J1H-MC-LAJB(b) Clinical Protocol

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of LY3451838 in Adults With Treatment-Resistant Migraine

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Protocol J1H-MC-LAJB(b)
A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of LY3451838 in Adults with Treatment-Resistant Migraine

LY3451838

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1. Synopsis

Title of Study:
A Phase 2, randomized, double-blind, placebo-controlled study of LY3451838 in adults with treatment-resistant migraine.

Rationale:
LY3451838 is a fully human immunoglobulin G (IgG4-variant monoclonal antibody) that potently and selectively binds and neutralizes pituitary adenylate cyclase-activating polypeptide (PACAP). Evidence suggests that PACAP-38 is involved in migraine pathophysiology. Provocation studies have shown that PACAP infusion can induce migraine episodes in migraine patients, and plasma PACAP levels are elevated during a migraine attack. The objective of the Study J1H-MC-LAJB (LAJB hereafter) is to evaluate the safety and efficacy of LY3451838 to placebo in a treatment-resistant, adult patient population with episodic or chronic migraine.

Objectives/Endpoints:

Primary	
To test the hypothesis that LY3451838 is superior to placebo in the prevention of migraine in treatment-resistant migraine patients	The mean change from baseline in the number of monthly migraine headache days during the 1-month treatment phase (episodic and chronic migraine)[a]
Secondary	
To compare LY3451838 with placebo with respect to prevention of monthly headache days	The mean change from baseline in the number of monthly headache days during the 1-month treatment phase
To compare LY3451838 with placebo with respect to 50% response rate	The percentage of patients with ≥50% reduction from baseline in monthly migraine headache days during the 1-month treatment phase
To evaluate the safety and tolerability of a single dose of LY3451838 in treatment-resistant migraine patients	TEAEs SAEs
To characterize the pharmacokinetics of LY3451838 following a single IV dose in treatment-resistant migraine patients	LY3451838 C_{max} and AUC

Abbreviations: AEs = adverse events; AUC = area under the concentration-time curve from time 0 to infinite; C_{max} = maximum observed drug concentration; ECGs = electrocardiograms; SAEs = serious adverse events; TEAEs = treatment-emergent adverse events

[a] Episodic migraine is defined as 4 to 14 migraine headache days and <15 headache days per 1-month period in the prospective baseline period. Chronic migraine is defined as at least 15 headache days per 1-month period in the prospective baseline period, of which at least 8 are migraine.

Summary of Study Design:

Study LAJB is a multicenter, randomized, double-blind, parallel, placebo-controlled study of LY3451838 in patients who meet the International Classification of Headache Disorders version 3 (ICHD-3) criteria for a diagnosis of migraine with or without aura, or chronic migraine, and who have previously failed 2 to 4 categories of standard-of-care treatments for migraine prevention. The study has 4 periods, including the screening period, baseline for

eligibility, double-blind treatment phase, and follow-up assessment of headache episodes and related information.

Treatment Arms and Duration:

The study has 2 treatment arms: LY3451838 (1500 mg intravenous [IV]) and matching placebo. Following a 4-week prospective baseline period, eligible patients will be stratified by type of migraine (episodic or chronic) and then randomly assigned in a 1:1 ratio within each stratum to receive a single dose of LY3451838 or placebo. Patients will be followed for approximately 140 days post the study drug administration for safety assessment.

Number of Patients:

The study will screen an estimated 110 potential patients to ensure randomization of approximately 60 migraine patients, of which approximately 30 patients with chronic migraine.

Statistical Analysis:

A Bayesian analysis for the primary endpoint will be performed using an analysis of covariance (ANCOVA). The ANCOVA model for the change from baseline in the monthly number of migraine headache days will include terms for treatment and type of migraine, and baseline number of migraine headache days as a covariate will be used.

Frequentist analyses for change from baseline in the monthly number of migraine headache days and change from baseline in the monthly number of headache days will be performed using the same ANCOVA model.

Comparisons between the treatments in rate of responders will be conducted using Cochran Mantel Haenszel tests that are stratified by the type of migraine.

For continuous variables, descriptive statistics will include the number of patients, mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized using the number and percentage of patients.

2. Schedule of Activities

Table LAJB 2.1 Schedule of Activities

	Screening	Baseline	Treatment Phase			Follow-up						ED[b]
(Target) Interval (days) since previous visit	**-**	**-**	**30**	**15**	**15**	**15**	**15**	**15**	**15**	**30**	**30**	
Allowable range (days) between visits	**3-90**	**30-40[a]**										
Interval allowance (days)			**+5**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Month	**-**	**-**	**0**	**.5**	**1**	**1.5**	**2**	**2.5**	**3**	**4**	**5**	
Informed consent	X											
Demographics	X											
Physical examination[c]	X	X	P	X	X	X	X	X	X	X	X	X
Neurological examination	X	X	P	X	X		X		X	X	X	X
Height[d] and weight	X		P								X	X
Medical history[e] and concurrent conditions	X											
Vital signs[f]	X		P, 1 h	X	X	X	X	X	X	X	X	X
12-lead ECG[g]	X	X	P	X	X		X		X		X	X
Serum pregnancy test (WOCBP only) or FSH	X											
Urine pregnancy test (WOCBP only)[h]		X	P		X		X		X	X	X	X
HIV, hepatitis B and C	X											
Hematology, chemistry[i] (include eGFR)	X	X	P	X	X	X	X	X	X	X	X	X
Creatine kinase (Total CK)	X		P	X	X		X				X	X
HbA1c			P		X							
Urinalysis	X	X	P		X		X					
CCI			P	X	X							
ePRO and headache medication log training		X										
Inclusion and exclusion criteria	X	X	P									
ePRO daily patient diary entry		X	X	X	X	X	X	X	X			
Headache medication log		X	X	X	X	X	X	X	X			
CCI		X	X	X	X	X	X	X	X			
CCI		X	X	X	X	X	X	X	X			
Randomization			P									
Study drug administration			X									
MSQ v2.1			X		X		X		X			
HIT-6			X		X		X		X			

	Screening	Baseline	Treatment Phase			Follow-up						ED[b]
(Target) Interval (days) since previous visit	**-**	**-**	**30**	**15**	**15**	**15**	**15**	**15**	**15**	**30**	**30**	
Allowable range (days) between visits	**3-90**	**30-40[a]**										
Interval allowance (days)			**+5**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Month	**-**	**-**	**0**	**.5**	**1**	**1.5**	**2**	**2.5**	**3**	**4**	**5**	
C-SSRS Baseline and Screening	X											
C-SSRS Since Last Visit		X	X	X	X	X	X	X	X	X	X	X
Self-Harm Supplement Form	X	X	X	X	X	X	X	X	X	X	X	X
Self-Harm Follow-up Form[k]	X	X	X	X	X	X	X	X	X	X	X	X
Cogstate Brief Battery[l]		X	P	X	X						X	X
AE[m] / Concomitant medications	← X →											
PK sample[n]			P, EOI, 3h	X	X	X	X	X	X	X	X	X
Immunogenicity sample[n]			P	X	X				X		X	X
PACAP sample			P, EOI, 3h	X	X	X	X	X	X	X	X	X
IRR/Hypersensitivity sample[o]												
IRR/Hypersensitivity Follow-up Form[p]												
[redacted]												
Pharmacogenetic sample			P									
Biomarker sample (serum and plasma)			P	X								

Abbreviations: AE = adverse event; ANCA = anti-neutrophil cytoplasmic antibody; [redacted] ECG = electrocardiogram; ED = early discontinuation; eGFR: estimated glomerular filtration rate; EOI = end of infusion; ePRO = electronic patient-reported outcomes; [redacted]; h = hours after end of infusion; HbA1C = glycosylated hemoglobin; HIT-6 = Headache Impact Test-6; HIV = human immunodeficiency virus; IRR = infusion related reaction; MSQ = Migraine-Specific Quality of Life Questionnaire; P = predose assessment; PK = pharmacokinetic; PACAP = pituitary adenylate cyclase-activating polypeptide; WOCBP = women of child-bearing potential

[a] The eligibility period of the prospective baseline assessment will last from 30 to 40 days. Investigators and patients may have up to an additional 5 days to schedule their Visit 3 appointment (beyond the 40 days); however, eligibility will be based on the 30- to 40-day period.

[b] Patients who discontinue the study prior to study completion should complete the ED visit procedures.

[c] Complete physical examination at screening, Visit 11 and ED. Targeted physical examination to be performed at the remaining visits, which includes examination of skin, lungs, and skeletomuscular system; symptom-driven physical examination may also be performed at these visits based on PI discretion.

[d] Height collected at Visit 1 only.
[e] Includes substance usage (drugs, alcohol, tobacco, and caffeine) and family history of premature cardiovascular disease.
[f] Includes body temperature, sitting blood pressure, and pulse. Predose vital signs should be taken approximately 1 hour prior to the scheduled dosing. For all post-dose time points, the vital signs should be performed before any blood sample is drawn.
[g] For all post-dose time points, the ECG should be performed before any blood sample is drawn.
[h] A positive test must be followed by a serum pregnancy test for confirmation.
[i] Chemistry should be collected in a fasting state.
[j] Wearing of the device and entering data in the exploratory app is expected unless an exemption is allowed by the investigator and approved by Lilly.
[k] Required if triggered by the Self-Harm Supplement Form per instructions.
[l] For the Cogstate Brief Battery, two pre-baseline familiarization assessments will be conducted at Baseline/Visit 2, with at least 15 minutes break in-between. The baseline for the Cogstate Brief Battery will be assessed at Visit 3 and must occur prior to administration of study drug to provide a treatment free evaluation of cognition.
[m] Nonleading AE collection should occur prior to administration of C-SSRS, except for screening C-SSRS administration.
[n] For all post-dose time points, immunogenicity sample should be collected as close to PK blood draw as possible.
[o] Post-treatment samples (up to 3) will only be collected in patients who experience moderate to severe infusion reactions or hypersensitivity reactions (as defined in Sections 7.6.1, 9.4.6.2, and 9.4.6.4).
[p] Required if triggered by a suspected systemic allergic/hypersensitivity reaction.
[q] In event of suspected vasculitis (Section 9.4.6.2) evaluations may include ANCA, LY concentration, and immunogenicity samples. Skin biopsy may also be considered.

