: A Study to Investigate the Efficacy and Safety of Galcanezumab Versus Rimegepant in Adult Participants with Episodic Migraine

Study Phase: 4

Acronym: CHALLENGE-MIG

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s)

IND: 111295

Approval Date: Protocol Amendment (d) Electronically Signed and Approved by Lilly on date provided below.

Document ID: VV-CLIN-075435

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment c	*22-Sep-2022*
Amendment b	*18-Feb-2022*
Amendment a	*06-Aug-2021*
Original Protocol	*09-Jun-2021*

Amendment d

The amendment is considered to be substantial because it is likely to have a significant impact on the safety or the rights of study participants.

Overall Rationale for the Amendment:

The purpose of this amendment is to modify the contraceptive requirements for women of child bearing potential.

Section # and Name	Description of Change	Brief Rationale
Section 5.1. Inclusion Criteria: Criterion 7(b)	Updated the contraception requirements from 2 effective forms to single form	Modified to align with recent internal guidance

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title:

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

Brief Title:

A Study to Investigate the Efficacy and Safety of Galcanezumab Versus Rimegepant in Adult Participants with Episodic Migraine

Rationale:

Identification of CGRP signaling in the pathophysiology of migraine led to the development and approval of 4 novel migraine-specific preventive biologics. One of these, galcanezumab, is a humanized monoclonal antibody that selectively and potently binds to CGRP and prevents CGRP from binding to the receptor and has demonstrated efficacy in migraine prevention with a favorable safety profile (Emgality package insert, 2019).

More recently, oral CGRP receptor antagonists, gepants, have been approved for the acute treatment of migraine. One of these, rimegepant, has recently been approved by the FDA for the preventive treatment of migraine (Nurtec ODT package insert, 2021).

To date, there are no studies that have directly compared the efficacy and safety between CGRP antagonists in migraine prevention, creating a gap in the information needed by healthcare providers and their participants to make informed decisions regarding their treatment.

This study will compare the efficacy and safety of galcanezumab to rimegepant in participants with episodic migraine.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
To assess whether galcanezumab is superior to rimegepant in the prevention of migraine in participants with episodic migraine.	The percentage of participants with ≥50% reduction from baseline in monthly migraine headache days across the 3-month double-blind treatment period.

Objectives	Endpoints
Key Secondary Objectives	
If galcanezumab is statistically superior to rimegepant on the primary objective, the following key secondary objectives will be tested with adjustment for multiplicity:	
• 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.
• 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: o Month 3 o Month 2 o Month 1	• 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.	• 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.

Overall Design

Study CGBD is a multi-site, randomized, double-blind, double-dummy, parallel-group, Phase 4 study with 3 study periods in participants who meet ICHD criteria for a diagnosis of migraine with or without aura with an episodic frequency of 4 to 14 migraine headache days per month.

Brief Summary:

The purpose of this study is to assess whether galcanezumab is superior to rimegepant in the prevention of migraine in participants with episodic migraine.

The study duration will be approximately 5 months.

The treatment duration will be approximately 3 months.

The visit frequency will be approximately monthly.

Number of Participants:

Approximately 1150 participants will be screened to achieve a minimum of approximately 575 randomized study participants.

Intervention Groups and Duration:

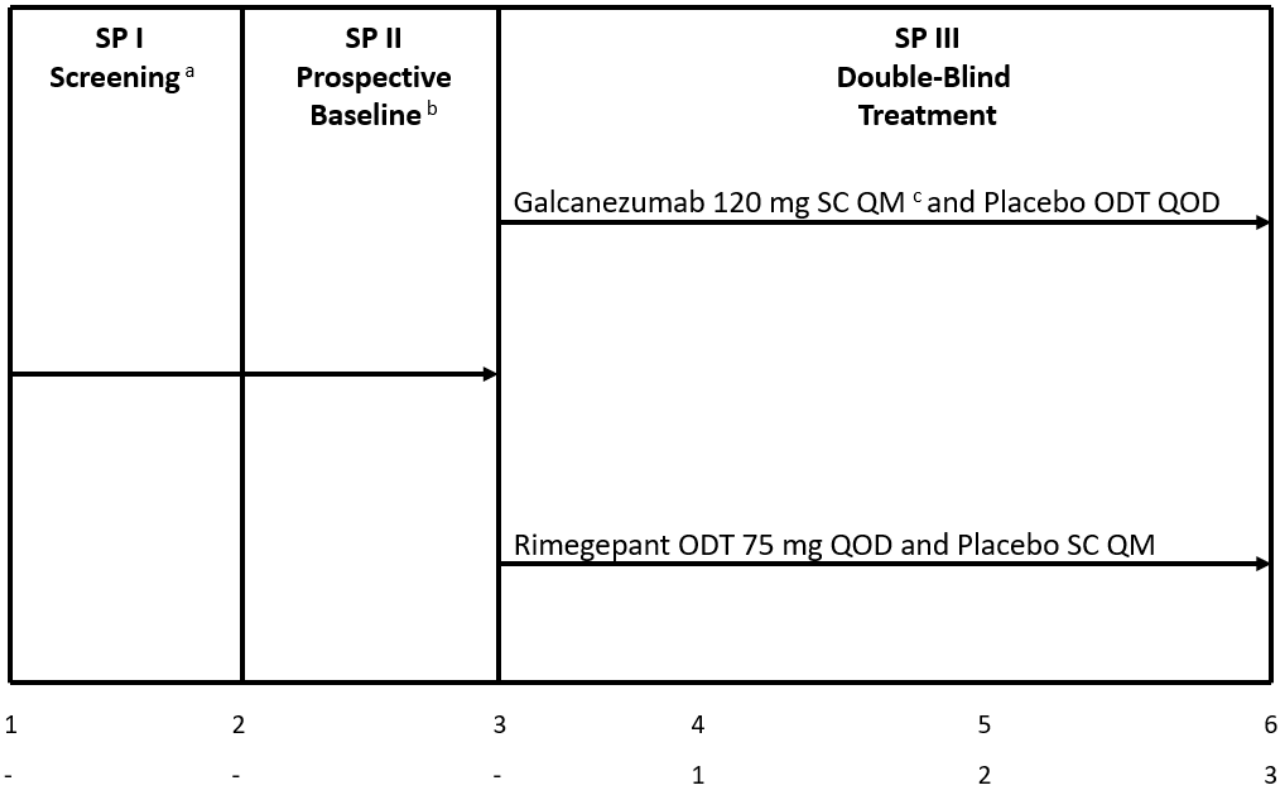
Interventions:

- Galcanezumab 120 mg subcutaneous injection once monthly, with a 240 mg loading dose as the initial dose
- Rimegepant 75 mg oral tablet every other day

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

Data Monitoring Committee: No

1.2. Schema



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

[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.

1.3. Schedule of Activities (SoA)

SP I – Screening Visit 1 procedures may be conducted over more than 1 day as long as all activities are completed within the allowable visit tolerance.		**SP II – Prospective Baseline**	**SP III – Double-Blind Treatment**				**ET**	**Comments**
Visit Number	1	2	3	4[a]	5[a]	6		
Month relative to randomization (V3)	*	**		1	2	3		*Screening lasts from 3 to 30 days. ** 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. For scheduling purposes, a month is 30 days.
Interval allowance (days)			-	±2	±2	±2		
Telephone Visit				X	X			See footnote a.
Informed consent	X							The ICF must be signed before any protocol-specific tests or procedures are performed.
Inclusion and exclusion, review and confirm	X	X	X					
Demographics	X							
Medical history	X							
Substance use	X							Substances: alcohol, caffeine, nicotine, tobacco
Concomitant medications	X	X	X	X	X	X	X	
AE	X	X	X	X	X	X	X	Any events that occur after signing the ICF are considered AEs as defined in Section 10.3.
Physical Evaluation								
Height	X							
Weight	X							
12-lead ECG (local)	X					X	X	ECGs should be collected prior to blood draws. Participants should be supine for approximately 5 to 10 minutes before ECG collections and remain supine but awake during the ECG collection. See Section 8.2.3 for additional details.
Vital signs	X		X			X	X	Includes body temperature, sitting blood pressure, and pulse.

SP I – Screening Visit 1 procedures may be conducted over more than 1 day as long as all activities are completed within the allowable visit tolerance.		**SP II – Prospective Baseline**	**SP III – Double-Blind Treatment**				**ET**	**Comments**
Visit Number	1	2	3	4[a]	5[a]	6		
Month relative to randomization (V3)	*	**		1	2	3		*Screening lasts from 3 to 30 days. ** 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. For scheduling purposes, a month is 30 days.
Interval allowance (days)			-	±2	±2	±2		
Telephone Visit				X	X			See footnote a.
								Blood pressure and pulse will be measured in triplicate after participant has been sitting for at least 5 minutes, and prior to blood draws.
Physical examination	X							
Neurological examination	X							
Laboratory Tests and Sample Collections								
Hematology	X					X	X	
Clinical chemistry[b]	X					X	X	
Urinalysis	X					X	X	
UDS	X							Participants may re-test, but must be negative at or prior to V2
Serum pregnancy or FSH for female participants[c]		X				X	X	Collect serum pregnancy for WOCBP only. Collect FSH at V2 to confirm post-menopausal status in women aged 40 to 55 (inclusive) as outlined in footnote c. Additional pregnancy tests (beyond those required per the SoA) should be performed at any time during the trial if a menstrual period is missed, there is clinical suspicion of pregnancy, or as required by local law or regulation.

SP I – Screening Visit 1 procedures may be conducted over more than 1 day as long as all activities are completed within the allowable visit tolerance.		**SP II – Prospective Baseline**	**SP III – Double-Blind Treatment**				**ET**	**Comments**
Visit Number	1	2	3	4[a]	5[a]	6		
Month relative to randomization (V3)	*	**		1	2	3		*Screening lasts from 3 to 30 days. ** 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. For scheduling purposes, a month is 30 days.
Interval allowance (days)			-	±2	±2	±2		
Telephone Visit				X	X			See footnote a.
Urine pregnancy	X		X	X	X			Collect for WOCBP only. Prior to dosing at V3, V4, and V5, a patient must test negative for pregnancy. Patients will self-administer urine pregnancy tests at home at V4 and V5. If the urine pregnancy test is positive, both SC and oral study interventions should be withheld and a serum pregnancy test conducted.
Scales, Questionnaires, and Outcome Measures								
ePRO and headache medication log training		X						
ePRO daily diary		Participant completes daily						
Headache medication log (paper)		The participant records the date, name, dose, and number of acute medications taken						The headache medication log should be returned to site staff at the final office visit or ET visit.
Collect ePRO diary and paper headache medication log						X	X	
Participant training video (participation in a clinical trial)		X						Videos may be viewed at either V2 or V3.

