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A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF ORAL ATOGEPANT FOR THE PREVENTION OF MIGRAINE IN PARTICIPANTS WITH EPISODIC MIGRAINE (ADVANCE)

Protocol Number:	3101-301-002
Phase:	3
Name of Study intervention:	Atogepant
Sponsor:	Allergan Pharmaceuticals International Limited [redacted]
US Agent	Allergan (Sales, LLC) [redacted]
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Serious Adverse Event Reporting: Fax number: Back up fax number: Email	[redacted] IR-Clinical-SAE@allergan.com
Allergan Medical Safety Physician Contact Information:	Refer to the Study Contacts Page
Sponsor Signatory:	[redacted]
Original Protocol Date:	25 September 2018
Amendment 1 Date	30 November 2018

Amendment 2 Date	25 February 2019
Amendment 3 Date	14 May 2020

Refer to the final page of this protocol for approval signature.

The following information can be found on FDA Form 1572 and/or study contacts page: Name and contact information of Allergan study personnel and Emergency Telephone Numbers; name, address, and statement of qualifications of each investigator; name of each subinvestigator working under the supervision of the investigator; name and address of the research facilities to be used; name and address of each reviewing IRB; US 21 CFR 312.23 section 6(iii)b.

INVESTIGATOR SIGNATURE PAGE

INVESTIGATOR:

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations.
- Maintain all information supplied by Allergan in confidence and, when this information is submitted to an IRB, IEC or another group, it will be submitted with a designation that the material is confidential.
- Ensure that all persons assisting with the trial are adequately informed about the protocol, the study intervention(s), and their trial-related duties and functions.

I have read this protocol in its entirety and I agree to all aspects.

Investigator Printed Name	Signature	Date

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Protocol Summary

Study Compound: Atogepant

Phase: 3

Study Objectives:

To evaluate the safety and tolerability of atogepant 10 mg, atogepant 30 mg, and atogepant 60 mg for the prevention of migraine in participants with episodic migraine.

To prospectively test for superiority of atogepant 10 mg, atogepant 30 mg, and atogepant 60 mg versus placebo for the prevention of migraine in participants with episodic migraine.

Clinical Hypotheses:

In individuals with episodic migraine, at least one of the atogepant doses, 10 mg, 30 mg, and 60 mg, is superior to placebo as measured by the change from baseline in mean monthly migraine days across the 12-week treatment period.

Atogepant has an acceptable safety profile and is well tolerated in participants with episodic migraine.

Study Design

Structure: Multicenter, randomized, double-blind, placebo-controlled, parallel-group study.

Duration: The study will consist of a 4-week screening and baseline period, a 12-week double-blind treatment period, and a follow-up period of 4 additional weeks, for a total duration of 20 weeks.

Study Intervention: Atogepant 10 mg, atogepant 30 mg, and atogepant 60 mg tablets.

Control: Atogepant-matching placebo.

Dosage/Dose Regimen: Atogepant 10 mg, atogepant 30 mg, atogepant 60 mg, or placebo will each be administered once a day for 12 weeks duration.

Randomization/Stratification: Participants will be randomized to the following 4 arms in a 1:1:1:1 ratio:

- Placebo (n = 218)
- Atogepant 10 mg (n = 218)
- Atogepant 30 mg (n = 218)
- Atogepant 60 mg (n = 218)

Approximately 70% of randomized participants will have taken at least 1 prior migraine prevention medication, with proven efficacy (see Attachment 12.3). Randomization will be stratified based on prior exposure (yes/no) to a migraine prevention medication with proven efficacy (see Attachment 12.3).

Visit Schedule: Individual participant participation will begin with a 4-week screening/baseline period. Participants who complete the 4-week screening/baseline period and meet all entry criteria will be randomized at Visit 2 (Randomization Visit). The double-blind treatment period will last 12 weeks, with a follow-up period of 4 additional weeks.