3. Introduction

3.1. Study Rationale

The purpose of Study J1H-MC-LAJB (LAJB) is to assess the efficacy and safety of LY3451838 in a treatment-resistant episodic and chronic migraine population. Blocking calcitonin gene-related peptide (CGRP) has been shown to reduce the migraine burden in both migraine phenotypes, including patients who had not responded to other anti-migraine preventive drug classes. Treatment resistant population, in this study, will be defined as previous failure to respond to 2 to 4 different standard-of-care migraine preventive medications either due to inadequate efficacy and/or due to safety/tolerability reasons, including the new anti-CGRP medications.

Additional rationale for the study design is provided in Section 5.4.

3.2. Background

According to the global burden of disease study, among 289 diseases and injuries that cause sequelae and disability, migraine appears as the third in global sequelae prevalence, behind dental caries of permanent teeth and tension-type headache; and as the eighth in global years lived with disability (Vos et al. 2012).

No approved migraine preventive treatment completely blocks the onset of migraine attacks. A substantial number of patients does not improve satisfactorily and/or is burdened with unacceptable side effects with a significant impact on productivity and quality of life. (Blumenfeld et al. 2011; Lanteri-Minet et al. 2011; Abu Bakar et al. 2016). Approximately 43% of the patients have a history of previous preventive medication failure or treatments switching. (Pike et al. 2016).

Pituitary adenylate cyclase-activating peptide-38 (PACAP-38) is a peptide belonging to the secretin/glucagon/vasoactive intestinal peptide (VIP) superfamily and is widely expressed in nociceptive pathways within the central and peripheral nervous systems (Jolivel et al. 2009; Vaudry et. al 2009). There is evidence to suggest that PACAP-38 is involved in migraine pathophysiology. Contrary to VIP, intravenous PACAP-38 injections provoke migraine-like attacks in migraineurs (Schytz et al. 2009). The plasma levels of PACAP-38 (Tuka et al. 2013) rise during migraine attacks (Zagami et al. 2014), suggesting an association between the plasma PACAP-38 levels and migraine episodes.

LY3451838 is a CCI [redacted] that potently and selectively binds and neutralizes PACAP. In the preclinical pharmacology studies, LY3451838 demonstrated selective binding and prevention of PACAP activities. The general toxicity of LY3451838 was assessed in 8-week rat and monkey studies and reproductive and developmental toxicity was assessed in rats (male and female fertility) and in pregnant rats and rabbits (embryofetal development).

Safety, tolerability and pharmacokinetics of LY3451838 were evaluated in a single ascending dose study in healthy subjects within a dose range of 25 to 1500 mg administered intravenously

(IV), or a single subcutaneous (SC) dose of 250 mg. CCI [redacted] Further details about LY3451838 PK in healthy subjects can be found in the Investigator's Brochure (IB).

3.3 Benefit/Risk Assessment

LY3451838 is being developed as a novel therapy for migraine prevention, as PACAP was hypothesized as another mediator of migraine attacks. Preclinical pharmacology data indicated that LY3451838 bound and prevented PACAP activities in vitro. CCI [redacted] These data support testing the efficacy of LY3451838 in patients with treatment-resistant migraine.

CCI [redacted]

More information about the known and expected benefits, risks, SAEs and reasonably anticipated AEs of LY3451838 are to be found in the IB.

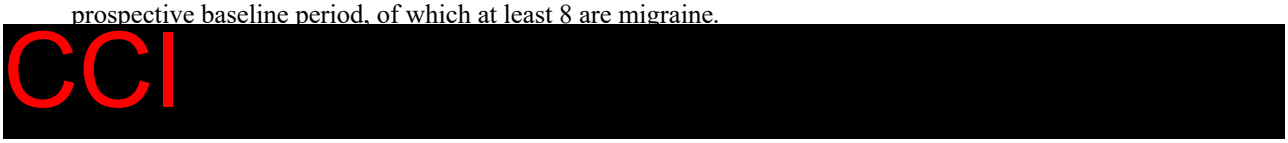
4. Objectives and Endpoints

Objective	Endpoint
Primary	
To test the hypothesis that a single IV dose of LY3451838 is superior to placebo in the prevention of migraine in treatment-resistant migraine patients	The mean change from baseline in the number of monthly migraine headache days during the 1-month treatment phase (episodic and chronic migraine)[a]
Secondary	
To compare LY3451838 with placebo with respect to prevention of monthly headache days	The mean change from baseline in the number of monthly headache days during the 1-month treatment phase
To compare LY3451838 with placebo with respect to 50% response rate	The percentage of patients with ≥50% reduction from baseline in monthly migraine headache days during the 1-month treatment phase
To evaluate the safety and tolerability of a single dose of LY3451838 in treatment-resistant migraine patients	TEAEs SAEs
To characterize the pharmacokinetics of LY3451838 following a single IV dose in treatment-resistant migraine patients	LY3451838 C_{max} and AUC
Exploratory	

CCI

Abbreviations: AUC = area under the concentration-time curve; CAS = Cranial Autonomic Symptoms; C_{max} = maximum observed drug concentration; HIT-6 = Headache Impact Test; MSQ = Migraine Specific Quality of Life Questionnaire; SAEs = serious adverse events; TEAEs = treatment-emergent adverse events; TE-ADA = treatment-emergent antidrug antibody

[a] Episodic migraine is defined as 4 to 14 migraine headache days and <15 headache days per 1-month period in the prospective baseline period. Chronic migraine is defined as at least 15 headache days per 1-month period in the prospective baseline period, of which at least 8 are migraine.



5. Study Design

5.1. Overall Design

Study LAJB is a multicenter, randomized, double-blind, parallel, placebo-controlled study of LY3451838 in patients who meet the International Classification of Headache Disorders version 3 (ICHD-3) criteria for a diagnosis of migraine with or without aura, or chronic migraine, and who have previously failed 2 to 4 categories of standard-of-care treatments for migraine prevention. The study has 4 periods as described below.

Figure LAJB 5.1 illustrates the study design.

Study Period I (Screening): The study and potential risks will be explained to the patient at Visit 1. The informed consent form (ICF) must be signed before any study procedures are performed, which includes discontinuing excluded medications. Patients are required to discontinue all excluded medications or treatments for migraine prevention at least 2 weeks prior to Visit 2. Botulinum toxin A or B 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 for migraine prevention are not allowed within 30 days before Visit 2.

The screening visit (Visit 1) will consist of a full clinical assessment (see Schedule of Activities, Section 2). Visit 1 will be complete when the last scheduled procedure of the screening assessment for the patient is completed.

Study Period II (Baseline): Qualified patients will enter Study Period II (prospective baseline) to determine their eligibility for the study and to establish baseline data for comparison of endpoints during the treatment phase. Beginning at Visit 2, patients will log in daily to the electronic patient-reported outcomes (ePRO) system to answer questions about the occurrence of headaches, headache duration, headache features, severity of headache, and whether any acute headache medication was taken. At Visit 2 and if available, patients will receive the devices required for digital biomarkers assessments as well as the necessary instructions and training. Also beginning at Visit 2, patients will record the name, dose, and date of any acute headache medication on a headache medication log which will be returned to site staff at each study visit. At the end of the prospective baseline period, sites will be notified whether their patient met criteria and are eligible to be randomized at Visit 3.

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

Study Period III (Double-Blind Treatment): At the start of the 1-month double-blind treatment phase (Visit 3), patients meeting all eligibility requirements will be stratified by type of migraine (episodic or chronic) and then randomly assigned in a 1:1 ratio within each stratum to receive a single dose of LY3451838 or placebo.

Patients will be given IV study drug (LY3451838 or placebo) at the study site. Patients will continue to log in and complete the ePRO diary each day. Patients may continue to take their

allowed acute migraine headache medication (with some limitations; see Section 7.8) during the treatment phase and will continue to record this use.

Study Period IV (Follow-up): Patients who complete the double-blind treatment phase (Study Period III) will be followed for safety for 140 days postdose. Patients will continue to have safety assessed, including daily completion of the ePRO diary and recording of acute headache medication use (see Schedule of Activities, Section 2).

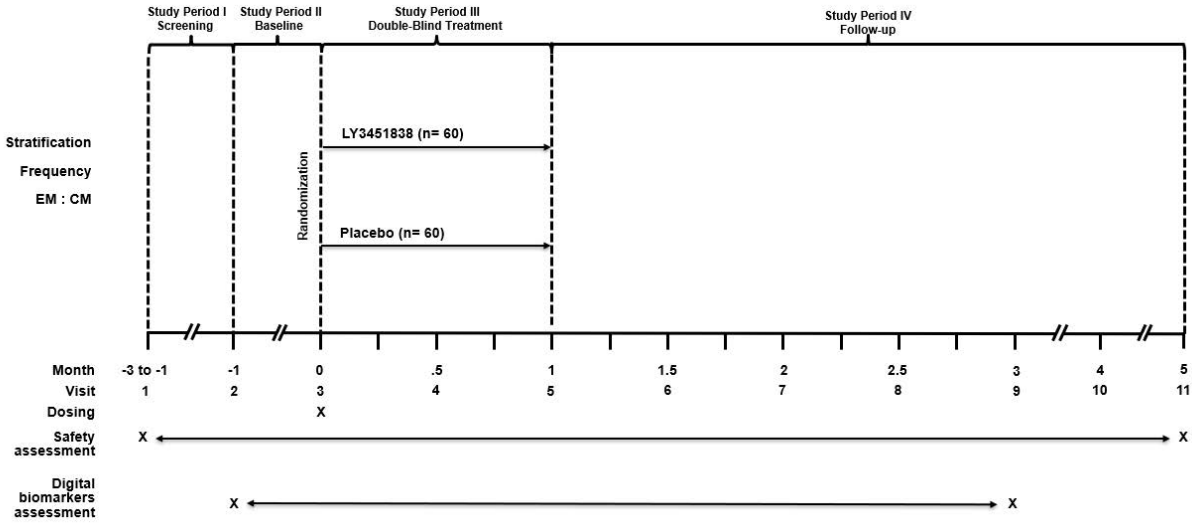


Figure LAJB 5.1 Illustration of study design for Clinical Protocol J1H-MC-LAJB.