SP I – Screening Visit 1 procedures may be conducted over more than 1 day as long as all activities are completed within the allowable visit tolerance.		**SP II – Prospective Baseline**	**SP III – Double-Blind Treatment**				**ET**	**Comments**
Visit Number	1	2	3	4[a]	5[a]	6		
Month relative to randomization (V3)	*	**		1	2	3		*Screening lasts from 3 to 30 days. ** 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. For scheduling purposes, a month is 30 days.
Interval allowance (days)			-	±2	±2	±2		
Telephone Visit				X	X			See footnote a.
Participant training video (self-injection of study intervention)		X						
MSQ v2.1			X			X	X	Participant-rated assessments completed onsite should be completed prior to administration of study intervention and clinical examination.
MIDAS			X			X	X	
PGI-S			X			X	X	
Randomization and Dosing								
Randomization			X					
Study intervention administration at site (SC and ODT)			X					Study intervention will be administered by unblinded study personnel onsite at V3 (both SC and ODT) after all other visit procedures are completed.
Dispense study intervention and ancillary supplies			X					Study intervention is dispensed by unblinded study personnel in ancillary containers.
Administration of ODT study intervention at home				X				Participants will self-administer their ODT every other day at home.
Administration of SC study intervention at home				X	X			Participants to self-administer the SC study intervention at home prior to the telephone visit with the study site.
Return unused study intervention and ancillary supplies						X	X	Return any unused study intervention in the ancillary containers to unblinded site personnel.

Abbreviations: AE = adverse event; ECG = electrocardiogram; ePRO = electronic patient-reported outcomes; ET = early termination; FSH = follicle stimulating hormone; ICF = informed consent form; MIDAS = Migraine Disability Assessment; MSQ v2.1 = Migraine-Specific Quality of Life Questionnaire version 2.1; ODT = orally disintegrating tablet; PGI-S =Patient Global Impression of Severity; SC = subcutaneous; SP = study period; UDS = urine drug screen; V = visit; WOCBP = woman of childbearing potential.

[a]Visits 4 and 5 are to confirm/assess the following: administration of study intervention prior to the telephone call; WOCBP completed a urine pregnancy test prior to administration of study intervention; and collection/review spontaneously reported AEs and concomitant medications. Participants to be reminded to complete the ePRO diary daily and record any acute migraine medication use into the headache medication log.

[b]Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with participants in consultation with Lilly, or its designee. See Section 10.5 for more details regarding specific hepatic monitoring tests. If the participant has discontinued the trial and returns for hepatic follow-up, the site should use the 800 series as the visit designation.

[c]FSH is collected to confirm post-menopausal status at V2 in women aged 40 to 55 (inclusive) with an intact uterus, not on hormone therapy, who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with an FSH >40 mIU/mL.

2. Introduction

2.1. Study Rationale

Identification of CGRP signaling in the pathophysiology of migraine led to the development and approval of 4 novel migraine-specific preventive biologics. One of these, galcanezumab, is a humanized monoclonal antibody that selectively and potently binds to CGRP and prevents CGRP from binding to the receptor and has demonstrated efficacy in migraine prevention with a favorable safety profile (Emgality package insert, 2019).

More recently, oral CGRP receptor antagonists, gepants, have been approved for the acute treatment of migraine. One of these, rimegepant, has recently been approved by the FDA for the preventive treatment of episodic migraine (Nurtec ODT package insert, 2021).

To date, there are no studies that have directly compared the efficacy and safety between CGRP antagonists in migraine prevention, creating a gap in the information needed by healthcare providers and their participants to make informed decisions regarding their treatment.

This study will compare the efficacy and safety of galcanezumab to rimegepant in participants with episodic migraine.

2.2. Background

Migraine is a chronic, debilitating condition that is the second highest cause of disability worldwide (Vos et al. 2017), and is associated with a substantial impact on the participant's quality of life and ability to work (Leonardi and Raggi 2019). Guidelines recommend preventive treatment in participants with more than 3 days per month of headache-related disability (Lipton and Silberstein 2015).

CGRP is a potent vasodilator (Brain et al. 1985) with well-established roles in neurogenic inflammation and nociception (Hirsch et al. 2013) and has been established as a valid therapeutic target in migraine (Chiang and Schwedt 2020). Early studies suggesting a role of CGRP in migraine showed increased plasma or serum levels of CGRP during migraine attacks (Goadsby et al. 1990; Goadsby and Edvinsson 1993; Juhasz et al. 2003; Juhasz et al. 2005). Additionally, CGRP infusion was shown to induce migraine attacks that were indistinguishable from a spontaneous attack in individuals with migraine (Lassen et al. 2002; Hansen et al. 2010). Subsequently, studies demonstrated that inhibition of CGRP signaling was efficacious in reducing the frequency of migraine (Charles and Pozo-Rosich 2019).

The efficacy and safety of galcanezumab, a humanized monoclonal antibody that potently and selectively binds to CGRP to prevent CGRP-mediated biological effects, has been established in several clinical trials in episodic and chronic migraine, including 2 placebo-controlled, Phase 3 clinical trials for preventive treatment in episodic migraine (Skljarevski et al. 2018; Stauffer et al. 2018).

In addition, the efficacy and safety of rimegepant, a small molecule oral CGRP receptor antagonist, has been evaluated in a Phase 2/3 study for preventive treatment of migraine (Croop et al. 2021).

No data are currently available that directly compare galcanezumab with an oral CGRP antagonist in a clinical study. This study will evaluate galcanezumab and rimegepant using the

same endpoints in the same clinical setting and will provide important information to clinicians when making treatment decisions for their participants.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of galcanezumab may be found in the IB and USPI (Emgality package insert, 2019).

More detailed information about the known and expected benefits and risks and reasonably expected AEs of rimegepant may be found in the Package Insert (Nurtec ODT package insert, 2021).

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
To assess whether galcanezumab is superior to rimegepant in the prevention of migraine in participants with episodic migraine.	The percentage of participants with ≥50% reduction from baseline in monthly migraine headache days across the 3-month double-blind treatment period.
Key Secondary Objectives	
If galcanezumab is statistically superior to rimegepant on the primary objective, the following key secondary objectives will be tested with adjustment for multiplicity:	
• 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.
• 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: o Month 3 o Month 2 o Month 1	• 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.	• 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.

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

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 2 A criteria and 0 B criteria, or 1 A criteria and at least 1 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).

Abbreviations: ICHD = International Classification of Headache Disorders; IHS = International Headache Society.

Primary estimand/coprimary estimand

See Sections 9.3.2 and 9.3.3 for estimands.

4. Study Design

4.1. Overall Design

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.

Interventions:

- Galcanezumab 120 mg SC once monthly, with a 240 mg loading dose as the initial dose
- Rimegepant 75 mg ODT every other day

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

Designated unblinded site personnel will be responsible for the receipt of study intervention shipments, handling, dispensing, and at V3, training administration of study interventions (galcanezumab, rimegepant, and respective placebo). The designated unblinded site personnel are also responsible for recording information in the Study Drug Administration Log and confirming treatment assignments. CCI [redacted] CCI [redacted]
Unblinded site personnel will not be involved in participant screening, enrollment, and assessment of efficacy or safety. It is critical that the blind is maintained throughout the study (3 months).

4.1.1. Study Period I: Screening (Visit 1)

At Visit 1:

- The study and potential risks will be explained to the participant.
- The ICF must be signed before any study procedures are performed.
- A full clinical assessment (including a comprehensive medical evaluation documenting medical history, and a physical and neurological examination [see SoA, Section 1.3]).

Visit 1 may occur across more than 1 day and is complete when the last scheduled procedure of the screening assessment for the participant is completed. Participants are required to discontinue all excluded medications (see Sections 5, 6.8 and 10.2).

Qualified participants will enter Study Period II (prospective baseline; Section 4.1.2) to determine their eligibility for the study (Inclusion Criteria #4 and #5) and to establish baseline data for comparison of endpoints during the treatment period.

4.1.2. Study Period II: Prospective Baseline (Visit 2)

At Visit 2:

- Participants are to be set-up and trained on their ePRO diary and instructed to begin logging in daily (beginning the day of Visit 2) to the ePRO diary to answer questions about the occurrence of
  - headaches,
  - headache duration,

  - headache features,
  - severity of headache, and
  - whether any acute headache medication was taken.
- Participants will record the name, dose, and date of any acute headache medication on a separate paper headache medication log.
  NOTE: The headache medication log should be returned to site staff at the final office visit or early termination visit.

Processing of Visit 2 in IWRS triggers the initial shipment of study intervention; therefore, ensure Visit 2 is completed in IWRS promptly.

Sites will be notified via an eligibility report whether the participant met criteria and are eligible to be randomized at Visit 3 (See Section 4.1.3). Eligibility is assessed beginning on Day 30 through Day 40, if needed, of the prospective baseline period. Investigators have up to 5 additional days if needed to schedule participant's Visit 3 appointment.

To avoid biased reporting, participants must not be told the number of migraine headache days on which study qualification is based.

At either Visit 2 or Visit 3:

- If available and where local regulations and Ethical Review Boards allow, participants will also watch two training videos
  - Video 1: is designed to address participant expectation with regards to participation in trial which includes placebo and the difference between medical treatment and research
  - Video 2: self-injection of SC study intervention video

  NOTE: If the participant watched the video at Visit 2, they do not need to watch the video again at Visit 3. However, if the participant watched 1 video at Visit 2, the participant must watch the remaining video at Visit 3.

4.1.3. Study Period III: Double-Blind Treatment (Visits 3–6)

At Visit 3:

- Participants meeting all eligibility requirements will be randomized in a 1:1 ratio to receive either galcanezumab subcutaneously or rimegepant ODT.
  - A participant will be considered enrolled in the study when randomization occurs. To preserve blinding throughout the study, each treatment group will receive both SC injection(s) monthly and an ODT every other day, as described in Section 6.1.
- Participants receive first dose of study intervention as the last procedure of Visit 3.
  - The participant (or caregiver) will also be appropriately trained in how to administer SC injection and take the orally dissolving tablet. All participants will receive:
    - 2 SC injections of study intervention (2 galcanezumab injections of 120 mg or 2 placebo injections), and
    - 1 ODT of study intervention (rimegepant 75 mg ODT or placebo ODT).