There will be 8 scheduled clinic visits: Visit 1 (Screening/Baseline), Visit 2 (Randomization), Visit 3 (Week 2), Visit 4 (Week 4), Visit 5 (Week 6), Visit 6 (Week 8), Visit 7 (Week 12), and Visit 8 (Follow-up). The Visit 8 (Follow-up) must be completed for all participants who take at least one dose of study intervention, except for participants rolling over into Study 3101-309-002 (longterm safety extension study). For these participants Visit 8 is not required, as the Follow-up Visit will be performed in the longterm safety study. For participants who screen fail for the longterm safety, the Follow-up Visit must be completed. For details, please see Table 1 (Schedule of Visits and Procedures for In-Person Visits Conducted Prior to or During the COVID-19 Pandemic). To eliminate immediate potential hazards to participants and study staff due to the COVID-19 pandemic while ensuring participant safety and maintaining data integrity, the protocol was updated to allow

investigators/appropriately designated study staff to perform study visits remotely (as described in Table 2 Schedule of Visits and Procedures for Visits Conducted Remotely Due to the COVID-19 Pandemic). If Visit 7 is conducted remotely, the participant will not be eligible to roll over into Study 3101-309-002; therefore, Visit 8 (Follow-up/End of Study) should be conducted as part of Study 3101-301-002. During the COVID-19 pandemic,Visit 8 (Follow-up/End of Study) should be conducted remotely for all participants in all cases.

Study Population Characteristics

Number of Participants/sites: Approximately 872 participants will be randomized into the study from approximately 110 sites in the United States.

Condition/Disease: Migraine with aura or migraine without aura.

Key Inclusion Criteria:

- Male or female participants age 18 to 80 years, inclusive, at Visit 1.
- At least a 1-year history of migraine with or without aura consistent with a diagnosis according to ICHD-3, 2018.
- Age of the participant at the time of migraine onset < 50 years.
- History of 4 to 14 migraine days per month (see Section 6.1 for definition) in the 3 months prior to Visit 1 in the investigator's judgment.
- 4 to 14 migraine days in the 28-day baseline period per eDiary.

Key Exclusion Criteria:

- Has a history of migraine accompanied by diplopia or decreased level of consciousness or retinal migraine as defined by ICHD-3, 2018.
- Has a current diagnosis of chronic migraine, new persistent daily headache, trigeminal autonomic cephalgia (eg, cluster headache), or painful cranial neuropathy as defined by ICHD-3, 2018.
- Has ≥ 15 headache days per month (see Section 6.1 for the definition of a headache day) on average across the 3 months prior to Visit 1 in the investigator's judgment.
- Has ≥ 15 headache days (see Section 6.1 for the definition of a headache day) in the 28-day baseline period per eDiary.
- History of an inadequate response to > 4 medications (2 of which have different mechanisms of action) prescribed for the prevention of migraine (see Attachment 12.3 for classification of inadequate response to migraine-preventive medications).
- Usage of opioids or barbiturates > 2 days/month**,** triptans or ergots ≥ 10 days/month, or simple analgesics (eg, aspirin, non-steroidal anti-inflammatory drugs, acetaminophen) ≥ 15 days/month in the 3 months prior to Visit 1 per investigator's judgment, or during the baseline period (barbiturates are excluded 30 days prior to screening and through the duration of the study) (see Attachment 12.2).
- Participants with clinically significant hematologic, endocrine, cardiovascular, pulmonary, renal, hepatic, gastrointestinal, or neurologic disease.

Response Measures

Efficacy: Migraine days; headache days; acute medication use days.

Health Outcomes: Activity Impairment in Migraine – Diary (AIM-D); Patient Satisfaction with Study Medication; Headache Impact Test (HIT-6); Migraine Disability Assessment (MIDAS); Patient Global Impression of Change (PGIC); Work Productivity and Activity Impairment Questionnaire: Migraine v2.0 (WPAI:MIGRAINE); European Quality of Life – 5-Dimensional – 5-Level (EQ-5D-5L); Patient Global Impression – Severity (PGI-S); Migraine-Specific Quality of Life Questionnaire, version 2.1 (MSQ v2.1);

Activity Level and Activity Limitation; and Patient-Reported Outcomes Measurement Information System Pain Interference – Short Form 6a (PROMIS-PI).