Study governance considerations are described in detail in Appendix 3.

5.2. Number of Participants

The study will screen an estimated 110 potential patients to ensure randomization of approximately 60 migraine patients, of which approximately 30 patients have episodic migraine (defined as 4 to 14 migraine headache days and <15 headache days per 1-month period in the prospective baseline period). To ensure an appropriate balance of patients with episodic and chronic migraine, the sponsor will stop enrollment of patients with chronic migraine if the number of patients exceeds approximately 50%. Chronic migraine will be defined as at least 15 headache days per 1-month period in the prospective baseline period, of which at least 8 are migraine. Similar frequency of headache days must also be present during the 2 months previous to baseline for both episodic and chronic categories, according to investigator's assessment.

5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last patient.

5.4. Scientific Rationale for Study Design

The double-blind, randomized, placebo-controlled design is the internationally recommended approach to test efficacy of migraine preventive medications by the International Headache Society (IHS; Tfelt-Hansen et al. 2012). In line with the recommendations for migraine clinical trials, we include a 3-month retrospective migraine history, and a 1-month baseline period to confirm the headache diagnosis and frequency. Patients selection, diagnostic criteria, and outcome measurements are in accordance with current IHS recommendations and have been used in similar preventive clinical trials.

Since LY3451838 CCI or matching placebo will be administered only once, the 1-month treatment period is adequate in length. Nevertheless, ePRO daily data entry will continue for up to 12 weeks, allowing further analyses in possible late headache outcomes.

Because blocking PACAP signaling is an attractive alternative to anti-CGRP mAb treatments, which have proved to be efficacious in patients who experienced previous preventive treatment failures, this study is designed to specifically select treatment-resistant patients.

The safety / tolerability of LY3451838 has previously been assessed in a Phase 1 study (LAJA). Study LAJB will enable a clinical assessment of LY3451838 in a treatment-resistant migraine patient population, including patients who may potentially have failed up to 4 different categories of standard-of-care migraine preventives. Treatment resistance is more prevalent among patients with chronic migraine than episodic; however, the episodic form of migraine (ie, 4 to 14 migraine headache days and fewer than 15 headache days per month) is the most common, with approximately 7% of the migraine population suffering from the chronic form (ie, at least 15 headache days per month, of which at least 8 are migraine; Buse et al. 2012; Katsarava et al. 2012; Blumenfeld et al. 2013; ICHD-3 2018).

5.5. Justification for Dose

The planned LY3451838 dose for this study is CCI IV CCI for a 60-kg individual). This dose is selected based on the available preclinical pharmacology, toxicology, and clinical data.

Based on the CCI model, the predicted therapeutic concentration of LY3451838 is approximately CCI In Study LAJA the observed plasma concentration of LY3451838 28 days after a single IV dose of CCI This dose is chosen to ensure adequate target engagement that enables testing the efficacy of LY3451838 for migraine prevention, and to account for uncertainty in the translation of preclinical model to human efficacy.

The CCI dose was the highest dose administered in the single ascending dose study, LAJA. Interim analysis of the ongoing LAJA study suggested that LY3451838 was well-tolerated after a single IV dose up to CCI No dose-limiting toxicity was identified in this study, and no evidence of immune complex disease or vasculitis was observed. Vital signs and safety

laboratory tests were also unremarkable. The available safety / tolerability data from the ongoing study LAJA support the administration of CCI single IV dose in Study LAJB.

This dose is also supported by the available toxicology data. CCI

summarized in IB Section 4.2). CCI

Based on the available toxicology and limited clinical data, this dose is acceptable in this single-dose efficacy study.

6. Study Population

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

6.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria at Visit 1, unless stated otherwise in respective criterion:

1. Are 18 to 75 years of age (inclusive).
2. Have a diagnosis of migraine as defined by IHS ICHD-3 guidelines (1.1, 1.2.1.1, or 1.3) (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 at least 4 migraine headache days and at least 1 headache-free day per month on average within the past 3 months (documented by medical record or by physician's confirmation).
4. From Visit 2 to 3 (prospective baseline period), have a frequency of 4 or more migraine headache days and at least 1 headache-free day over 30 day period. If more than 15 headache days are present, at least 8 of them must fulfill criteria for migraine.
5. From Visit 2 to 3 (prospective baseline period), must achieve sufficient compliance with ePRO daily headache entries as demonstrated by completion of at least 80% of daily diary entries.
6. Prior to Visit 1, have documentation (by medical or pharmacy record or by physician's confirmation) of previous failure of 2 to 4 standard-of-care migraine preventive medication categories from the following list and in the past 10 years due to inadequate efficacy (that is, maximum tolerated dose for at least 2 months, (3 months in case of Botulinium toxin A or B) and/or safety/tolerability reasons:
    a. Propranolol or metoprolol
    b. Topiramate
    c. Valproate or divalproex
    d. Amitriptyline or nortriptyline
    e. Flunarizine
    f. Candesartan
    g. Anti-CGRP antibodies (either ligand or receptor)
    h. Botulinium toxin A or B (if documented that botulinium toxin was taken for chronic migraine)
    i. Rimegepant ODT
    j. Atogepant
7. Are available and willing to give signed informed consent.
8. Are reliable and willing to follow study procedures.
9. Women of child-bearing potential must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy test within 24 hours prior to exposure.

10. Women of child-bearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or agree to avoid sexual relationships with males. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.
11. Women of child-bearing potential who are not abstinent, as defined above, must agree to use one highly effective method (less than 1% failure rate) of contraception, or a combination of two effective methods of contraception for the entirety of the study as well as 5 months after study drug administration.

    Highly effective methods of contraception include combination oral contraceptives, implanted contraceptives or intrauterine device. Effective methods of contraception include male or female condoms with spermicide, and diaphragms with spermicide or cervical sponges. The patient may choose to use a double barrier method of contraception. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. Thus, each barrier method must include use of a spermicide. It should be noted that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these methods are combined.
12. Women not of child-bearing potential may participate and include those who are:
    a. infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as mullerian agenesis; or
    b. post-menopausal – defined as either
        i. a woman at least 40 years of age with an intact uterus, not on hormone therapy, who has cessation of menses for at least 1 year without an alternative medical cause, and a follicle-stimulating hormone >40 mIU/mL; or
        ii. a woman 55 or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea; or
        iii. a woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.
13. Agree not to voluntarily change habits or routines that represent a potential migraine trigger factor or protective measure including, but not limited to, substantial diet changes, physical exercise, or sleep habits.
14. 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 (eg, Facebook, Twitter, LinkedIn, YouTube, Instagram, etc.) excluding the patient's personal health care providers' site(s) until the entire study has completed.
15. Men, regardless of their fertility status, with non-pregnant women of child-bearing potential (WOCBP) partners must agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms plus one additional highly effective (less than 1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives or intrauterine device) or effective method of contraception, (such as diaphragms with

spermicide or cervical sponge) for the duration of the study as well as 5 months after study drug administration.

a. Men and their partners may choose to use a double–barrier method of contraception. (Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method of contraception. Thus, each barrier method must include use of a spermicide. It should be noted however that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these barrier methods are combined.)
b. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

16. Men with pregnant partners should use condoms during intercourse for the duration of the study as well as 5 months after study drug administration.
17. Men should refrain from sperm donation for the duration of the study as well as 5 months after study drug administration.
18. Men who are in exclusively same sex relationships (as their preferred and usual lifestyle) are not required to use contraception.

6.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at Visit 1, unless stated otherwise in respective criterion:

19. Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.
20. Have participated, within the last 30 days or 5-half-lives (whichever is longer), in a clinical study involving any investigational product. If the half-life of the investigational product is unknown, 6 months should have passed prior to Visit 1.
21. Have previously completed or withdrawn from this study or any other study investigating LY3451838.
22. Known hypersensitivity or intolerance to monoclonal antibodies or other therapeutic proteins, or to common antihistamines, epinephrine, methylprednisone or other systemic corticosteroids.
23. Are currently receiving medication or other treatment for prevention of migraine headaches. Patients must have discontinued such medications or treatments at least 2 weeks prior to Visit 2. Botulinum toxin A and B that has been administered in the head or neck area use must be discontinued at least 3 months prior to Visit 2. Nerve blocks or device use (such as transcranial magnetic stimulation or electrical nerve stimulation) in the head or neck area for migraine treatment must be discontinued at least 30 days prior to Visit 2. Anti-CGRP antibodies (to either ligand or receptor) must be discontinued at least 5 half-lives prior to Visit 2.
24. Have previously failed more than 4 migraine preventive medication categories in the past 10 years from the medication list in Inclusion Criterion # 6 due to inadequate efficacy (that is, maximum tolerated dose for at least 2 months) and/or safety/tolerability reasons. Previous failures to medications not on the above list will not be considered toward this exclusion.