After Visit 3

The monthly SC injections of study intervention will be administered by the participant or caregiver on the same day, but prior to, the scheduled telephone visits (Visits 4 and 5). Similarly, after Visit 3, participants will self-administer the ODT study intervention every other day.

Visit 5 is the last dose of the injectable study intervention.

The last dose of the ODT study intervention should be taken no later than the last scheduled office visit (Visit 6 [approximately 90 days after Visit 3]) or early termination.

Participants will continue to log in and complete the ePRO diary each day.

Participants may continue to take their allowed acute migraine headache medication (with some limitations; see Section 6.8 and 10.2) during the treatment period and will continue to record this use in the headache medication log.

4.2. Scientific Rationale for Study Design

This study will examine the effect of galcanezumab versus rimegepant in participants with episodic migraine.

The length of the randomized, parallel, double-blind treatment period (3 months) is considered a sufficient duration to demonstrate the efficacy of a migraine preventive medication, given the validated mechanism in migraine prevention and observed onset of action for the CGRP antagonists, including galcanezumab and rimegepant (Dodick et al. 2014a, 2014b; Schwedt et al. 2018; Croop et al. 2021; Kuruppu et al. 2021).

The primary endpoint, 50% or greater reduction in monthly migraine headache days, was selected as it is a direct and clinically relevant measure, and it provides a reliable and valid measurement of the intended treatment effect (AHS 2019).

4.3. Justification for Dose

The galcanezumab dosing regimen used in this study is the approved dose for the treatment of migraine in adults (Emgality package insert, 2019).

The rimegepant dosing regimen used in this study is the approved dose for the preventive treatment of episodic migraine in adults (Nurtec ODT package insert, 2021).

4.4. End of Study Definition

The end of the study is defined as the date of last scheduled procedure shown in the SoA for the last participant in the trial.

A participant is considered to have completed the study if the participant has completed all periods of the study including the last scheduled procedure shown in the SoA.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be 18 to 75 years of age (inclusive) at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Have a diagnosis of migraine as defined by IHS ICHD-3 guidelines (1.1 or 1.2) (ICHD-3 2018), with a history of migraine headaches of at least 1 year prior to Visit 1, and migraine onset prior to age 50.
3. Prior to Visit 1, have a history of 4 to 14 migraine headache days and at least 2 migraine attacks per month on average within the past 3 months.
4. From Visit 2 to Visit 3 (prospective baseline period), have a frequency of 4 to 14 migraine headache days and at least 2 migraine attacks (Section 3, Migraine and Headache Endpoint Definitions table).
   To avoid biased reporting, participants must not be told the number of migraine headache days on which study qualification is based.
5. From Visit 2 to Visit 3 (prospective baseline period), must achieve sufficient compliance with ePRO daily headache entries as demonstrated by completion of at least 80% of daily ePRO diary entries.

Weight

6. Body mass index (BMI) <40 kg/m^2.

Sex and Contraceptive/Barrier Requirements

7. Males and females may participate in this trial.
   a. Males
      i. No male contraception is required except in compliance with specific local government study requirements.
   b. Females
      i. WOCBP must test negative for pregnancy at Visit 1.
      ii. WOCBP must agree to use 1 form of highly effective contraception during the study as well as for 5 months after the last dose of study intervention or remain completely abstinent as their preferred and usual lifestyle, or in a same-sex relationship, as part of their preferred and usual lifestyle during the study and for 5 months after the last dose of study intervention (refer to the Reference Manual for acceptable forms of contraception).
      Birth control is not required if the female is infertile due to surgical sterilization (examples of surgical sterilization include bilateral salpingo-oophorectomy, bilateral salpingectomy, bilateral oophorectomy, or total hysterectomy) or is post-

menopausal. The post-menopausal state is defined as at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy at any age, confirmed by operative note; or a cessation of menses for at least 12 consecutive months not induced by a medical condition or hormone therapy, and a follicle-stimulating hormone level >40 mIU/mL in women aged 40 to 55 years with an intact uterus; or at least 12 months of spontaneous amenorrhea in women aged 55 years or older not on hormone therapy, or who have a diagnosis of menopause prior to starting hormone replacement therapy.

Informed Consent

8. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
9. Agree not to post any personal medical data related to the study or information related to the study on any website or social media site (for example, Facebook, Twitter, LinkedIn, and Google+) until the entire trial has completed.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

10. Known hypersensitivity to rimegepant or galcanezumab, and their excipients, or to monoclonal antibodies or other therapeutic proteins.
11. Have local reading of ECG at Visit 1 showing abnormalities compatible with acute cardiovascular events and/or serious cardiovascular risk, or have had myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass graft, or stroke within 6 months of screening, or have planned cardiovascular surgery or percutaneous coronary angioplasty. QTcF >450 msec for males or >470 msec for females based on the ECG at Visit 1 must be discussed and judged not clinically significant by the principal investigator and Lilly Medical informed prior to enrollment.
12. Any liver tests outside the normal range at Visit 1 that are clinically significant. ALT >2x ULN, or TBL >1.5x ULN, or ALP >2x ULN must be judged not clinically significant by the principal investigator, and Lilly Medical informed prior to enrollment.
13. Evidence of psychiatric disease by medical history, such as schizophrenia, personality disorders, or other serious mood or anxiety disorders.
    Note: Participants with major depressive disorder (MDD), an anxiety disorder, or bipolar disorder whose disease state is considered stable and expected to remain stable throughout the course of the study, in the opinion of the investigator, may be considered for inclusion if they are not on excluded medications.
14. Participants who, in the clinician's judgment, are actively suicidal and therefore deemed to be at significant risk for suicide, or have had clinically significant suicidal ideation within the past month (for example, includes some plan or intent to act), or have had any suicidal behavior within the past month.
15. Women who are pregnant or nursing.

16. Have an acute, serious, or unstable medical condition that, in the judgment of the investigator, indicates a medical problem that would preclude study participation.

Prior/Concomitant Therapy

17. Current use or prior exposure to **any** CGRP antagonist (small molecule or antibody) for any indication, including those who have previously completed or withdrawn from this study or any other study investigating a CGRP antagonist (small molecule or antibody).
18. Are currently receiving medication or other treatments for the prevention of migraine. Participants must have discontinued such treatment at least 5 days prior to Visit 2. Botulinum toxin A and B that has been administered in the head or neck area for therapeutic use must be discontinued at least 3 months prior to Visit 2. Nerve blocks or device use (such as transcranial magnetic stimulation) in the head or neck area or for migraine prevention must be discontinued at least 30 days prior to Visit 2.
19. Exclusion Criterion [19] was removed.
20. Concomitant use of inhibitors of P-gp and BCRP are prohibited, and use of moderate or strong CYP3A4 inhibitors and moderate or strong CYP3A inducers is prohibited.
21. Participants who have used opioids or barbiturate containing analgesic >4 days per month for the treatment of pain in more than 2 of the past 3 months (opioid administration in an emergency setting may be an exception).
22. History of drug or alcohol abuse/dependence within 1 year prior to Visit 1 (excessive or compulsive use as judged by the investigator), or currently using drugs of abuse (including opioids, barbiturates, and marijuana), or any prescribed or over-the-counter medication in a manner that the investigator considers indicative of abuse/dependence.
23. Have a positive urine drug screen for any substances of abuse at Visit 1.
    Note: A retest is allowed if the urine drug screen is positive for any prescribed substance or if, in the judgment of the investigator, there is an acceptable medical explanation for the positive result. The results of the retest must be negative at or prior to Visit 2.
    i. Participants who have a positive urine drug screen for an amphetamine or benzodiazepine that are prescribed for an approved indication other than migraine or headache may be allowed in the study at the Investigator's discretion providing the dose of the medication is stable for at least 2 months prior to Visit 2 and is expected to remain stable during Visit 2 through 6. The investigator must document their determination in the participant's source medical records.
    ii. Participants who have a positive urine drug screen for cannabis or cannabinoids which is prescribed (not recreational) for a condition other than migraine or headache may be allowed in the study provided the use is not expected to affect the interpretation of study results or safety of the participant. The usage should remain consistent for the duration of the study. The investigator must document their determination in the participant's source medical records.

Prior/Concurrent Clinical Study Experience

24. Are currently enrolled in any other clinical trial involving a study intervention or any other type of medical research judged not to be scientifically or medically compatible with this study.
25. Have participated within the last 30 days or within 5 half-lives (whichever is longer) in a clinical trial involving an investigational product. If the investigational product's half-life is not known, 6 months should have passed prior to Visit 1.

Diagnostic Assessments

26. History of new daily persistent headache, cluster headache or migraine subtypes including hemiplegic (sporadic or familial) migraine, retinal migraine, and migraine with brainstem aura (basilar-type migraine) defined by IHS ICHD-3.
27. In the 3 months prior to randomization, have other types of headache besides migraine or tension type headache as defined by IHS ICHD-3. In other words, participants can have migraine or tension-type headache, but they cannot have other types of headache in that time. For instance, medication overuse headache or cluster headache.

33. Prior to Visit 1, a history of ≥15 headache days (migraine, probable migraine or any other headache) per month on average during the past 3 months or are suspected of suffering from chronic migraine as defined per IHS ICHD-3.

28. History of head or neck injury within 6 months prior to Visit 1.
29. History of traumatic head injury associated with significant change in the quality or frequency of their headaches.

Other Exclusions

30. Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
31. Are Lilly employees.
32. In the opinion of the investigator have other issues which would interfere with compliance with the study requirements and completion of evaluations required for this study.

5.3. Lifestyle Considerations

Not applicable.

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once with approval from Lilly Medical for only the criteria shown below. If rescreening is performed, the participant must sign a new ICF and will be assigned a new participant number.

A participant may rescreen when sufficient time has passed for the participant to meet the duration requirement or condition of the following criteria during the study enrollment period:

- Inclusion Criterion [1] (Age): if the participant is less than age 18 at the time of informed consent, they may be rescreened if they reach age 18 during the study enrollment period
- Inclusion Criterion [7]: Negative pregnancy test
- Exclusion Criterion [15]: Women who are pregnant or nursing
- Exclusion Criterion [16]: Acute, serious, or unstable medical condition. Some patients may qualify for rescreen if the acute illness resolves or unstable condition is stabilized (e.g., uncontrolled or unstable hypertension or blood pressure)
- Exclusion Criterion [18]: Washout of previous preventives for migraine headache
- Exclusion Criterion [25]: Washout of previous investigational product
- Participants who have become eligible to enroll in the study as a result of a protocol amendment

Use of concomitant medication that requires a stable dose for a specific duration prior to Visit 2 may be rescreened if additional time is needed to meet the duration requirement.