Pharmacokinetics: Pharmacokinetic samples will be collected for analysis for participants who consent.

Safety: Adverse events, physical examinations, clinical laboratory determinations, vital sign measurements, electrocardiogram (ECG) parameters, and the Columbia-Suicide Severity Rating Scale (C-SSRS).

General Statistical Methods and Types of Analyses:

All efficacy analyses will be performed using the modified intent-to-treat (mITT) population which consists of all randomized participants who received at least 1 dose of study intervention, had an evaluable baseline period of eDiary data and at least 1 evaluable postbaseline 4-week period (Weeks 1 to 4, 5 to 8, and 9 to 12) of eDiary data during the double-blind treatment period. All safety analyses will be performed using the safety population which consists of all participants who took at least 1 dose of study intervention. The analysis population for Off-treatment Hypothetical Estimand includes all randomized participants who received at least 1 dose of study treatment, had an evaluable baseline period of eDiary data and had at least 1 evaluable post-baseline 4-week period (Weeks 1 to 4, 5 to 8, 9 to 12) of eDiary data during the double-blind treatment period and follow-up period, regardless of whether on study treatment or off study treatment. This population is used for the primary estimand in support of EU filing.

For the United States and European Union regulatory submissions, and for submissions in other global regions, the primary efficacy parameter will be the same. The primary efficacy endpoint is the change from baseline in mean monthly migraine days across the 12-week treatment period.

The primary comparison between treatment groups will be done by a mixed-effects model for repeated measures (MMRM) of the change from baseline. The statistical model will include treatment group, visit, prior exposure (yes/no) to a migraine prevention medication with proven efficacy, and treatment group by visit interaction as categorical fixed effects. It will also include the baseline score and baseline-by-visit interaction as covariates. An unstructured covariance matrix will be used to model the covariance of within-participant repeated measurements. The Kenward-Roger approximation (Kenward 1997) will be used to estimate the denominator degrees of freedom. The analysis will be performed based on all postbaseline values using only the observed cases without imputation of missing values. Pairwise contrasts in the MMRM model will be used to make the pairwise comparisons of each atogepant dose to placebo.

Secondary efficacy endpoints for the United States and the European Union:

- Change from baseline in mean monthly headache days across the 12-week treatment period.
- Change from baseline in mean monthly acute medication use days across the 12-week treatment period.
- ≥ 50% reduction in 3-month average of monthly migraine days.
- Change from baseline in MSQ v2.1 Role Function-Restrictive domain score at Week 12
- Change from baseline in mean monthly Performance of Daily Activities domain score of the AIM-D across the 12-week treatment period.
- Change from baseline in mean monthly Physical Impairment domain score of the AIM-D across the 12-week treatment period.

The secondary endpoints for headache days, acute medication use days, MSQ v2.1 Role Function-Restrictive domain score, Performance of Daily Activities domain score of the AIM-D, and Physical Impairment domain score of the AIM-D will be analyzed in the same manner as that used to analyze the primary endpoint.

The secondary endpoint of 50% responders, defined as participants with at least a 50% reduction from baseline in the 3-month average of monthly migraine days, will be assessed for each individual. A logistic regression model will be used to analyze the 50% responders across the 12-week treatment period. This model assumes a binary distribution for the response and uses a logit link. The analysis model will include treatment group, prior exposure (yes/no) to a migraine prevention medication with proven efficacy, and baseline monthly migraine days. The treatment difference in terms of odds ratio between each atogepant dose group and placebo will be estimated and tested from this model.

Incidence of treatment-emergent adverse events (TEAEs) will be tabulated by primary system organ class (SOC) and by specific event within each primary SOC. Treatment-emergent adverse events will be analyzed after treatment start on Day 1 through the end of the study.