25. History of cluster headache or migraine subtypes including hemiplegic (sporadic or familial) migraine, ophthalmoplegic migraine, retinal migraine, typical aura without headache, complications of migraine and migraine with brainstem aura (basilar-type migraine) defined by IHS ICHD-3.
26. In the 3 months prior to randomization, have other types of headache besides migraine, tension type headache, or medication overuse headache (MOH) as defined by IHS ICHD-3. (In other words, patients can have migraine, tension type headache, or MOH in the 3 months prior to randomization, but they cannot have other types of headache in that time.)
27. History of head or neck injury within 6 months prior to Visit 1.
28. History of traumatic cervical or head injury associated with significant change in the quality or frequency of their headaches.
29. Have reading of electrocardiogram (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. Fridericia-corrected QT interval (QTcF) >450 msec for males or >470 msec for females based on the reading of the ECG at Visit 1 must be discussed and judged not clinically significant by the principal investigator and Lilly Medical prior to enrollment.
30. Any liver tests outside the normal range at Visit 1 that are clinically significant. Alanine aminotransferase (ALT) >2X upper limit of normal (ULN), or total bilirubin (TBL) >1.5X ULN, or alkaline phosphatase (ALP) >2X ULN must be discussed and judged not clinically significant by the principal investigator and Lilly Medical prior to enrollment.
31. Evidence of significant active or unstable cognitive, behavioral or psychiatric disease by medical history, such as bipolar disorder, schizophrenia, personality disorders, or other serious mood or anxiety disorders. Note: Patients with major depressive disorder (MDD) or generalized anxiety disorder (GAD) 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.
32. Patients 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 (eg, includes some plan or intent to act), or have had any suicidal behavior within the past month.
33. Women who are pregnant or nursing.
34. Patients who have used opioids or barbiturate-containing analgesic >4 days per month for the treatment of pain in each of the past 3 months.
35. 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.
36. Have a positive urine drug screen for illicit drugs at Visit 1. Prescribed drugs compatible with the protocol and not considered by the investigator to be used abusively are allowed. 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.

37. Have an acute, serious, or unstable medical condition that, in the judgment of the investigator, indicates a medical problem that would preclude study participation.
38. 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.
39. 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.
40. Are Eli Lilly and Company employees.
41. Are unwilling or unable to comply with the use of data collection devices. Wearable digital biomarker device and/or investigational app may be exempted by the study investigator if approved by Lilly.
42. Have clinically significant proteinuria or hematuria at screening and enrollment.

CCI

44. Show evidence of human immunodeficiency virus (HIV) and/or positive human HIV antibodies; current hepatitis C infection with positive hepatitis C antibody and positive hepatitis C virus RNA; or hepatitis B and/or positive hepatitis B surface antigen.
45. Have an abnormal blood pressure (supine) defined as diastolic blood pressure >95 or <50 mmHg and/or systolic blood pressure >160 or <90 mmHg. Retesting may occur once during the screening visit within 2 hours of the initial abnormal blood pressure measurement at the discretion of the investigator.
46. Have a history or presence of serious or unstable illnesses including cardiovascular, hepatic, renal, gastrointestinal, respiratory, endocrine, immunologic, hematologic disease, neurological (excluding migraine) and other conditions that, in the investigator's opinion, could interfere with the analyses in this study, or increase risk for study intervention administration, or result in a participant's life expectancy of <24 months.

6.3. Lifestyle Restrictions

No changes in lifestyle or dietary requirements are required during the study.

Patients should be instructed not to donate blood or blood products during the study or for 5 months following the last administration of investigational product.

Women of child-bearing potential and men should adhere to the contraceptive requirements as specified in the protocol (Section 6.1). No contraception is required for women of non-child-bearing potential, except in compliance with specific local government study requirements.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be considered for rescreen with approval from Lilly Medical.

Patients using a 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.

Repeating of laboratory tests during the screening period does not constitute rescreening.

7. Treatments

7.1. Treatments Administered

This study involves a comparison of LY3451838 CCI with placebo and is administered once by IV infusion. Trained site staff will administer LY3451838 or placebo at the study site during the double-blind treatment phase.

The study drug will be administered as a slow IV infusion over at least 60 minutes. Infusion duration may be increased or stopped as deemed necessary based on the standard operation procedure, or if an infusion reaction is observed (Section 7.6.1). Sites must have resuscitation equipment, emergency drugs, and appropriately trained medical staff available during the infusion and for at least 6 hours after patients have completed their infusion. The actual start and stop time of infusion will be recorded in the electronic data capture (EDC) system. If the infusion is terminated early, this will also be recorded in the EDC.

LY3451838 Drug Product is a CCI antibody formulated for IV administration. LY3451838 is supplied for clinical trial use as a solution in a single-use glass vial. The vial is manufactured to deliver CCI of LY3451838 at CCI. In order to ensure complete withdrawal and delivery of the label amount of CCI of LY3451838, vials contain an approximate 10% volume overfill. The drug product is filled into a glass vial, and sealed with a stopper and flip-off 2 piece aluminum seal.

This study is double-blinded and the placebo prepared at the site by unblinded dispensing personnel will be 0.9% sodium chloride for injection, compendial. This solution is indistinguishable in appearance from the reconstituted active drug solution. Study drug preparation will be conducted and verified by unblinded personnel. Study drug will be administered by blinded personnel.

The unblinded dispensing personnel will receive training and instructions for preparation of each dose of LY3451838 and the preparation of the placebo solutions.

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the investigational agent(s) to the patient
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing and collection
- at the end of the study, returning all unused medication to Lilly, or its designee, unless the sponsor and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law.

7.1.1. Packaging and Labelling

The drug product will be manufactured, tested, packaged, and labeled in accordance with all applicable Good Manufacturing Practice (GMP) requirements and country's regulatory requirements. A certificate of analysis confirming the materials are released for human use in

clinical trials will be supplied. LY3451838 drug products are for investigational use only and are to be used only within the context of this study.

7.2. Method of Treatment Assignment

Following a 1-month prospective baseline period, eligible patients will be stratified by type of migraine (episodic or chronic) and then randomly assigned in a 1:1 ratio within each stratum to receive LY3451838 or placebo. Treatment assignment will be determined by a computer-generated randomization sequence using an interactive web response system (IWRS).

To ensure an appropriate balance of patients with episodic and chronic migraine, the sponsor will stop enrollment of patients with chronic migraine if the number of patients exceeds approximately 50%.

7.2.1. Selection and Timing of Doses

This is a fixed-dose study where the single dose of the study drug will be administered at the site by a trained staff member. The actual time of dose administration will be recorded in the EDC.

7.3. Blinding

This is a double-blind study; subjects, investigator, and site personnel performing trial related activities or with the ability to influence study outcomes will be blinded with respect to LY3451838 and placebo treatment. To preserve the blinding, only a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete. Site staff who are responsible for drug preparation will not be blinded; laboratory personnel will also not be blinded.

After the reporting database is locked for statistical analysis of the double-blind treatment phase, a limited number of sponsor personnel will be unblinded to complete the study report. However, any sponsor personnel continuing with the management and oversight of the study will remain blinded to patients' treatment assignments.

Emergency unblinding may be performed through the IWRS. This option may be used only if the patient's well-being requires knowledge of the patient's treatment assignment. All unblinding events will be recorded and reported by the IWRS.

In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted for medical management of the event. The patient's safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, it is the responsibility of the Investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

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

patient to continue in the study. During the study, emergency unblinding should occur only by accessing the IWRS.

7.4. Dosage Modification

Not applicable.

7.5. Preparation/Handling/Storage/Accountability

The investigator or his/her designee is responsible for the following:

- confirming appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- ensuring that only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments 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 site staff.
- the investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation and final disposition records).

Detailed instructions for the preparation and handling of LY3451838 will be provided to the unblinded site pharmacy personnel by the Sponsor.

LY3451838 for Injection vials are to be stored in refrigerated condition (2ºC to 8ºC).

7.6. Special Treatment Considerations

7.6.1. Management of Infusion Reactions

There is a risk of infusion reactions with any biological agent; therefore, all patients should be monitored closely. Symptoms and signs that may occur as part of an infusion reaction include, but are not limited to: fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash, pruritus, myalgia, and dizziness. Infusion site reactions may include erythema, induration, pain, pruritus, and edema. In the event that a significant infusion reaction occurs, the following guidance should be followed:

- The drug product infusion should be slowed (for example, reduce infusion rate by 50% [for example, an infusion rate of 12 mL/hr becomes 6 mL/hr or slower]) or stopped based on severity and in accordance with the investigator's assessment:
    - if slowed, the infusion should be completed at the slower rate, as tolerated
    - if determined by the investigator that the infusion should no longer continue, no further attempts to dose the patient should be made
- Supportive care will be administered as determined by the study investigator(s)

- Appropriate medication may be used as determined by the study investigator(s)

For specific laboratory testing, please see Section 9.4.6.4.

7.7. Treatment Compliance

The study drug will be administered at the site. Investigators will be required to document the administration of study drug in the EDC.

Study drug must be administered per Section 2 of this protocol. If the investigator is unable to administer the study drug in the allowed window, the situation should be discussed with Lilly to determine if the patient may continue.

7.8. Concomitant Therapy

Table LAJB 7.1 contains the 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 and non-pharmacological interventions, are not allowed at any time during Treatment Phase and Follow-up Phase. Patients 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. Anti-CGRP antibodies (to either ligand or receptor) must be discontinued at least 5 half-lives prior to Visit 2.

Patients will capture whether they took any acute headache medication as part of their daily diary entry during Treatment Phase and Follow-up Phase. Acute headache medication name, dose, and date will be recorded by patients during Treatment Phase and Follow-up Phase on a headache medication log, which will be returned to site staff at each study visit.

Table LAJB 7.1 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) up to 3000 mg/day, NSAIDs; Triptans; Ergotamine and derivatives; Isometheptene mucate, dichloralphenazone and acetaminophen combination (Midrin); or combinations thereof; ubrogepant;

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, III, IV).
3. Short term use of steroids, < 7days, for medical circumstances that may arise.

B. Medications, Procedures or Devices not allowed for any reason/indication in Study Period II (Baseline), III (Double-Blind Treatment), and IV (Follow-up):

ACE inhibitors
Acetazolamide

Acupuncture
Anticonvulsants/Antiepileptics
Antipsychotics
Angiotensin receptor blockers (ARBs)
Beta-blockers
Botulinum toxin applied to head/neck area for therapeutic use
Cannabis / Cannabinoids / Cannabidiol
Chiropractic procedures, physiotherapy, TENS or other electric devices on head and neck
Corticosteroids for oral use
Flunarizine
Gabapentin
Herbals with anti-inflammatory effect (feverfew, willow bark, petasites/butterbur)
Monoamine oxidase inhibitors (MAOIs)
Memantine
Methysergide
Nerve block in head/neck area
Oxetorone
Pizotifen
Pregabalin
Serotonin 5HT2a/2c antagonists, eg, trazodone, nefazodone
Stimulants (prescription strength), eg, methylphenidate, dextroamphetamine, mixed amphetamine salts
Tizanidine
Tricyclic antidepressants (TCAs)
Triptans for prophylaxis of menstrual related migraine
Venlafaxine
Verapamil

C. Restricted medication during Study Period III (Double-Blind Treatment) and Study Period IV (Follow-up): 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 the Treatment Phase.