In addition, after consultation with and approval by a Lilly Medical representative, a participant may be rescreened if there is an unexpected technical difficulty with the ePRO diary capture during the prospective baseline period.

5.5. Criteria for Temporarily Delaying Enrollment of a Participant

Not applicable.

6. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to/used by a study participant according to the study protocol. It is a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (FDA 2018).

6.1. Study Intervention(s) Administered

Group Name	Galcanezumab		Rimegepant	
Intervention Name	Galcanezumab	Rimegepant placebo	Rimegepant	Galcanezumab placebo
Type	Biologic	Placebo	Drug	Placebo
Dose Formulation	Solution	Placebo ODT	ODT	Placebo Solution
Unit Dose Strength(s)	120 mg	N/A	75 mg	N/A
Dosage Level(s)	240 mg (2 injections) loading dose, then 120 mg monthly	1 tablet every other day	75 mg every other day	2 SC injections loading dose, then 1 SC injection monthly
Route of Administration	SC	Oral	Oral	SC
Use	Experimental			
IMP and NIMP	IMP			
Sourcing	Provided centrally by the sponsor			
Packaging and Labeling	Study interventions will be provided in containers. Each container will be labeled as required per country requirement.			

Abbreviations: IMP = investigational medicinal product; N/A = not applicable; NIMP = non-investigational medicinal product; ODT = orally disintegrating tablet; SC = subcutaneous.

6.2. Preparation, Handling, Storage, and Accountability

- The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, prepare, or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.
- The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).
- The designated unblinded site personnel will handle all study intervention preparation, handling and accountability CCI [redacted] CCI [redacted]
- Further guidance and information for the final disposition of unused study interventions are provided CCI [redacted].

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a randomized, double-blind, double-dummy study.

Participants will be randomly assigned in a 1:1 ratio to receive study intervention. All participants will be centrally assigned to randomized study intervention using an IWRS. Before the study is initiated, the log in information and directions for the IWRS will be provided to each site. Participants will be stratified by baseline migraine frequency (<8 migraine headache days versus ≥8 migraine headache days). Randomization into 1 stratum may be discontinued at the discretion of the sponsor.

Study intervention will be dispensed to the participant by the designated unblinded site personnel at Visit 3 as summarized in SoA. The participants will receive enough tablets and syringes for the double-blind treatment period with the longest possible visit interval between visits.

Returned study intervention should not be re-dispensed to the participants.

Treatment assignments will remain blinded to investigators, study site personnel directly involved in participant assessments, and participants. To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is completed. Designated unblinded site personnel are responsible for receipt of study intervention shipments, dispensing study intervention, confirming treatment assignments, and receipt of any unused study intervention by the participant. Designated unblinded site personnel will not be involved in any clinical aspects of the study, including clinical evaluations and AE assessments. It is critical that the blind is maintained throughout the study (3 months).

As the last procedure of Visit 3, the unblinded site personnel will train the participant/caregiver on SC administration, which may include injecting the contents of the first syringe and supervising the participant/caregiver in the administration of the second injection. The unblinded

site personnel should also train the participant how to take the ODT and supervise the participant opening the blister pack and taking the first dose of ODT.

At the telephone visits at which an injection is to occur, self-injections are to occur on the same day as the scheduled telephone visit, prior to the start of visit procedures.

CCI

In the event of a quality assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

Emergency Unblinding

This is a double-blind study in which participants, caregivers, and study site personnel who are performing clinical assessments are blinded to study intervention. The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted.

Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant. If a participant's intervention assignment is unblinded, the sponsor must be notified immediately after breaking the blind. The date and reason that the blind was broken must be recorded.

If an investigator, site personnel performing assessments, or participant is unblinded, the participant must be discontinued from the study. In cases where there are ethical reasons to have the participant remain in the study, the investigator must obtain specific approval from a sponsor medical monitor for the participant to continue in the study.

6.4. Study Intervention Compliance

At Visit 3, the dose of study intervention and study participant identification will be confirmed by unblinded site personnel prior to the time of dosing. The date and time of each dose administered will be recorded.

Compliance will be assessed by the unblinded site personnel at the study site by counting returned unused ODT/syringes at Visit 6, and documented.

- Participants should be instructed to return the unused ODT and syringes at Visit 6 in the ancillary containers provided at Visit 3. Other closed containers are acceptable as long as study intervention is not visible.

A record of the number of syringes and ODT dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

6.5. Dose Modification

No dose modification will be allowed during the study.

6.6. Continued Access to Study Intervention after the End of the Study

Study intervention will not be made available to participants after conclusion of the study.

6.7. Treatment of Overdose

In the event of an overdose, it is recommended that the participant be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately. The treating physician should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted.

Refer to Nurtec ODT® USPI (2021) for details related to overdose of rimegepant ODT.

6.8. Concomitant Therapy

See Section 10.2 for a list of medications that are, and are not, allowed in this study.

Any changes in the list of allowed/not allowed medications will be communicated to investigators and will not constitute a protocol amendment. The concomitant use of acute medications to treat migraine is allowed, with some limitations. Treatments used for the prevention of migraine, including nutraceuticals, pharmacological and nonpharmacological interventions, are not allowed at any time during Study Period II or III. Participants should have washed out all migraine preventive treatments at least 5 days prior to Visit 2.

Botulinum toxin A or B in the head or neck area for therapeutic use is not allowed within 3 months prior to Visit 2. Nerve blocks or use of therapeutic devices (such as transcranial magnetic stimulation) in the head or neck area or for migraine prevention are not allowed within 30 days before Visit 2.

Participants will capture whether they took any acute headache medication as part of their daily ePRO diary entry during Study Periods II and III. Acute headache medication name, dose, and date will be recorded by participants during Study Periods II and III on a headache medication log, which will be returned to site staff at Visit 6 (the final study visit) or early discontinuation visit.

For acetaminophen (or paracetamol), the maximal allowed dose will be 3 g/day from all acetaminophen-containing medicinal products.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates

- Dosage information including dose and frequency for concomitant therapy of special interest

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Treatments used for the prevention of migraine, including nutraceuticals, pharmacological and nonpharmacological interventions, are not allowed at any time during Study Periods II and III.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.8.

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant should remain in the study to be evaluated for safety and efficacy assessments, unless criteria in Section 7.2 apply.

A participant should be permanently discontinued from study intervention if:

- the participant becomes pregnant during the study (see Section 8.3.2)
- the participant requests to discontinue study intervention
- clinical judgment of the investigator

7.1.1. Liver Chemistry Stopping Criteria

Interrupting study drug based on liver test elevations in participants with normal or near-normal baseline liver tests

In study participants with normal or near normal baseline liver tests (ALT, AST, ALP <1.5x ULN), the study drug should be **interrupted** and close hepatic monitoring initiate (see Section 10.5.2) if one or more of these conditions occur:

Elevation	Exception
ALT or AST >8x ULN	
ALT or AST >5x ULN for more than 2 weeks	
ALT or AST >3x ULN and either TBL >2x ULN or INR >1.5	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then the doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2x ULN.
ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
ALP >3x ULN when the source of increased ALP is the liver	
ALP >2.5x ULN and TBL >2x ULN	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then the doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2x ULN.
ALP >2.5x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
Source: FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009 and other consensus guidelines, with minor modifications.	

Interrupting study drug based on elevated liver tests in participants with abnormal baseline liver tests

In study participants with abnormal baseline liver tests (ALT, AST, ALP ≥1.5x ULN), the study drug should be **interrupted** if one or more of these conditions occur:

Elevation	Exception
ALT or AST >4x baseline	
ALT or AST >3x baseline for more than 2 weeks	
ALT or AST >2x baseline and either TBL >2x ULN or INR >1.5	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then the doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2x ULN.
ALT or AST >2x baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
ALP >2.5x baseline when the source of increased ALP is the liver	
ALP >2x baseline and TBL >2x ULN	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then the doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2x ULN.
ALP >2x baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	

Source: FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009 and other consensus guidelines, with minor modifications.

Resuming study drug after elevated liver tests

Resumption of the study drug can be considered only in consultation with the Lilly-designated medical monitor, if the liver test results return to baseline, and if a self-limited non-drug etiology is identified. Otherwise, the study drug should be discontinued.

For suggested actions and follow-up hepatic assessments, see Section 10.5.

7.1.2. QTc Stopping Criteria

If a clinically significant finding is identified (including, but not limited to, changes from baseline in QT interval corrected using Fridericia's formula [QTcF]) after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study:

- at any time at his/her own request
- at the request of his/her designee (for example, parents or legal guardian)

- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent.

Discontinuation is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued from both the study intervention and the study at that time.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel or designee are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. Efficacy Assessments

8.1.1. Primary Efficacy Assessment

8.1.1.1. ePRO Diary

Starting at Visit 2, participants will be asked to use an ePRO device to record headache information, including reporting headaches, intensity of headache, headache features, and whether any acute headache medication was taken. The system also will be used to collect information about migraine-associated symptoms (for example, photophobia, phonophobia, nausea, and/or vomiting).

8.1.2. Secondary Efficacy Assessments

8.1.2.1. Migraine-Specific Quality of Life Questionnaire Version 2.1

The Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) is a self-administered health status instrument that was developed to address the physical and emotional impact on functioning that is of specific concern to individuals suffering from migraine headaches.

The instrument consists of 14 items that address 3 domains: (1) Role Function-Restrictive; (2) Role Function-Preventive; and (3) Emotional Function (Jhingran et al. 1998b). The restrictive domain specifically measures disability as related to the impact on performance of normal activities, with the preventive domain addressing complete functional impairment and the emotional domain assessing the feelings related to disabling monthly migraine headache days. Responses are given using a 6-point Likert-type scale, ranging from “none of the time” to “all of the time.” Raw scores for each domain are computed as a sum of item responses, with the collective sum providing a total raw score that is then converted to a 0 to 100 scale, with higher scores indicating a better health status, and a positive change in scores reflecting functional improvement (Jhingran et al. 1998a; Martin et al. 2000). The instrument was designed with a 4-week recall period and is considered reliable, valid, and sensitive to change in functional impairment due to migraine (Jhingran et al. 1998b; Bagley et al. 2012).