Sample Size Calculation: A sample size of 218 randomized participants per treatment group will provide at least 98% power to detect the treatment difference between each of the 3 atogepant doses (assumed equally effective) and placebo for the primary efficacy endpoint. This sample size was selected to provide sufficient power for each of the primary and first 3 secondary endpoints. The power calculations are based on the following assumptions: 1) the standard deviation and treatment difference from placebo will be similar to the average value across the migraine prevention studies for atogepant (Phase 2/3 Study CGP-MD-01), telcagepant (Ho 2014) and monoclonal antibodies (Dodick 2014a; Dodick 2014b; Bigal 2015). In particular, the assumed treatment difference from placebo in change from baseline in mean monthly migraine days across the 12-week treatment period is –1.5 days, and the standard deviation is 3.5 days; and 2) the study statistical testing plan controls the overall type I error at 5%. The power calculations of the primary and secondary endpoints have taken the multiple comparisons into consideration by testing each dose versus placebo at a 0.0167 significance level, 2-sided.

Figure 1 Study Diagram

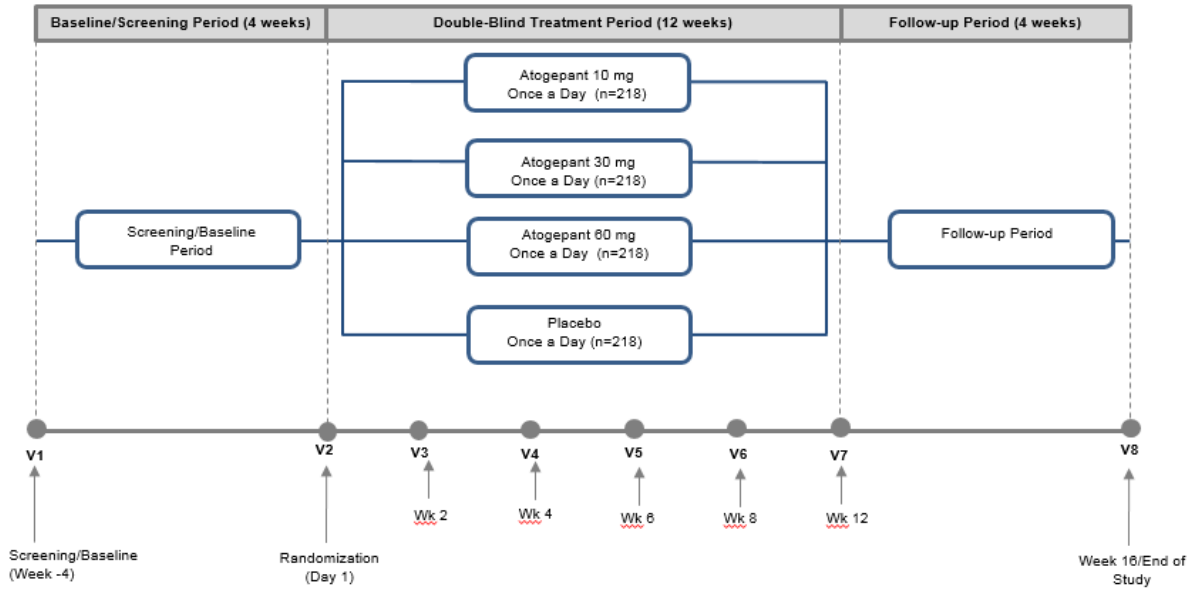

Table 1 Schedule of Visits and Procedures for In-Person Visits Conducted Prior to or During the COVID-19 Pandemic