Benzodiazepines
Bupropion
Calcium-channel blockers (except verapamil, flunarizine, and lomerizine)
Clonidine
Guanfacine
Mirtazapine
SSRIs/NRIs/SNRIs (other than venlafaxine)
Use of electric devices (ie, TENS), physiotherapy, chiropractic procedures on low back and extremities

D. Restricted medication during Study Period IV (Follow-up):

Medications from List B.
Medications or treatments for migraine prevention.
Medications in List C may now be started, stopped, or have dose modification as long as not being used for migraine prevention.

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.

7.9. Treatment after the End of the Study

Not applicable.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

8.1.1. Permanent Discontinuation from Study Treatment

Possible reasons leading to permanent discontinuation of the study drug:

- Unacceptable toxicity
- Patient request
- Pregnancy
- Discontinuation due to a hepatic event or liver test abnormality:
- Patients who are discontinued from study drug due to a hepatic event or liver test abnormality should have additional hepatic safety data collected and entered into EDC.
    - Discontinuation of the study drug for abnormal liver tests **should be** considered by the investigator when a patient meets one of the following conditions after consultation with the Lilly designated medical monitor:
        - ALT or aspartate aminotransferase (AST) >8X ULN
        - ALT or AST >5X ULN for more than 2 weeks
        - ALT or AST >3X ULN and TBL >2X ULN or international normalized ratio (INR) >1.5
        - 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
        - ALP >2.5X ULN and TBL >2X ULN
        - ALP >2.5X ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- If the investigator, after consultation with the sponsor-designated medical monitor, determines that a systemic hypersensitivity reaction has occurred related to study drug administration, the participant should be permanently discontinued from the investigational drug.
- In addition, study drug may be discontinued if participants
    - answered “yes” to Question 4 or Question 5 on the “Suicidal Ideation” portion of the Columbia-Suicide Severity Rating Scale (C-SSRS), or
    - answered “yes” to any of the suicide-related behaviors on the Suicidal Behavior portion of the C-SSRS.

  A psychiatrist or appropriately trained professional may assist in the decision to discontinue the participant.

Patients discontinuing from the study drug prematurely for any reason should complete adverse event and other follow-up procedures per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.1.2. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identify a patient who did not meet enrollment criteria and was inadvertently enrolled, then the patient should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the patient to continue on study treatment. If the investigator and the Lilly medical monitor agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly medical monitor to allow the inadvertently enrolled patient to continue in the study with or without treatment with investigational product. Safety follow up is as outlined in Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.2. Discontinuation from the Study

Patients will be discontinued in the following circumstances:

- 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
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- investigator decision or patient request
- patients discontinuing from the study prematurely for any reason should complete adverse event and other follow-up procedures per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.3. Lost to Follow-Up

A patient 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 are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, with the study procedures and their timing (including tolerance limits for timing).

Appendix 2 lists the laboratory tests that will be performed for this study.

Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.1. Efficacy Assessments

9.1.1. Primary Efficacy Assessments

ePRO Diary: Patients will be asked to use an ePRO instrument to record headache information, including reporting frequency, intensity, features (eg, locations and quality), and whether any acute headache medication was taken. The system also will be used to collect information about migraine-associated symptoms (CCI , photophobia, phonophobia, nausea, and/or vomiting).

9.1.2. Secondary Efficacy Assessments

Secondary efficacy assessments in this study (Section 4) are intended to facilitate the collection and analysis of information such as response (≥50% reduction from baseline in the number of migraine headache days per month and number of monthly headache days) with data from the ePRO Diary (see above), and safety and tolerability of the study drug via analysis of TEAEs and SAEs.

9.1.3. Appropriateness of Assessments

The efficacy and safety assessments used in this study have been well documented and are generally regarded as reliable, accurate, and relevant in this patient population.

9.2. Adverse Events

A clinical trial AE is any untoward medical event associated with the use of a drug or drug delivery system in humans, whether or not it is considered related to that drug or drug delivery system.

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of patients during the study.

Investigators must document their review of each laboratory safety report and ECG.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational

product or the study, or that caused the patient to discontinue the investigational product before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect. However, any worsening of the primary study condition should be recorded as an AE.

After the ICF is signed, study site personnel will record via EDC the occurrence and nature of each patient's pre-existing conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record via eCRF any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure or investigational product via EDC.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, study device, or a study procedure, taking into account the disease, concomitant treatment, and pathologies.

A "reasonable possibility" means that there potentially is a cause and effect relationship between the investigational product, study device, and/or study procedure and the AE.

The investigator will use AE follow-up forms to record additional details regarding AEs related to injection sites and hypersensitivity events.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a patient's study drug is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via EDC, clarifying if possible the circumstances leading to discontinuation of treatment.

9.2.1. Adverse Event Monitoring with a Systematic Questionnaire

Nonleading AE collection should occur prior to the collection of the C-SSRS.

If a suicide-related event is discovered during the C-SSRS but was not captured during the nonleading AE collection, sites should not change the AE form.

If an AE is serious or leads to discontinuation, it needs to be included on the AE form and the process for reporting SAEs is followed.

9.2.2. Serious Adverse Events

An SAE is any AE from this study that results in one of the following:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)

- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

The study site personnel must alert the Lilly, or its designee, of any SAE as soon as practically possible.

Additionally, study site personnel must alert Lilly, or its designee, of any SAE within 24 hours of Investigator awareness of the event via a Sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Although all AEs are recorded in the case report form or EDC after signing informed consent, SAE reporting to the Sponsor begins after the patient has signed informed consent and has received the study drug. However, if an SAE occurs after signing informed consent, but prior to receiving the study drug, AND is considered Reasonably Possibly Related to a study procedure then it MUST be reported.

Investigators are not obligated to actively seek AEs or SAEs in patients once they have discontinued from and/or completed the study (the patient disposition EDC has been completed). However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the Investigator must promptly notify Lilly.

Pregnancy (maternal or paternal exposure to the study drug) does not meet the definition of an adverse event. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

The designated medical monitor of the Sponsor will monitor safety data throughout the course of the study. The Sponsor and/or its designee will review SAEs within appropriate timeframes to meet reporting obligations imposed by regulatory authorities. All serious and unexpected AEs for this study will be reported to regulatory authorities in accordance with local laws, directives, and regulations.

9.2.2.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. Lilly has procedures that will be followed for the identification, recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.3. Complaint Handling

Lilly collects product complaints on investigational products 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.

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the study drug so that the situation can be assessed.

9.3. Treatment of Overdose

An overdose is not anticipated, as the study drug will be administered by a trained staff member.

In case of overdose, use supportive therapy. There is no known antidote to LY3451838 overdose.

9.4. Safety

Planned time points for all safety assessments are provided in the Schedule of Activities (Section 2).

9.4.1. Physical and Neurological Examinations

- A complete physical examination will be performed at screening and at time of discharge (Section 2). Targeted physical examination of skin, lungs, and skeletomuscular system will be performed according to the Schedule of Activities (Section 2). Symptom-driven physical examinations will be performed if deemed clinically necessary.
- A complete neurological examination will be performed by a physician at the time points specified in the Schedule of Activities (Section 2). If abnormalities are noted at these time points, additional examinations should be repeated until the participant has returned to baseline. The examiner should be familiar with the participant's baseline examination. Mandated elements of the examination include mental status, gait, balance, coordination, cranial nerves, sensory and motor systems, and reflexes. Work-up for participants with clinically significant changes in neurological examinations should be considered. Additional neurological examination will be performed as soon as possible, along with any other methodical follow-ups deemed necessary by the investigator.

9.4.2. Vital Signs

Vital signs will include body temperature, sitting blood pressure, and pulse. For each patient, vital signs measurements should be conducted according to the Schedule of Activities (Section 2).

Predose vital signs should be taken approximately 1 hour prior to the scheduled dosing.

Any clinically significant findings from vital signs measurement that result in a diagnosis should be reported to Lilly, or its designee, as an AE via EDC.

9.4.3. Electrocardiograms

For each patient, a single 12-lead digital ECG should be collected according to the Schedule of Activities (Section 2). Electrocardiograms should be collected prior to blood draws and dosing.

Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms may be obtained at additional times, when deemed clinically necessary.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, to determine whether the patient meets entry criteria at the relevant visits and for immediate patient management, should any clinically relevant findings be identified.

If a clinically significant quantitative or qualitative change from baseline is identified after enrollment, the investigator will assess the patient for symptoms (for example, palpitations, near syncope, syncope) to determine whether the patient can continue in the study. The investigator or qualified designee is responsible for determining if any change in patient management is needed and must document his/her review of the ECG printed at the time of evaluation.

9.4.3.1. Digital Electrocardiogram Storage

Digital ECGs collected from the study will be electronically transmitted to a central ECG laboratory designated by Lilly. The central ECG laboratory will perform a basic quality control check (for example, demographics and study details) then store the ECGs in a database. At a future time, the stored ECG data may be overread at the central ECG laboratory for further evaluation of machine-read measurements or to meet regulatory requirements.

The machine-read ECG intervals and heart rate will be used for data analysis and report writing purposes unless a cardiologist overread of the ECGs is conducted prior to completion of the final study report, in which case the overread data would be used.

Any clinically significant findings from ECGs that result in a diagnosis should be reported to Lilly, or its designee, as an AE via EDC.

9.4.4. Laboratory Tests

For each patient, laboratory tests detailed in (Appendix 2) should be conducted according to the Schedule of Activities (Section 2).

With the exception of laboratory test results that may unblind the study, Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor. Note that any result that may unblind a site would not be shared.