8.1.2.2. Migraine Disability Assessment

The Migraine Disability Assessment (MIDAS) is a patient-rated scale which was designed to quantify headache-related disability over a 3-month period. This instrument consists of 5 items that reflect the number of days reported as missed, or with reduced productivity at work or home and social events. Each question is answered as the number of days during the past 3 months of assessment, ranging from 0 to 90, with the total score being the summation of the 5 numeric responses. A higher value is indicative of more disability (Stewart et al. 1999a, 1999b, 2001).

This instrument is considered highly reliable and valid, and is correlated with clinical judgment regarding the need for medical care (Stewart et al. 1999a, 1999b, 2001). For clinical interpretability, 4 categorical grades were developed based on the total score: Grade I (0 to 5) is for little or no disability, Grade II (6 to 10) is for mild disability, Grade III (11 to 20) is for moderate disability, and Grade IV (21+) is for severe disability. The severe disability category has subsequently been subdivided into Grade IV-A (severe [21 to 40]) and Grade IV-B (very severe [41 to 270]) because a high proportion of patients with chronic migraine are in Grade IV (Blumenfeld et al. 2011).

8.1.3. Tertiary Efficacy Assessment

8.1.3.1. The Patient Global Impression of Severity

The Patient Global Impression of Severity (PGI-S) scale (Guy 1976) is a patient-rated instrument that measures illness severity. For this study, the participant will be instructed as follows: "Considering migraine as a chronic condition, how would you rate your level of illness?" The PGI-S includes a range of possible responses, from 1 ("normal, not at all ill") to 7 ("extremely ill").

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded.
- Neurological examinations will be conducted to assess for any signs of preexisting or treatment-emergent neurological abnormalities.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

Vital signs will 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 (Section 1.3), and following the study-specific recommendations included in the Reference Manual for the study.

8.2.3. Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) and Reference Manual using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. In the event the ECG machine does not automatically calculate the QTcF interval, the QTcF interval may be manually calculated. ECGs should be collected prior to blood draws and dosing. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Refer to Section 5.2 for exclusion criteria related to ECG findings.

8.2.4. Clinical Safety Laboratory Tests

See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.

The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during the double-blind treatment period should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the SoA, standard collection requirements, and laboratory manual.

If laboratory values from non-protocol specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are considered clinically significant by the investigator (for example, SAE or AE or dose modification), then report the information as an AE.

8.2.5. Pregnancy Testing

WOCBP must undergo pregnancy testing according to the SoA.

8.2.6. Suicidal Ideation and Behavior Risk Monitoring

Participants with migraine may occasionally develop SIB.

Participants who experience signs of SIB should undergo a risk assessment. All factors contributing to SIB should be evaluated and consideration should be given to discontinuation of the study intervention.

When informed consent or assent has been given, participants/caregivers should be alerted about the emergence of unusual changes in behavior, as well as the emergence of SIB and to report such symptoms immediately to the study investigator.

8.3. Adverse Events, Serious Adverse Events, and Product Complaints

The definitions of the following events can be found in Appendix 3:

- AEs
- SAEs

These events will be reported by the participant (or, if necessary, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet these definitions and remain responsible for following up events that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or the study (see Section 7).

Care will be taken not to introduce bias when detecting events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about event occurrences.

After the initial report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

For PCs, the unblinded site personnel are responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality.

A PC is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a trial intervention. When the ability to use the study intervention safely is impacted, the following are also PCs:

- Deficiencies in labeling information, and
- Use errors for device or drug-device combination products due to ergonomic design elements of the product.

Sponsor collects PCs on study interventions and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Participants will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the study interventions so that the situation can be assessed. Note: The designated unblinded site personnel are responsible for handling all aspects of PCs.

Note: AEs/SAEs that are associated with a PC will also follow the processes outlined in Section 8.3.1 of the protocol.

For the time periods for detecting and reporting PCs, see Section 8.3.1.

- Follow-up applies to all participants, including those who discontinue study intervention.

- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the PC.
- New or updated information will be recorded on the originally completed PC form with all changes signed and dated by the investigator and submitted to the sponsor.
  Note: An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC and as an AE/SAE.

8.3.1. Timing and Mechanism for Collecting Events

This table describes the timing, deadlines, and mechanism for collecting events.

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-Up Method of Reporting
Adverse Event					
AE	Signing of the ICF	Participation in study has ended	As soon as possible upon site awareness	AE CRF	N/A
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related with study procedures	Signing of the ICF	Start of intervention	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE and SAE updates – after start of study intervention	Start of intervention	Participation in study has ended	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE[a] – after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-Up Method of Reporting
Pregnancy					
Pregnancy in WOCBP and female partners of male participants	After the start of study intervention	At least 5 months after the last subcutaneous injection of study intervention	Within 24 hours (see Section 8.3.2)	Pregnancy paper form	N/A
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	PC form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	PC form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed PC form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	PC form	

Abbreviations: AE = adverse event; CRF = case report form; ICF = informed consent form; N/A = not applicable; PC = product complaint; SAE = severe adverse event; WOCBP = woman of childbearing potential.

[a] SAEs after study participation should not be reported unless the investigator deems them to be possibly related to study treatment or study participation.

8.3.2. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at ≥20 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in protocol Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention. If the participant is discontinued from the study, follow the standard discontinuation process. The follow up on the pregnancy outcome should continue independent of intervention or study discontinuation.

8.4. Pharmacokinetics

PK parameters are not evaluated in this study.

8.5. Pharmacodynamics

PD parameters are not evaluated in this study.

8.6. Genetics

Genetics is not evaluated in this study.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity assessments are not evaluated in this study.

8.9. Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

9. Statistical Considerations

The SAP will be finalized prior to unblinding, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

9.1. Statistical Hypotheses

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:*

$$H0: \pi_G \leq \pi_R \text{ against } Ha: \pi_G > \pi_R$$

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:

$$H0: \mu_G \leq \mu_R \text{ against } Ha: \mu_G > \mu_R$$

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.

9.1.1. Multiplicity Adjustment

The statistical comparisons for the primary efficacy endpoint and the key secondary endpoints will be carried out in the hierarchical order as indicated in Section 3. 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.

9.2. Analyses Sets

Participant Analysis Set	Description
Intention to Treat (ITT) set	All randomized participants and receive at least 1 dose of study intervention. Participants will be included in the analyses according to their randomized treatment.
Safety analysis set	All participants who are exposed to study intervention. Participants will be analyzed according to the treatment they actually received.

9.3. Statistical Analyses

9.3.1. General Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. Details of statistical analysis methods will be described in the 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 population for efficacy analyses and on the safety population for safety analyses (see Section 9.2). When change from baseline is assessed, the participant will be included in the analysis only if he/she has a baseline and a postbaseline measurement.

Binary efficacy variables with repeated measures will be analyzed using a GLIMMIX as pseudo-likelihood-based mixed effects repeated measures analysis. The GLIMMIX model 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.

For binary efficacy variables without repeated measures, comparisons between treatment groups will be performed using logistic regressions with LOCF imputation being used. This model will include the main effects of treatment and a continuous effect for baseline monthly migraine headache days.

Continuous efficacy variables 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. A list of other covariance structures to be used in case of nonconvergence will be given within the SAP.

For continuous efficacy variables without repeated measures, an ANCOVA model with LOCF imputation will be used, 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 safety variables with repeated measures, MMRM methods will be used, as well as an ANCOVA model with LOCF imputation if deemed appropriate. When an ANCOVA

model is used for safety measures, the model will contain the main effect of treatment, as well as the continuous fixed covariate of baseline. Type III sum-of-squares for the LSMeans will be used for the statistical comparisons.

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.

Treatment effects will be evaluated based on a 2-sided significance level of 0.05 for all the efficacy and safety analyses unless otherwise stated. The 95% confidence intervals for the difference in LSMeans between treatment groups will be presented. Type I error due to multiple comparisons for the primary and key secondary objectives will be controlled using sequential gating procedure (see Section 9.1.1). There will be no adjustments for multiplicity for analyses of other data (other secondary objectives or tertiary objectives).

9.3.2. Primary Endpoint(s)/Estimand(s) Analysis

The primary endpoint is based on the percentage of participants showing a 50% response on each month, defined as showing 50% or fewer migraine headache days within the month than was seen during the baseline period. 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 GLIMMIX model. Here 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 analysis method will be the GLIMMIX given in Section 9.3.1 above for binary data.

If the sample size is increased as a result of the interim analysis, the CHW procedure (Cui et al. 1999) will be applied to the primary endpoint to control the type I error at a one-sided $\alpha = 0.025$ significance level. The CHW method ensures strong control of type I error when the sample size is increased in a data dependent manner.

If the sample size is increased as a result of the interim analysis, an unadjusted point estimate for the primary efficacy analysis will be calculated and reported. A median unbiased point estimate and a stage-wise adjusted confidence interval for the primary efficacy analysis will be calculated and reported based on the approach described by Brannath et al. (2009) to assess sensitivity of the point estimate.

9.3.3. Secondary Endpoints/Estimands Analysis

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 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 corresponding analyses for each of these endpoints will be as stated within Section 9.3.1 based on the type of endpoint measured (that is, binary or continuous).

If the sample size is increased, the CHW test statistic will be calculated for the key secondary endpoints before applying multiple testing procedure.

9.3.4. Safety Analyses

The safety and tolerability of treatment will be assessed by summarizing the following:

- TEAEs
- SAEs
- AEs leading to discontinuation
- AEs related to injection sites
- vital signs
- laboratory measurements

Unless specified otherwise, the categorical safety analyses will include both scheduled and unscheduled visits. Comparisons between treatment groups for all categorical safety measures will be made using Fisher's exact test within the safety population.

9.3.4.1. Treatment-Emergent Adverse Events

TEAEs are defined as the reported AEs that first occurred or worsened during the postbaseline period compared with the baseline period. For each TEAE, the reported severity level of the event (mild, moderate, or severe) will be determined by physician opinion. The MedDRA 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 postbaseline is greater than the maximum baseline severity, the event is considered to be treatment-emergent for the specific postbaseline period. Safety analyses for each study period will use all visits up through the last scheduled visit in the prior study period as baseline. For each participant and TEAE, the maximum severity for the MedDRA level being displayed (preferred term, High-Level Term, or System Organ Class [SOC]) is the maximum postbaseline severity observed from all associated LLTs mapping to that MedDRA level.