Study Period	**Screening Period (4 weeks)**	**Double-blind Treatment Period (12 weeks)**						**Follow-up Period (4 weeks)**
Visit #	**Visit 1 (Screening/ Baseline)**	**Visit 2 (Randomization)**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7/ET[a]**	**Visit 8 (End of Study)[b]**
Day/Week	***Week -4***	***Day 1***	***Week 2 (Day 14)***	***Week 4 (Day 28)***	***Week 6 (Day 42)***	***Week 8 (Day 56)***	***Week 12 (Day 84)***	***Week 16 (Day 112)***
Visit Windows	Day -35 to Day -28	NA	± 3 day	± 3 day	± 3 day	± 3 days	+ 3 days	± 3 days
Obtain informed consent and participant privacy	X							
Obtain informed consent for future biomedical research (optional)	X							
Obtain informed consent for PK (optional)	X							
Access IWRS	X	X	X	X	X	X	X	X
Obtain VCT consent and perform verification	X							
Assess inclusion/exclusion criteria	X	X						
Collect demographic information	X							
Collect medical history	X							
Collect migraine headache history	X							
Review prior medications including all migraine prophylactic medication use	X							
Perform physical examination	X						X	X
Collect vital sign measurements[c]	X	X	X	X	X	X	X	X
Perform and transmit ECG	X				X		X	
Perform urine pregnancy test[d]	X	X	X	X	X	X	X	X
Perform urine drug screen	X							
Clinical laboratory determinations[e]	X	X	X	X	X	X	X	X
PK sample collection (for those participating)[f]		X	X	X	X	X	X	
Collect blood for future biomedical research (for those participating)	X							

Study Period	**Screening Period (4 weeks)**	**Double-blind Treatment Period (12 weeks)**						**Follow-up Period (4 weeks)**
Visit #	**Visit 1 (Screening/ Baseline)**	**Visit 2 (Randomization)**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7/ET[a]**	**Visit 8 (End of Study)[b]**
Day/Week	***Week -4***	***Day 1***	***Week 2 (Day 14)***	***Week 4 (Day 28)***	***Week 6 (Day 42)***	***Week 8 (Day 56)***	***Week 12 (Day 84)***	***Week 16 (Day 112)***
Visit Windows	Day -35 to Day -28	NA	± 3 day	± 3 day	± 3 day	± 3 days	+ 3 days	± 3 days
Provide eDiary, and eDiary instructions and training[g]	X							
Participant eDiary data collection (eg, daily entries for headache frequency, duration, characteristics, symptoms, and acute medication use)	X	X	X	X	X	X	X[l]	X[m]
AIM-D (eDiary)	X	X	X	X	X	X	X[l]	X[m]
Activity Level and Activity Limitation (eDiary)	X	X	X	X	X	X	X[l]	X[m]
Review eDiary data (eg, headache duration, frequency, characteristics and symptoms, acute medication use, compliance)[h]		X	X	X	X	X	X[l]	X[m]
C-SSRS (eTablet)[i]	X	X	X	X	X	X	X	X
ASC-12 (eTablet)[j]	X							
HIT-6 (eTablet)[j,k]		X		X		X	X	
PGIC (eTablet)[j,k]							X	
PGI-S (eTablet)[j,k]		X		X		X	X	
WPAI:MIGRAINE (eTablet)[j,k]		X		X		X	X	
Patient Satisfaction with Study Medication (eTablet)[j,k]				X		X	X	
EQ-5D-5L (eTablet)[j,k]		X		X		X	X	X
MIDAS (eTablet)[j,k]		X					X	
MSQ v2.1 (eTablet)[j,k]		X		X		X	X	X
PROMIS-PI (eTablet)[j,k]		X		X		X	X	
Collect eDiary		X[n]					X[o]	X[p]

Study Period	**Screening Period (4 weeks)**	**Double-blind Treatment Period (12 weeks)**						**Follow-up Period (4 weeks)**
Visit #	**Visit 1 (Screening/ Baseline)**	**Visit 2 (Randomization)**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7/ET[a]**	**Visit 8 (End of Study)[b]**
Day/Week	***Week -4***	***Day 1***	***Week 2 (Day 14)***	***Week 4 (Day 28)***	***Week 6 (Day 42)***	***Week 8 (Day 56)***	***Week 12 (Day 84)***	***Week 16 (Day 112)***
Visit Windows	Day -35 to Day -28	NA	± 3 day	± 3 day	± 3 day	± 3 days	+ 3 days	± 3 days
Review of study intervention compliance and accountability			X	X	X	X	X	
Dispense study intervention		X	X	X	X	X		
Adverse events	X							
Concomitant medications/concurrent procedures	X							