Any clinically significant findings from laboratory tests that result in a diagnosis should be reported to Lilly, or its designee, as an AE via EDC.

9.4.5. Immunogenicity Assessments

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 10 mL each will be collected to determine antibody production against LY3451838. Antibodies may be further characterized for their ability to neutralize the activity of the LY3451838. To interpret the results of immunogenicity, a venous blood sample will be

collected at the same time points to determine the plasma concentrations of LY3451838. All samples for immunogenicity should be taken predose when applicable and possible.

Treatment-emergent antidrug antibodies (TE-ADAs) are defined in Section 10.3.6. If the immunogenicity sample at the last scheduled assessment or discontinuation visit is TE-ADA positive, additional samples may be taken until the signal returns to baseline (ie, no longer TE-ADA positive) or for up to 1 year after last dose.

Samples will be retained for a maximum of 15 years after the last patient visit, or for a shorter period if local regulations and Ethical Review Boards (ERBs) allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to the study drug. Any samples remaining after 15 years will be destroyed.

9.4.6. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

9.4.6.1. Hepatic Safety Monitoring

If a study patient experiences any of the following abnormal liver test results, liver testing (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing:

- elevated ALT ≥3X ULN
- ALP ≥2X ULN
- elevated TBL ≥2X ULN

If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator and in consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels.

Hepatic Safety Data Collection

Additional safety data should be collected if 1 or more of the following conditions occur:

- elevation of serum ALT to ≥5X ULN on 2 or more consecutive blood tests
- elevated serum TBL to ≥ 2X ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥2X ULN on 2 or more consecutive blood tests
- patient discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be an SAE

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9.4.6.3. Hypersensitivity Reaction

Many drugs, but particularly biologic agents, carry the risk of systemic hypersensitivity reactions. If such a reaction occurs, additional data should be provided to the sponsor in the EDC.

Sites should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving study drug. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per national and international guidelines.

In the case of generalized urticaria or anaphylaxis, additional blood samples should be collected as described in Appendix 5. Laboratory results are provided to the sponsor via the central laboratory.

Acute and serious hypersensitivity reactions will be assessed and managed as clinically indicated. The clinical information, including examination findings, laboratory testing and treatment for all serious adverse events, including hypersensitivity reactions, will be captured in the EDC.

Non-acute hypersensitivity reactions, including type 3 hypersensitivity reaction will be assessed by clinical presentation. Routine monitoring of vital signs with regular physical examinations, and laboratory testing (including hematology, liver and renal testing, CCI

CCI , and urine analysis) will be undertaken to assess for the development of CCI serum sickness and other manifestations of type 3 hypersensitivity reactions.

Unscheduled stored serum samples for possible immune safety laboratory testing (including, but not limited to: β-tryptase, total IgE, immune-complex testing, and cytokine panel) should be collected approximately 60 to 120 minutes and 4 to 6 weeks after hypersensitivity reactions.

9.4.6.4. Infusion Reaction

Symptoms and signs that may occur as part of an infusion reaction include, but are not limited to: fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash, pruritus, myalgia, and dizziness. Signs and symptoms of a local infusion site reaction may include erythema, induration, pain, pruritus, and edema. In the event that an infusion reaction occurs during the infusion, please see Section 7.6.1 for guidance on administration of remaining study drug, if applicable. In the event that an infusion reaction occurs at any other time, appropriate supportive care and/or medication may be used as determined by the study investigator(s). These adverse events should be captured as specified in Section 9.2.

Unscheduled stored serum samples for possible immune safety laboratory testing (including, but not limited to: β-tryptase, total IgE, immune-complex testing, and cytokine panel) should be collected approximately 60 to 120 minutes and 4 to 6 weeks after moderate or severe infusion reactions.

The clinical information, including examination findings, laboratory testing and treatment for all adverse events, including infusion reactions, will be captured in the EDC.

9.4.6.5. Suicidal Ideation and Behavior Risk Monitoring

Patients being treated with LY3451838/placebo should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior, especially at the beginning and end of the course of treatment, or at the time of dose changes, either increases or decreases. Consideration should be given to discontinuing the study medication in patients who experience signs of suicidal ideation or behavior, following a risk assessment.

Columbia Suicide-Severity Rating Scale is a scale that captures the occurrence, severity, and frequency of suicidal ideation and behavior during the assessment period via a questionnaire. The scale was developed by the National Institute of Mental Health (NIMH) trial group (TASA) for the purpose of being counterpart to the Columbia Classification Algorithm of Suicide Assessment (C-CASA) categorization of suicidal events.

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9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 2 mL each will be collected to determine the serum concentrations of LY3451838.

The actual date and time of each sampling must be recorded.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable exposure or response to study drug. Assessment of variable response may include evaluation of AEs or differences in efficacy.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the investigative site personnel.

Samples will be retained for a maximum of 15 years after the last patient visit, or for a shorter period if local regulations and/or IRBs impose shorter time limits, for the study at a facility selected by Lilly or its designee.

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9.9. Health Economics

The health outcome measures will be collected according to the Schedule of Activities (Section 2).

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 (Jinghran 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 (Jinghran et al. 1998a; Marting 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 (Jinghran et al. 1998b; Bagley et al. 2012).

Six-item Headache Impact Test (HIT-6): HIT-6 is a tool used to measure the impact headaches have on patient's ability to function on the job, at school, at home and in social situations. The HIT-6 consists of six items: pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress. The patient answers each question using one of the following 5 responses: "never," "rarely," "sometimes," "very often," or "always." These responses are summed to produce a total HIT-6 score that ranges from 36 to 78, where a higher score indicates a greater impact of headache on the daily life of the respondent (Shin et al. 2008). A validation study showed that the HIT-6 is a reliable and valid tool for measuring the impact of headache on daily life in both episodic and chronic migraine sufferers (Yang et al. 2011).

10. Statistical Considerations

10.1. Sample Size Determination

The study will screen an estimated 110 potential patients to ensure randomization of approximately 60 migraine patients. Enrollment will be stratified by type of migraine, episodic versus chronic, and patients will be randomly assigned to either LY3451838 or placebo in a 1:1 allocation ratio within each stratum. Enrollment in the chronic migraine stratum will be capped so that no more than approximately 50% of the randomized population will be patients with chronic migraine.

The analysis will be conducted using all randomized patients, and it is assumed that approximately 2% of the patient population will dropout during the 28 days treatment period.

The study will be considered successful if there is at least a CCI probability that the number of monthly migraine headache days with LY3451838 treatment is CCI days less than the number of monthly migraine headache days with placebo treatment CCI

Enrolling approximately 60 patients who are stratified by type of migraine, episodic versus chronic, and randomly assigned to either LY3451838 or placebo in a 1:1 allocation ratio within each stratum will provide approximately CCI

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10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All patients who sign informed consent
Randomized	All patients who are assigned a study treatment. Patients who had no post randomization efficacy measure for the parameter being analyzed will be excluded.
Safety	All randomized patients who take at least 1 dose of double-blind study treatment. Patients will be included in the treatment group they were randomized to. In the event of a treatment error, patients will be analyzed according to the treatment they actually received.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. Details of statistical analysis methods will be described in the SAP.

Efficacy analyses will be conducted on the randomized set. Safety analyses will be conducted on the safety population. When mean change from baseline is assessed, the patient will be included in the analysis only if the patient has a baseline and a postbaseline measurement.

In general, for analyses of numeric outcome measures during the treatment phase, baseline value is defined as the last observation at or before Visit 3. Treatment effects will be evaluated based on a 2-sided significance level of 0.05. No adjustments for multiplicity will be applied to comparisons of baseline characteristics or safety parameters.

A Bayesian analysis will be performed for the primary efficacy endpoint, and the corresponding frequentist analyses will be conducted as a sensitivity analysis. All other statistical inference will be performed using frequentist methods.

For continuous variables, descriptive statistics will include the number of patients, mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized using the number and percentage of patients.

Any change to the data analysis methods described in the protocol will require a protocol amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

SAS® software version 9.4 or higher will be used to perform statistical analyses, unless otherwise specified.

10.3.2. Treatment Group Comparability

10.3.2.1. Patient Disposition

A detailed description of patient disposition will be provided at the end of the study. All patients who discontinue from the study will be identified, and the extent of their participation in the study will be summarized by treatment. If known, a reason for their discontinuation will be given.

10.3.2.2. Patient Characteristics

The following patient characteristics at baseline will be summarized by treatment.

- Demographic (age, sex, ethnic origin, height, weight, body mass index)
- Migraine and/or headache-related measures from the ePRO diary per 1-month baseline period

- Number of prior migraine preventive treatment failures from the list in Section 6.1 (Inclusion Criterion #6):
    - Failed 2 medication categories
    - Failed 3 medication categories
    - Failed 4 medication categories
- Medical history and pre-existing conditions

Medical history and pre-existing conditions will be summarized by preferred term within system organ class (SOC).

10.3.2.3. Concomitant Therapy

The proportion of patients who received concomitant medication and acute medications will be summarized.

10.3.2.4. Treatment Compliance

Any dose reduction, overdose, or dose delay will be summarized for all treated patients by cohort.

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

The primary analysis will be performed using an analysis of covariance (ANCOVA) model for the change from baseline in the monthly number of migraine headache days. The model will include randomized treatment and type of migraine as fixed effects and the baseline number of monthly migraine headache days as a covariate. The analysis will use a non-informative prior for the treatment effect. The treatment group means, treatment contrast, and their respective 95% credible regions as well as the success criterion will be based on the posterior treatment effect distributions.

10.3.3.2. Secondary Analyses

Frequentist analyses for change from baseline in the monthly number of migraine headache days and change from baseline in the monthly number of headache days will be performed using the ANCOVA model. Comparisons between the treatments in rate of responders will be conducted using Cochran Mantel Haenszel tests that are stratified by the type of migraine.

10.3.3.3. Exploratory Analyses

Details on exploratory analysis will be provided in the SAP.