For events that are sex-specific, the denominator and computation of the percentage will include only participants from the specific sex.

9.3.4.2. Vital Signs

Vital signs collected during the study include systolic and diastolic blood pressure, pulse, and temperature. For vital signs procedures see Section 8.2.2.

The number and percentage 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.

9.3.4.3. Laboratory Tests

The incidence rates of participants with treatment-emergent abnormal, high, or low laboratory values at any time postbaseline will be assessed using Fisher's exact test for each laboratory test.

9.3.5. Other Analyses

Details of analyses of other endpoints not falling under either efficacy or safety will be provided within the SAP.

9.4. 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 the 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.

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 the unblinding plan section of the SAP or a separate unblinding plan document.

9.5. 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 this 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.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (for example, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
- Investigator sites are compensated for participation in the study as detailed in the CTA.

10.1.2. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant, and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant and is kept on file.

Participants who are rescreened are required to sign a new ICF.

10.1.3. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for his/her data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The sponsor has processes in place to ensure data protection, information security and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

10.1.4. Committees Structure

Potential cardiovascular events will be adjudicated by an external CEC. The role of the CEC is to adjudicate defined clinical events in a blinded, consistent, and unbiased manner throughout the course of a study. The purpose of the CEC for adjudication of cardiovascular events is to ensure that all reported events are evaluated uniformly by a single group.

Death, resuscitated cardiac arrest, and potential treatment-emergent cardiovascular events from the CRF will be identified using a search strategy based on the 9 MedDRA SMQs listed below. Narrow terms from these SMQs will be adjudicated if they are reported as a SAE. Potential non-serious cardiovascular events may be selected for adjudication following blinded medical review. Details of membership, operations, recommendations from the Committee, and the communication plan will be documented in the charter.

Narrow terms in the following SMQs will be adjudicated:

- Cardiac arrhythmias (includes sub SMQs; SMQ 20000049)
- Cardiac failure (SMQ 20000004)
- Cardiomyopathy (SMQ 20000150)
- Central nervous system vascular disorders (includes sub SMQs; SMQ 20000060)
- Embolic and thrombotic events (includes sub SMQs; SMQ 20000081)
- Hypertension (SMQ 20000147)
- Ischemic heart disease (includes sub SMQs; SMQ 20000043)
- Pulmonary hypertension (SMQ 20000130)
- Torsade de pointes/QT prolongation (SMQ 20000001)

Case unblinding may be performed for above reviews, only if necessary

10.1.5. Dissemination of Clinical Study Data

A clinical study report will be provided for this study and a summary of study information provided on publicly available websites.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on electronic CRFs unless transmitted to the sponsor or designee electronically (for example, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- QTLs will be pre-defined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important excursions from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy (for example, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.

- The sponsor assumes accountability for actions delegated to other individuals (for example, contract research organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the CTA unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition, sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An EDC system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Additionally, eCOA data (participant-focused outcome instrument) will be directly recorded by the participant into an instrument (handheld smart phone and/or tablet). The eCOA data will serve as the source documentation and the investigator does not maintain a separate, written or electronic record of these data.

Data collected via the sponsor-provided data capture system(s) will be stored at third parties. The investigator will have continuous access to the data during the study and until decommissioning of the data capture systems. Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and reports or electronic transfers will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the sponsor data warehouse.

Data from complaint forms submitted to sponsor will be encoded and stored in the global PC management system.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Section 10.1.6.

10.1.8. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first participant visit and will be the study start date.

Study or Site Termination

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.9. Publication Policy

In accordance with the sponsor's publication policy, the results of this study will be submitted for publication by a peer-reviewed journal.

10.1.10. Investigator Information

Physicians with a specialty in neurology, headache specialist, or other physicians with experience in headache clinical trials and diagnosing and treating migraine participants will participate as investigators in this clinical trial.

10.2. Appendix 2: Treatments Allowed and Treatments not Allowed as Concomitant Therapy

A. Medications allowed for the ACUTE treatment of migraine headaches or other pain or injury:

Acetaminophen (paracetamol), NSAIDs; Triptans; Ergotamine and derivatives; aspirin, caffeine, and acetaminophen combination; or combinations thereof. For acetaminophen, the maximal allowed dose will be 3 g/day from all acetaminophen-containing medicinal products.

The following medications are allowed with restrictions:

1. Opioid and barbiturates no more than 4 days/month.
2. Single dose of injectable steroids allowed only once during the study, in an emergency setting (SP II and III).

B. Medications, procedures or devices not allowed for any reason/indication during SP II and III:

Acetazolamide

Acupuncture

Anticonvulsants/Antiepileptics[a]

Antipsychotics

Beta-blockers

Botulinum toxin applied to head/neck area for therapeutic use

Cannabis/Cannabinoids[b]

Chiropractic procedures, physiotherapy, TENS or other electric devices on head and neck

Corticosteroids for oral use[c]

CYP3A4: Moderate and strong inhibitors of CYP3A4 (includes Paxlovid)[d]

CYP3A: Moderate and strong inducers of CYP3A

Efflux transporters: Inhibitors of P-gp and BCRP

Flunarizine

Herbals with anti-inflammatory effect (feverfew, willow bark, petasites/butterbur), herbals with sympathomimetic effect (ma huang, ephedra, bitter orange, synephrine) and herbals with catecholamine transmitter reuptake inhibition (St. John's Wort)

Migravent

Monoamine oxidase inhibitors (MAOIs)

Memantine

Neurotropin®

Nerve block in head/neck area

Serotonin 5HT2a/2c antagonists, for example: nefazodone

Tizanidine

Tricyclic antidepressants (TCAs)

Triptans for prophylaxis of menstrual-related migraine

Venlafaxine and desvenlafaxine

Verapamil

C. Restricted medication during SP II and III: Use of the following medications for indications other than migraine prevention is allowed providing the dose is stable 2 months prior to Visit 2 and is expected to remain stable during Visit 2 through 6.

ACE inhibitors

Angiotensin receptor blockers (ARBs)

Benzodiazepines

Bupropion

Calcium-channel blockers (except verapamil and flunarizine)

Clonidine

Gabapentin Guanfacine Mirtazapine Pregabalin SSRIs/NRIs/SNRIs (other than venlafaxine) Stimulants (prescription strength), for example: methylphenidate, dextroamphetamine, mixed amphetamine salts Trazadone (for sleep only and must be taken in a stable fashion) Use of electric devices (that is, TENS), physiotherapy, chiropractic procedures on low back and extremities
D. Restricted medication during SP II-III: Use of the following medications for indications other than migraine prevention is allowed: Beta-blockers, ophthalmic Cyproheptadine Melatonin

Abbreviations: 5HT = 5-hydroxytryptamine; ACE = angiotensin-converting enzyme; NRI = norepinephrine reuptake inhibitor; NSAID = nonsteroidal anti-inflammatory drug; SNRI = serotonin-norepinephrine reuptake inhibitor; SP = Study Period; SSRI = selective serotonin reuptake inhibitor; TENS = transcutaneous electrical nerve stimulation.

[a] Gabapentin and pregabalin may be allowed if the criteria in Part C are met.

[b] It may be allowed in the study if prescribed for a condition other than migraine or headache, as long as the use of Cannabis/Cannabinoids is not expected to affect the interpretation of study results or the safety of the participant. The usage should remain consistent for the duration of the study and criteria in exclusion 23ii are met.

[c] Topical and inhaled corticosteroids allowed for conditions other than migraine or headache.

[d] Paxlovid is authorized by the FDA for emergency use for treatment of mild-to-moderate COVID-19 and contains ritonavir - a strong CYP3A4 inhibitor; thus, is excluded in CGBD.

10.3. Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (for example, endoscopy and appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed:

a. Results in death

b. Is life-threatening

The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted to hospital or emergency ward (usually involving at least an overnight stay) for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (for example, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording and Follow-Up of AE and/or SAE

For PCs, see Section 8.3.

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate CRF or paper form, respectively.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to sponsor or designee in lieu of completion of the CRF page or paper form, respectively, for AE/SAE.
- There may be instances when copies of medical records for certain cases are requested by sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing

discomfort but poses no significant or permanent risk of harm to the research participant.

- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as "serious" when it meets at least 1 of the pre-defined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide sponsor or designee with a copy of any post-mortem findings including histopathology.

10.3.4. Reporting of SAEs

SAE Reporting via Paper Form
• Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the sponsor or designee. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in site training documents.

10.3.5. Regulatory Reporting Requirements

SAE Regulatory Reporting
Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met. ● The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators. ● An investigator who receives an investigator safety report describing an SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the IB or Product Information and will notify the IRB/IEC, if appropriate according to local requirements.

10.4. Appendix 4: Clinical Laboratory Tests

- The tests detailed in the table below will be performed by the central laboratory unless specified otherwise.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time, if feasible. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.
- In circumstances where the sponsor allows the use of local laboratory testing in lieu of central laboratory testing (in the table below), the local laboratory must be qualified in accordance with applicable local regulations.
- Protocol-specific laboratory result requirements for inclusion or exclusion of participants are detailed in Section 5.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of the laboratory safety results.

Clinical Laboratory Tests

Hematology	**Clinical Chemistry**[a]
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume	Total bilirubin (TBL)
Mean cell hemoglobin concentration	Direct bilirubin
Leukocytes (WBC)	Alkaline phosphatase (ALP)
Neutrophils, segmented	Alanine aminotransferase (ALT)
Lymphocytes	Aspartate aminotransferase (AST)
Monocytes	Blood urea nitrogen (BUN)
Eosinophils	Creatinine
Basophils	Uric acid
Platelets	Calcium
	Glucose
	Albumin
Urinalysis	Total cholesterol
Specific gravity	Creatine kinase (CK)
pH	
Protein	**Pregnancy Test** (females only)[b]
Glucose	Serum pregnancy or FSH
Ketones	Urine pregnancy test (local)
Blood	
Urine leukocyte esterase[c]	
UDS[b]	

Abbreviations: FSH = follicle stimulating hormone; RBC = red blood cells; UDS = urine drug screen; WBC = white blood cells.

[a] Fasting not required.

[b] May be repeated during the study at the discretion of the investigator.

[c] A positive urine leukocyte esterase result will require a follow-up sample with microscopic analysis and possibly a urine culture.

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

10.5.1. Hepatic Evaluation Testing

See Sections 10.5.2 and 10.5.3 below for guidance on appropriate test selection.

The Lilly-designated central laboratory must complete the analysis of all selected testing except for microbiology testing.

Local testing may be performed in addition to central testing when necessary for immediate participant management.

Results will be reported if a validated test or calculation is available.

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	ALP isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
	Copper
Coagulation	Ethyl alcohol (EtOH)
Prothrombin time, INR (PT-INR)	Haptoglobin
Serology	Immunoglobulin (Ig)A (quantitative)
Hepatitis A virus (HAV) testing:	IgG (quantitative)
HAV total antibody	IgM (quantitative)
HAV IgM antibody	Phosphatidylethanol (PEth)
Hepatis B virus (HBV) testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug screen
Hepatitis B surface antibody (anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (anti-HBc)	**Other Serology**

Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)
Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA)[a]
HBV DNA[b]	Anti-actin antibody[c]
Hepatis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody
HCV RNA[b]	EBV DNA[b]
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA[b]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA[b]	HSV (Type 1 and 2) DNA[b]
Microbiology[d]	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
Blood	
Urine	

[a] Not required if anti-actin antibody is tested.

[b] Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

[c] Not required if anti-smooth muscle antibody (ASMA) is tested.

[d] Assayed ONLY by investigator-designated local laboratory; no central testing available.

10.5.2. Close Hepatic Monitoring

Laboratory tests (Section 10.4), including ALT, AST, ALP, TBL, D. Bil, GGT, and CK, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur:

For participants enrolled with normal or near normal hepatic biochemical tests

If a participant with baseline results of ...	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN
ALP <1.5x ULN	ALP ≥2x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for participants with Gilbert's syndrome)
For participants enrolled with elevated baseline hepatic biochemical tests	
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline

TBL ≥1.5x ULN	TBL ≥1.5x baseline (except for participants with Gilbert's syndrome)

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, history of alcohol drinking and other substance abuse.

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and laboratory results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive hepatic evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if 1 or more of these conditions occur:

For participants enrolled with normal or near normal hepatic biochemical tests

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN with hepatic signs/symptoms[a], or ALT or AST ≥5x ULN
ALP <1.5x ULN	ALP ≥3x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for participants with Gilbert's syndrome)
For participants enrolled with elevated baseline hepatic biochemical tests	
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline with hepatic signs/symptoms[a], or ALT or AST ≥3x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥2x baseline (except for participants with Gilbert's syndrome)

[a]Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for PT-INR; tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or CT scan).

Based on the participant's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for hepatitis D virus (HDV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and blood phosphatidylethanol. Based on the circumstances and the

investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), cardiac echocardiogram, or a liver biopsy.

10.5.3. Additional Hepatic Data Collection (Hepatic Safety CRF) in Study Participants Who Have Abnormal Liver Tests During the Study

Additional hepatic safety data collection in hepatic safety CRFs should be performed in study participants who meet 1 or more of the following 5 conditions:

1. Elevation of serum ALT to ≥5x ULN on 2 or more consecutive blood tests (if baseline ALT <1.5x ULN)
    - In participants with baseline ALT ≥1.5x ULN, the threshold is ALT ≥3x baseline on 2 or more consecutive tests
2. Elevated TBL to ≥ 2x ULN (if baseline TBL <1.5x ULN) (except for cases of known Gilbert's syndrome)
    - In participants with baseline TBL ≥1.5x ULN, the threshold should be TBL ≥2x baseline
3. Elevation of serum ALP to ≥2x ULN on 2 or more consecutive blood tests (if baseline ALP <1.5x ULN)
    - In participants with baseline ALP ≥1.5x ULN, the threshold is ALP ≥2x baseline on 2 or more consecutive blood tests
4. Hepatic event considered to be an SAE
5. Discontinuation of study intervention due to a hepatic event

Note: the interval between the 2 consecutive blood tests should be at least 2 days.

10.6. Appendix 6: Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this appendix

The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the sponsor in partnership with the investigator.

Exceptional circumstances

Exceptional circumstances are rare events that may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the investigators, participants, or both to attend on-site visits or to conduct planned study procedures.

Implementing changes under exceptional circumstances

In an exceptional circumstance, after receiving the sponsor's written approval, sites may implement changes if permitted by local regulations.

After approval by local Ethical Review Boards, regulatory bodies and any other relevant local authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific requirements in which notification is required (for example, upon implementation and suspension of changes). All approvals and notifications must be retained in the study records.

If the sponsor grants written approval for changes in study conduct, the sponsor will also provide additional written guidance, if needed.

Considerations for making a change

The prevailing consideration for making a change is ensuring the safety of study participants. Additional important considerations for making a change are compliance with GCP, enabling participants to continue safely in the study and maintaining the integrity of the study.

Informed Consent

Additional consent from the participant will be obtained, if required, for:

- participation in remote visits, as defined in Section "Remote Visits,"
- alternate delivery of study intervention and ancillary supplies, and
- provision of their personal or medical information required prior to implementation of these activities.

Changes in Study Conduct During Exceptional Circumstances

Changes in study conduct not described in this appendix, or not consistent with applicable local regulations, are not allowed.

The following changes in study conduct will not be considered protocol deviations.

Remote visits

Types of remote visits

Telemedicine: Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include, but are not limited to: AE and concomitant medications.
Mobile healthcare: Healthcare visits may be performed by a mobile healthcare provider at locations other than the study site when participants cannot travel to the site due to an exceptional circumstance if written approval is provided by the sponsor. Procedures performed at such visits include, but are not limited to: vital signs, 12-lead ECG, collection of central laboratory blood and urine samples including serum pregnancy, collection of MSQ v2.1, MIDAS, and PGI-S via Slate, distribution and collection of the ePRO diary and paper headache medication log, and collection of unused study intervention and ancillary supplies.
Additionally, procedures listed above as telemedicine may be performed in the mobile healthcare setting.
Other alternative locations: Procedures that may be done at an alternate location, other than listed above, include local safety labs, if applicable.

Data capture

In source documents and the CRF, the study site should capture the visit method, with a specific explanation for any data missing because of missed in-person site visits.

Safety reporting

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of AEs, SAEs, and PCs remain unchanged.

Return to on-site visits

Every effort should be made to enable participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participants and the site staff.

Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing. The local laboratory must be qualified in accordance with applicable local regulations.

Study intervention and ancillary supplies (including participant diaries)

When a participant is unable to go to the site to receive study supplies during normal on-site visits, the site should work with the sponsor to determine appropriate actions. These actions may include:

- asking the participant to go to the site and receive study supplies from site staff without completion of a full study visit,
- asking the participant's designee to go to the site and receive study supplies on a participant's behalf,
- arranging delivery of study supplies, and

These requirements must be met before action is taken:

- Alternate delivery of study intervention should be performed in a manner that does not compromise treatment blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.
- When delivering supplies to a location other than the study site (for example, participant's home), the investigator, sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).
- Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

Screening period guidance

To ensure safety of study participants, laboratory values and other eligibility assessments taken at the screening visit are valid for a maximum of 45 days. The following rules will be applied for active, non-randomized participants whose participation in the study must be paused due to exceptional circumstances:

- If screening is paused for ≤15 days beyond what is allowed for the screening period (30 days): the participant will proceed to the next study visit per the usual SoA, provided that Visit 2 must be conducted within 45 days from Visit 1.
    - The site should conduct the next visit if the participant's Visit 1 eligibility criteria are confirmed, and the site should document the reason for delay.
    - Due to the pause in screening, sites should also reconfirm the impacted participant's consent and document this confirmation in the source documentation.
- If screening is paused for more than 15 days beyond what is allowed for the screening period (30 days): The participant must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen failure in the CRF. The participant can reconsent and be rescreened as a new participant. This rescreen is in addition to the one allowed by the main protocol. The screening and prospective baseline procedures per the usual SoA should be followed, starting at Visit 1 to ensure participant eligibility or ineligibility is confirmed by Visit 3.

Adjustments to Visit Windows

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual SoA. To maximize the possibility that these visits can be conducted as on-site visits, the windows for visits may be adjusted, upon further guidance from the sponsor. This minimizes missing data and preserves the intended conduct of the study.

This table describes the allowed adjustments to visit windows.

Visit Number	Tolerance

Visits 4 and 5	For telephone assessments only, from the intended date:
	• Up to 2 days prior
	  ○ Participants should be instructed to self-administer study intervention prior to telephone visit.
	• Up to 7 days after
	  ○ Participants should be instructed to self-administer study intervention per the original schedule.

Visit 6	For study procedures per SoA from the intended date: • Up to 2 days prior • Up to 15 days after The participant should be instructed to discontinue ODT as per the schedule in normal circumstances (eg. approximately 90 days after Visit 3).

Abbreviation: ECG = electrocardiogram.

Documentation

Changes to study conduct will be documented

Sites will identify and document the details of how participants, visits types, and conducted activities were affected by exceptional circumstances. Dispensing/shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.

Source documents at alternate locations

Source documents generated at a location other than the study site should be part of the investigator's source documentation and should be transferred to the site in a secure and timely manner.

10.7. Appendix 7: Abbreviations and Definitions

Term	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BCRP	Breast cancer resistant protein
blinding	A single-blind study is one in which the investigator and/or staff are aware of the treatment but the participant is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the participant are not. A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
CEC	Clinical Events Committee
CGRP	Calcitonin gene-related peptide
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine kinase
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRF	Case report form
CTA	Clinical Trial Agreement
CYP	Cytochrome P450
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcome Assessment
EDC	Electronic data capture
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.

ET	early termination
GCP	Good clinical practice
GGT	Gamma-glutamyl transferase
GLIMMIX	Generalized linear mixed model
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICHD	International Classification of Headache Disorders
IHS	International Headache Society
IMP	Investigational Medicinal Product
informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
INR	International normalized ratio
IRB/IEC	Institutional Review Board/Independent Ethics Committee
ITT	Intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participant allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	Interactive web-response system
LLT	Lowest Level Term
LOCF	Last observation carried forward
LSMeans	Least Squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-model repeated measures
NIMP	Non-investigational Medicinal Product
ODT	Oral disintegrating tablet

participant	Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control.
PC	Product complaint
P-gp	P-glycoprotein
PK/PD	Pharmacokinetics/Pharmacodynamics
PPS	Per-protocol set: The set of data generated by the subset of participant who sufficiently complied with the protocol to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model.
PRO/ePRO	Patient-reported outcomes/Electronic patient-reported outcomes
PT-INR	Prothrombin time – international normalized ratio
QOD	Every other day
QTc	Corrected QT interval
QTcF	Fridericia-corrected QT interval
QTLs	Quality tolerance limits
SAC	Statistical Analysis Center
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SMQ	Standardized MedDRA queries
SIB	Suicidal ideation and behavior
study intervention	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
ULN	Upper limit of normal

USPI	United States package insert
WOCBP	Women of childbearing potential

10.8. Appendix 8: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment c: (22-Sep-2022)

Overall Rationale for the Amendment:

The purpose of this amendment is to add language regarding an interim analysis with the potential for a sample size increase and make minor clarifications.