10.3.4. Safety Analyses

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

- TEAEs
- SAEs
- AEs leading to discontinuation

- Potential hypersensitivity events
- AEs related to injection site reactions
- Vital signs
- Physical and neurological examinations
- ECGs
- Laboratory measurements
- CBB

The parameters will be listed, and summarized using standard descriptive statistics. Additional analysis will be performed as required.

10.3.6. Evaluation of Immunogenicity

The frequency and percentage of patients with preexisting ADA and with TE-ADA+ to LY3451838 may be tabulated.

Treatment-emergent ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA). For the TE-ADA+ patients the distribution of maximum titers may be described. The frequency of neutralizing antibodies may also be tabulated in TE ADA+ patients, when available.

The relationship between the presence of antibodies and the PK parameters and PD response including safety and efficacy to LY3451838 may be assessed.

10.3.7. Other Analyses

10.3.7.1. Health Economics

The change from baseline for the treatment phase for MSQ v2.1 and HIT-6 will be analyzed. In addition, categorical analyses will be performed. Additional details will be provided in the SAP.

10.3.7.2. Analysis of C-SSRS Data

Suicide-related thoughts and behaviors occurring during treatment will be summarized based on responses to the C-SSRS consistent with the C-SSRS Scoring and Data Analysis Guide.

Additional details will be provided in the SAP.

10.3.8. Interim Analyses

An interim analysis is planned when data from the majority of randomized patients have completed the 1-month treatment period. The interim efficacy results may be used for internal decision-making to trigger planning activities associated with the investigational product. No adjustment of Type I error will be performed as the study will not be stopped for efficacy, and no modification of Study LAJB is expected based on these interim results. The assessment would be conducted by a sponsor assessment committee with a limited number of preidentified team members who do not have direct site contact or data entry/validation responsibilities. Unblinding details will be specified in the unblinding plan section of the SAP or in a separate unblinding plan document. Information that may unblind the study during the analyses will not be reported to study sites or to the blinded study team until the study has been unblinded.

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	anti-drug antibody
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under concentration-time curve
blinding/masking	A double-blind study is one in which neither the [patient] nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the patients are aware of the treatment received.
CAS	Cranial Autonomic Symptoms
CBB	Cogstate Brief Battery
CGRP	calcitonin gene-related peptide
C_{max}	maximum observed drug concentration
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRP	C-reactive protein
C-SSRS	Columbia Suicide Severity Rating Scale
CV	coefficient of variance
dBM	digital biomarker
ECG	electrocardiogram
EDC	electronic data capture system
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.

enter	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ePRO	electronic patient-reported outcomes
ESR	erythrocyte sedimentation rate
GCP	good clinical practice
HIT-6	Headache Impact Test
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICHD-3	International Classification of Headache Disorders version 3
Ig	immunoglobulins
IHS	International Headache Society
Informed consent	A process by which a patient 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 patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
IV	intravenous
IVRS/IWRS	interactive voice-response system/interactive web-response system
MOH	medication overuse headache
MSQ	Migraine Specific Quality of Life Questionnaire
NOAEL	no-observed-adverse-effect-level
PACAP	pituitary adenylate cyclase-activating peptide
PK/PD	pharmacokinetics/pharmacodynamics
QTc	corrected QT interval
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.

SUSARs	suspected unexpected serious adverse reactions
TBL	total bilirubin
TE-ADA	treatment-emergent antidrug antibody
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
VIP	Vasoactive intestinal peptide
WOCBP	Women of child-bearing potential

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology	**Clinical Chemistry**
Hemoglobin	Serum Concentrations of:
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume	Total bilirubin
Mean cell hemoglobin concentration	Direct bilirubin
Leukocytes (WBC)	Alkaline phosphatase
Neutrophils, segmented	Alanine aminotransferase (ALT)
Lymphocytes	Aspartate aminotransferase (AST)
Monocytes	Blood urea nitrogen (BUN)
Eosinophils	Creatinine
Basophils	Uric acid
Platelets	Calcium
Erythrocyte sedimentation rate (ESR)	Fasting Glucose
	Glycosylated hemoglobin (HbA1c)
Urinalysis	Albumin
Specific gravity	Cholesterol
pH	Creatine kinase (Total CK)
Protein	Estimated glomerular filtration rate (eGFR)[b]
Glucose	C-reactive protein (CRP)
Ketones	Complement component 3 (C3)
	Complement component 3a (C3a)
Blood	Complement component 4a (C4a)
Urine leukocyte esterase[a]	
	Pregnancy Test (serum[c]/urine[d]/follicle-stimulating hormone[e])
	Hepatitis B surface antigen[f]
	Hepatitis C antibody[f]
	Human immunodeficiency virus[f]
	Urine drug screen[f]

Abbreviations: CKD = chronic kidney disease; EPI = epidemiology collaboration; RBC = red blood cells; WBC = white blood cells.

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

[b] eGFR for serum creatinine calculated by the central laboratory using the CKD EPI method

[c] To be performed for women of child-bearing potential at screening only.

[d] In case of a positive result, the pregnancy must be confirmed by a serum test.

[e] To be performed for women of non-child-bearing potential with 6-12 months of spontaneous amenorrhea at screening only.

[f] To be performed at screening only.

Appendix 3. Study Governance Considerations

Appendix 3.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Appendix 3.1.1. Informed Consent

The investigator is responsible for:

- ensuring that the patient understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent form (ICF) prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the study.
- ensuring that a copy of the ICF is provided to the patient and is kept on file.
- ensuring that the medical record includes a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Appendix 3.1.2. Recruitment

Lilly or its designee is responsible for the central recruitment strategy for patients. Individual investigators may have additional local requirements or processes.

Appendix 3.1.3. Ethical Review

The investigator or an appropriate local representative must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Council for Harmonisation (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on Good Clinical Practice (GCP).

The study site's ERB(s) should be provided with the following:

- the protocol and related amendments and addenda, current Investigator Brochure (IB) and updates during the course of the study
- informed consent form
- other relevant documents (for example, curricula vitae, advertisements)

Appendix 3.1.4. Regulatory Considerations

This study will be conducted in accordance with the protocol and with the:

- consensus ethics principles derived from international ethics 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

Some of the obligations of the sponsor will be assigned to a third party.

Appendix 3.1.5. Investigator Information

Investigators in this clinical trial should be neurologists, headache specialists, or other specialists with experience in headache clinical trials and treating migraine patients.

Appendix 3.1.6. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Appendix 3.1.7. Final Report Signature

The CSR coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The study team will select the CSR coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the CSR coordinating investigator.

The sponsor's responsible medical officer and statistician will approve the final CSR for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Appendix 3.2. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site

- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate CRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

Appendix 3.2.1. Data Capture System

An EDC system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided EDC system, if collected external to the EDC system.

Electronic patient-reported outcome (ePRO) measures (for example, a diary) or other data reported directly by the patient (for example, a rating scale) may be entered in an ePRO instrument (for example, personal digital assistant [PDA]), or by means of an interactive response technology (IRT) at the time the information is obtained. In these instances where there is no prior written or electronic source data at the site, the ePRO instrument record will serve as the source.

If ePRO records are stored at a third party site, investigator sites will have continuous access to the source documents during the study and will receive an archival copy at the end of the study for retention.

Any data for which the ePRO instrument record will serve to collect source data will be identified and documented by each site in that site's study file.

Electronic case report form data will be encoded and stored in a clinical trial database. Data managed by a central vendor, such as laboratory test data or ECG data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the sponsor designated warehouse.

Any data for which paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient in this study may include, for example, a headache medication log on which patients will record their acute headache medication use during the study.

Data from complaint forms submitted to Lilly.

will be encoded and stored in the global product complaint management system.

Appendix 3.3. Study and Site Closure

Appendix 3.3.1. Discontinuation of Study Sites

Study site patients may be discontinued if Lilly, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 3.3.2. Discontinuation of the Study

The study will be discontinued if Lilly judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 3.4. Publication Policy

The publication policy for Study J1H-MC-LAJB is described in the Clinical Trial Agreement.

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly, or its designee, clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	
GGT	**Alkaline Phosphatase Isoenzymes[a]**
CPK	
	Anti-smooth muscle antibody (or anti-actin antibody)[a]

Abbreviations: ALT = alanine aminotransferase; AST = aspirate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalised ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by Lilly-designated or local laboratory.

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

Appendix 5. Recommended Laboratory Testing for Hypersensitivity Events

Lab testing should be performed at the time of a Systemic Hypersensitivity Event. Important information about why, when, and what to test for are provided below. The management of the adverse event may warrant lab testing beyond that described below and should be performed as clinically indicated.

Laboratory testing during a Systemic Hypersensitivity Event is not performed for diagnostic purposes. Its intent is several fold:

- To help characterize and classify systemic hypersensitivity reactions
- To meet regulatory expectations
- To improve subsequent clinical management by helping to distinguish between the various mechanistic bases of anaphylaxis

When should labs be obtained?

- In the presence of generalized urticaria or if anaphylaxis is suspected
- After the subject has been stabilized, obtain a sample within 1-2 hours of the event, however, samples may be obtained as late as 12 hours after the event as analytes can remain altered for an extended period of time. Record the time at which the sample was collected.
- Obtain a follow up sample at the next regularly scheduled visit or after 4 weeks, whichever is later.

What labs* should be obtained?

- Tryptase**
- ADA and LY concentration (PK)
  - ADA testing should include drug specific IgE or the basophil activation test (BAT)#. These tests are not routinely available and need to be developed for individual molecules based on their evolving safety profile. Samples are collected, and testing conducted once the assay is available, as appropriate. Please consult an immunologist within GPS for further guidance.
- Complement
  - C3a and C5a
- Cytokines
  - IL-6, IL-1β, IL-10 (or any cytokine panel that includes these 3 cytokines)

* these labs are bundled in the Clinical Laboratory Operations Hypersensitivity Lab Testing Kit

** If a tryptase sample is obtained more than 2 hours after the event (ie, within 2 to 12 hours), or is not obtained because more than 12 hours have lapsed since the event, obtain urine for

N-methylhistamine (NMH) testing. Note that for tryptase serum samples obtained within 2-12 hours of the event, urine NMH testing is performed in addition to tryptase testing. Collect the first void urine following the event. Obtain a follow up urine for NMH testing at the next regularly scheduled visit or after 4 weeks, whichever is later.