Section # and Name	Description of Change	Brief Rationale
Section 1.1. Synopsis and Section 9.5. Sample Size Determination	Original planned sample size reduced to 575	The sample size was decreased to allow for a sample size re-estimation based on interim results that will increase the likelihood that the study is adequately powered.
Section 1.3. Schedule of Activities (SoA)	Added footnote “c” to Serum pregnancy or FSH for female participants row	Updated to align with current internal guidance
Section 5.1. Inclusion Criteria	In inclusion criterion 7.b.ii, updated the examples of surgical sterilization and updated definition of menopause	Updated the examples of surgical sterilization and menopause to align with current internal guidance
Section 5.2. Exclusion Criteria	In exclusion criterion 10: deleted “multiple drugs”	Risk was discharged in previous clinical trials. History of hypersensitivity to “multiple drugs” does not pose a safety risk for use of galcanezumab.
Section 6.3. Measures to Minimize Bias: Randomization and Blinding	Updated guidance on self-injections during telephone visits	To clarify the timing of telephone visit with regards to the injection of study intervention
Section 6.4. Study Intervention Compliance	Updated text regarding the return of unused study intervention	To provide flexibility in the type of closed container the participants may use to return unused study drug

Section # and Name	Description of Change	Brief Rationale
Section 7.1.1. Liver Chemistry Stopping Criteria	Updated language based on most recent guidance	Revised due to Lilly protocol template update for consistency with FDA liver safety guidelines
Section 9.3.2. Primary Endpoint(s)/Estimand(s) Analysis	Added language regarding an interim analysis with the potential for a sample size increase and language regarding potential sample size increase	Addition
Section 9.3.3. Secondary Endpoints/Estimands Analysis	Added sentence regarding sample size and CHW test	Clarity
Section 9.3.4. Safety Analyses	Removed "potential hypersensitivity events"	Correction
Section 9.4. Interim Analysis	Added language regarding an interim analysis	Addition
Section 10.1.4. Committees Structure	Added "resuscitated cardiac arrest"	Addition to match finalized CEC charter
Section 10.2. Appendix 2: Treatments Allowed and Treatments not Allowed as Concomitant Therapy	Added footnotes "a," "b," "c," and "d" under Appendix 2 table; added Migravent, desvenlafaxine, and Paxlovid to table	Clarification for medications not allowed during SP II and III
Throughout	Other minor editorial changes	Minor therefore not described

Amendment b: (18-Feb-2022)

Overall Rationale for the Amendment:

The purpose of this amendment is to update SAE/pregnancy reporting via paper forms and make minor clarifications for sites and consistency within the document.

Section # and Name	Description of Change	Brief Rationale
1.2 Schema	Clarified footnotes within the schema and added placebo to each study intervention.	Minor change added for clarity.
1.2 Schema; 1.3 Schedule of Activities (SoA)	Clarified that investigators have up to 5 additional days if needed to schedule participant's Visit 3 appointment.	Minor clarification added for clarity and added additional flexibility for sites and participants.
1.3 Schedule of Activities (SoA)	Removed neurological examination for Visit 6 and early termination.	Based on established safety profiles for the study interventions, assessment is not required
1.3 Schedule of Activities (SoA); 10.4 Appendix 4: Clinical Laboratory Tests	Separated urine drug screen from urinalysis, clarified UDS is not required for Visit 6 and ET, and clarified participants may re-test but must be negative at or prior to Visit 2.	Corrected from previous protocol versions.
1.3 Schedule of Activities (SoA)	Clarified the headache medication log should be returned to site staff at the final office visit or early termination visit.	Minor clarification.
1.3 Schedule of Activities (SoA)	Moved both participant training videos lines so they are together and clarified videos may be viewed at either Visit 2 or Visit 3.	Minor clarification added for additional flexibility for sites and participants.

Section # and Name	Description of Change	Brief Rationale
4.1.1 Study Period I: Screening (Visit 1); 4.1.2 Study Period II: Prospective Baseline (Visit 2); 4.1.3 Study Period III: Double-Blind Treatment (Visits 3-6)	Sections were re-formatted.	Minor changes for clarity.
4.1.2 Study Period II: Prospective Baseline (Visit 2)	Clarified timing of initial study intervention shipment and eligibility.	Clarified for sites.
5.1 Inclusion Criteria	Changed age to 18 to 75 years of age (inclusive) in Inclusion Criterion #1.	Changed to include older patients consistent with recent studies for galcanezumab.
5.2 Exclusion Criteria	Removed “significant active or unstable” when describing psychiatric disease by medical history.	Minor clarification.
5.2 Exclusion Criteria	Removed Exclusion Criterion #19.	Changed to be consistent with recent studies for galcanezumab.
5.2 Exclusion Criteria	Revised Exclusion Criterion #21 to exclude participants who have used opioids or barbiturate containing analgesic >4 days per month for the treatment of pain in more than 2 of the past 3 months.	Changed to be consistent with recent studies for galcanezumab.
5.2 Exclusion Criteria	Added exceptions to a positive UDS for benzodiazepine to Exclusion Criterion #23.	Clarified to keep consistent with permitted concomitant medications.
5.2 Exclusion Criteria	Updated ophthalmoplegic to retinal migraine in Exclusion Criterion #26.	To align with current guidance.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Added Exclusion Criterion #33 to exclude participants with a history of ≥15 headache days per month during the past 3 months or are suspected of suffering from chronic migraine as defined per IHS ICHD-3.	To clarify exclusion criteria related to chronic migraine.
5.4 Screen Failures	Added rescreen allowance for Exclusion Criterion #16 which excludes patients with an acute, serious, or unstable medical condition that in the judgement of the investigator precludes study participation.	This change allows for participants to rescreen if their acute or unstable illness resolves and/or is controlled.
5.4 Screen Failures	Added to allow participants who have become eligible to enroll in the study as a result of a protocol amendment.	Clarification.
6.3 Measures to Minimize Bias: Randomization and Blinding	Clarified in the case of emergency unblinding that if a participant's intervention assignment is unblinded, the sponsor must be notified immediately after breaking the blind.	Clarification.
6.8 Concomitant Therapy	Clarified that botulinum toxin A or B in the head or neck area for therapeutic use is not allowed within 4 months prior to Visit 2.	Corrected error.
7.1 Discontinuation of Study Intervention	Clarified if study intervention is permanently discontinued, the participant should remain in the study to be evaluated for safety and efficacy assessments, unless criteria in Section 7.2 apply.	Minor clarification.

Section # and Name	Description of Change	Brief Rationale
8.2.3 Electrocardiograms	Clarified in the event the ECG machine does not automatically calculate the QTcF interval, the QTcF interval may be manually calculated.	Clarified for site flexibility.
8.3 Adverse Events, Serious Adverse Events, and Product Complaints; 8.3.2 Product Complaints; 8.3.2.1 Time Period for Detecting Product Complaints; 8.3.2.2 Follow-Up of Product Complaints	Moved text from Section 8.3.2, Section 8.3.2.1, and Section 8.3.2.2 into Section 8.3.	Minor changes for clarity.
8.3.1 Timing and Mechanism for Collecting Events; 10.3.3 Recording and Follow-Up of AE and/or SAE	Clarified the mechanism for reporting adverse events as the AE CRF, severe adverse events as the SAE paper form, and pregnancy as the pregnancy paper form.	Electronic methods are not used for this study.
10.1.4 Committees Structure	Updated text to include terms and events for adjudication.	Minor changes for clarity.
10.2 Appendix 2: Treatments Allowed and Treatments not Allowed as Concomitant Therapy	Clarified opioid and barbiturates are allowed no more than 4 days /month.	Clarified for flexibility.

Section # and Name	Description of Change	Brief Rationale
10.2 Appendix 2: Treatments Allowed and Treatments not Allowed as Concomitant Therapy	Clarified gabapentin, pregabalin, and stimulants (prescription strength) are restricted during SP II and III and may be used for indications other than migraine prevention provided the dose is stable 2 months prior to Visit 2 and is expected to remain stable during Visit 2 through 6.	Changed to be consistent with recent studies for galcanezumab.
10.3.3 Recording and Follow-Up of AE and/or SAE	Removed "product complaint" and clarified CRF.	To ensure consistency with protocol text.
10.3.4 Reporting of SAEs	Removed section for SAE reporting via an electronic data collection tool.	Not applicable to study.
10.3.4 Reporting of SAEs	Clarified facsimile transmission of the SAE paper form to the sponsor or designee.	Align with changes made throughout the protocol.
10.6 Appendix 6: Provisions for Changes in Study Conduct During Exceptional Circumstances	Clarified telemedicine and mobile healthcare example assessments.	Minor clarification.
10.6 Appendix 6: Provisions for Changes in Study Conduct During Exceptional Circumstances	Clarified at visit windows when participants should be instructed to self-administer study intervention and discontinue ODT.	Minor clarification.
Throughout	Reference to Manual of Operations was changed to Reference Manual.	Align with current manual.
Throughout	Other minor editorial changes were made to add clarity.	Minor therefore not described.

Amendment a: (6-Aug-2021)

Overall Rationale for the Amendment:

The current sample size and power estimates assume a scenario where the reduction in migraine days across Months 1, 2, and 3 for rimegepant in the current study will be consistent with the reduction in migraine days at Month 3 for rimegepant as published for their single phase 2/3 prevention study. The proposed sample size increase to approximately 700 randomized patients assumes a smaller reduction in migraine days with rimegepant during Months 1 and 2 compared to Month 3.

Section # and Name	Description of Change	Brief Rationale
Title Page	Added Study Acronym	Branding.
1.1. Synopsis 9.5. Sample Size Determination	Increased sample size and updated sample size determination.	Additional power to detect effect.
6. Study Intervention(s) and Concomitant Therapy	Added additional definition for “study intervention”.	Clarification.
Throughout	Minor editorial corrections.	Minor therefore not described.

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