[#] The BAT is an *in vitro* cell based assay that only requires a serum sample. It is a surrogate assay for drug specific IgE but is not specific for IgE.

Appendix 6. 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 one of the following: • Nausea and/or vomiting • Photophobia and phonophobia *(Definition adapted from the standard IHS ICHD-3 definition)*
Probable migraine headache	A headache of ≥30 minutes duration, with or without aura, but missing one of the migraine features in the IHS ICHD-3 definition. To be exact, it meets either at least two A criteria and zero B criteria, or one A criteria and at least one B criteria.
Migraine headache day (primary objective)	A calendar day on which a migraine headache or probable migraine headache occurs.
ICHD migraine headache day	A calendar day on which a 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).
Episodic migraine	Four to 14 migraine headache days and <15 headache days per 30-day period in the prospective baseline period.
Chronic migraine	At least 15 headache days per 30-day period in the prospective baseline period, of which at least 8 are migraine.

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

Appendix 7. Protocol Amendment J1H-MC-LAJB(b) Summary

Overview

Protocol J1H-MC-LAJB, A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of LY3451838 in Adults with Treatment-Resistant Migraine, has been amended. The new protocol is indicated by amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are described in the following table. Other general editorial corrections and formatting changes not affecting content have been made in the document, and these changes are not identified in the amendment summary table or with strikethrough/underscore.

Amendment Summary for Protocol J1H-MC-LAJB Amendment (b)

Section # and Name	Description of Change	Brief Rationale
1. Synopsis	Number of patients updated.	Statistical calculations confirmed that CSF could be achieved with less patients
5.2 Number of Participants	Number of patients updated.	Statistical calculations confirmed that CSF could be achieved with less patients
6.1 Inclusion Criteria	Criterion 6 added • Nortriptyline • Rimegepant and atogepant	• For clarification. • Approved post protocol approval
7.8 Concomitant Therapy	Added short term use of steroids to Table 7.1.	To allow short term use of steroids
10.1 Sample Size Determination	• Number of patients updated • Sample size calculation assumptions updated	Statistical calculations confirmed that CSF could be achieved with less patients
10.3.2.2 Patient Characteristics	Removed bullet, “Alcohol, tobacco, caffeine, and nicotine consumption”.	Said data is not being collected and thus, will not be statistically summarized
10.3.8 Interim Analysis	Replaced “all” with “majority of” patients to be included in the interim analysis.	To clarify what patients will be included

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

The numbering system used for inclusion and exclusion criteria provides a unique number for each criterion and allows for efficiency in data collection.

In case an amendment to the protocol adds a criterion, that criterion will receive the next available number, regardless of whether it is an inclusion or exclusion criterion.

1. Synopsis

Number of Patients:

The study will screen an estimated ~~215~~ 110 potential patients to ensure randomization of approximately ~~120~~ 60 migraine patients, of which approximately ~~60~~ 30 patients with chronic migraine.

5.2 Number of Participants

The study will screen an estimated ~~215~~ 110 potential patients to ensure randomization of approximately ~~120~~ 60 migraine patients, of which approximately ~~60~~ 30 patients have episodic migraine (defined as 4 to 14 migraine headache days and <15 headache days per 1-month period in the prospective baseline period). To ensure an appropriate balance of patients with episodic and chronic migraine, the sponsor will stop enrollment of patients with chronic migraine if the number of patients exceeds approximately 50%. Chronic migraine will be defined as at least 15 headache days per 1-month period in the prospective baseline period, of which at least 8 are migraine. Similar frequency of headache days must also be present during the 2 months previous to baseline for both episodic and chronic categories, according to investigator's assessment.

6.1 Inclusion Criteria

6. Prior to Visit 1, have documentation (by medical or pharmacy record or by physician's confirmation) of previous failure of 2 to 4 standard-of-care migraine preventive medication categories from the following list and in the past 10 years due to inadequate efficacy (that is, maximum tolerated dose for at least 2 months, (3 months in case of Botulinium toxin A or B) and/or safety/tolerability reasons:

   a. Propranolol or metoprolol
   b. Topiramate
   c. Valproate or divalproex
   d. Amitriptyline or nortriptyline
   e. Flunarizine
   f. Candesartan
   g. Anti-CGRP antibodies (either ligand or receptor)

h. Botulinium toxin A or B (if documented that botulinium toxin was taken for chronic migraine)
i. Rimegepant ODT
j. Atogepant

7.8 Concomitant Therapy

Table LAJB 12.1 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) up to 3000 mg/day, NSAIDs; Triptans; Ergotamine and derivatives; Isometheptene mucate, dichloralphenazone and acetaminophen combination (Midrin); or combinations thereof; ubrogepant;

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, III, IV).
3. Short term use of steroids, < 7days, for medical circumstances that may arise.

B. Medications, Procedures or Devices not allowed for any reason/indication in Study Period II (Baseline), III (Double-Blind Treatment), and IV (Follow-up):

ACE inhibitors
Acetazolamide
Acupuncture
Anticonvulsants/Antiepileptics
Antipsychotics
Angiotensin receptor blockers (ARBs)
Beta-blockers
Botulinum toxin applied to head/neck area for therapeutic use
Cannabis / Cannabinoids / Cannabidiol
Chiropractic procedures, physiotherapy, TENS or other electric devices on head and neck
Corticosteroids for oral use
Flunarizine
Gabapentin
Herbals with anti-inflammatory effect (feverfew, willow bark, petasites/butterbur)
Monoamine oxidase inhibitors (MAOIs)
Memantine
Methysergide
Nerve block in head/neck area
Oxetorone
Pizotifen
Pregabalin
Serotonin 5HT2a/2c antagonists, eg, trazodone, nefazodone
Stimulants (prescription strength), eg, methylphenidate, dextroamphetamine, mixed amphetamine salts
Tizanidine
Tricyclic antidepressants (TCAs)
Triptans for prophylaxis of menstrual related migraine
Venlafaxine
Verapamil

C. Restricted medication during Study Period III (Double-Blind Treatment) and Study Period IV (Follow-up): 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 the Treatment Phase.

Benzodiazepines
Bupropion
Calcium-channel blockers (except verapamil, flunarizine, and lomerizine)
Clonidine
Guanfacine
Mirtazapine
SSRIs/NRIs/SNRIs (other than venlafaxine)
Use of electric devices (ie, TENS), physiotherapy, chiropractic procedures on low back and extremities

D. Restricted medication during Study Period IV (Follow-up):

Medications from List B.
Medications or treatments for migraine prevention ~~of~~.
Medications in List C may now be started, stopped, or have dose modification as long as not being used for migraine prevention.

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.

10.1 Sample Size Determination

The study will screen an estimated ~~215~~ 110 potential patients to ensure randomization of approximately ~~120~~ 60 migraine patients. Enrollment will be stratified by type of migraine, episodic versus chronic, and patients will be randomly assigned to either LY3451838 or placebo in a 1:1 allocation ratio within each stratum. Enrollment in the chronic migraine stratum will be capped so that no more than approximately 50% of the randomized population will be patients with chronic migraine.

The analysis will be conducted using all randomized patients, and it is assumed that approximately 2% of the patient population will dropout during the 28 days treatment period.

The study will be considered successful if there is at least a 60% probability that the number of monthly migraine headache days with LY3451838 treatment is 1.5 days less than the number of monthly migraine headache days with placebo treatment (i.e., the success criterion is P(LY3451838 - Placebo <-1.5) ≥0.60).

Enrolling approximately ~~120~~ 60 patients who are stratified by type of migraine, episodic versus chronic, and randomly assigned to either LY3451838 or placebo in a 1:1 allocation ratio within each stratum will provide approximately ~~77~~ 94% probability for meeting the success criterion if the mean monthly number of migraine headache days with LY3451838 is ~~2.35~~ 2.57 days less than the mean monthly number of migraine headache days with placebo for ~~both~~ the episodic migraine population and 3.70 days less for the chronic migraine population.

Assumptions in this sample size calculation were based on data from previous Phase 2 and Phase 3 studies with galcanezumab in patients with episodic and chronic migraine. ~~It is assumed~~

~~that the baseline mean (± standard deviation) monthly migraine headache days will be 9.34 (±2.82) days for the episodic population and 18.65 (±4.68) days for the chronic population.~~ It is ~~also~~ assumed that the change from baseline mean (± standard deviation) monthly migraine headache days for placebo will be -0.31 (± ~~3~~2.50) days for the episodic migraine population and -2.21 (± ~~5.27~~3.75) days for the chronic migraine population.

10.3.2.2 Patient Characteristics

The following patient characteristics at baseline will be summarized by treatment.

- Demographic (age, sex, ethnic origin, height, weight, body mass index)
- Migraine and/or headache-related measures from the ePRO diary per 1-month baseline period
- Number of prior migraine preventive treatment failures from the list in Section 6.1 (Inclusion Criterion #6):
    - Failed 2 medication categories
    - Failed 3 medication categories
    - Failed 4 medication categories
- ~~Alcohol, tobacco, caffeine, and nicotine consumption~~
- Medical history and pre-existing conditions

10.3.8 Interim Analyses

An interim analysis is planned when data from the majority of ~~all~~ randomized patients have completed the 1-month treatment period. The interim efficacy results may be used for internal decision-making to trigger planning activities associated with the investigational product. No adjustment of Type I error will be performed as the study will not be stopped for efficacy, and no modification of Study LAJB is expected based on these interim results. The assessment would be conducted by a sponsor assessment committee with a limited number of preidentified team members who do not have direct site contact or data entry/validation responsibilities. Unblinding details will be specified in the unblinding plan section of the SAP or in a separate unblinding plan document. Information that may unblind the study during the analyses will not be reported to study sites or to the blinded study team until the study has been unblinded.

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