[a] Effort should be made by site to not schedule Visit 7 earlier than 12 weeks after Day 1 (Day 84) to ensure that participants complete the full 12 weeks of treatment and have eDiary data through Day 84.

[b] All participants who take at least one dose of study intervention must complete the follow-up period, except for participants rolling over into Study 3101-309-002 (longterm safety extension study). For these participants the Follow-up Visit will be performed in the longterm safety extension study. During the COVID- 19 pandemic, Visit 8 (Follow-up/End of Study) should be conducted remotely for all participants in all cases.

[c] Vital sign measurements: height, weight, sitting and standing pulse rate, respiratory rate, sitting and standing blood pressure, and body temperature. Height will be measured only at Visit 1.

[d] For women of childbearing potential only, a urine pregnancy test will be performed at all visits.

[e] Clinical laboratory determinations include chemistry, hematology, coagulation parameters (INR) and urinalysis to be collected for all visits. Samples for serology and the urine drug screen will be collected only at Screening (Visit 1).

[f] PK sample should be collected prior to the initial dose at Visit 2, 1 sample should be collected prior to the daily dose during one of the Visits 3 to 6, and the remaining samples should be collected 1 to 10 hours post the daily dose.

[g] Participants should begin using the eDiary as soon as it is dispensed. If it is subsequently determined that the participant has failed entry criteria, the eDiary should be returned to site.

[h] Participants should bring the eDiary to all visits and review with site personnel.

[i] At Visit 1, the "Screening/Baseline" assessment of the C-SSRS will be completed. At all other visits, the "Since the Last Visit" C-SSRS will be completed.

[j] Participants will complete on eTablet.

[k] PRO measures should be administered prior to any tests and/or evaluations unless indicated otherwise in the protocol (eg, during Randomization Visit, some tests will be conducted prior to PROs for eligibility).

[l] For participants who complete the double-blind treatment period only (Visit 2 to Visit 7/ET).

[m] For participants who terminate early from the double-blind treatment period only.

[n] Collected at Visit 2 only for participants who fail screening.

[o] Collected at Visit 7/ET only for participants who complete the double-blind treatment period.

[p] Collected at Visit 8/Follow-up only for participants who discontinue from the double-blind treatment period.

Table 2 Schedule of Visits and Procedures for Visits Conducted Remotely Due to the COVID-19 Pandemic

Study Period	**Double-blind Treatment Period (12 weeks)[a]**					**Follow-up Period (4 weeks)**
Visit #	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7/ET[b,c]**	**Visit 8 (End of Study)[d]**
Day/Week	***Week 2 (Day 14)***	***Week 4 (Day 28)***	***Week 6 (Day 42)***	***Week 8 (Day 56)***	***Week 12 (Day 84)***	***Week 16 (Day 112)***
Visit Windows	± 3 day	± 3 day	± 3 day	± 3 days	+ 3 days	± 3 days
Provide urine pregnancy test and instructions[e]	X	X	X	X	X	X
Participant eDiary data collection	X	X	X	X	X[f]	X[g]
Review eDiary data	X	X	X	X	X[f]	X[g]
C-SSRS[h]	X	X	X	X	X	X
HIT-6[i]					X	
PGIC[i]					X	
PGI-S[i]					X	
WPAI: MIGRAINE[i]					X	
Patient Satisfaction with Study Medication[i]					X	
EQ-5D-5L[i]					X	
MIDAS[i]					X	
MSQ v2.1[i]					X	
PROMIS-PI[i]					X	
Review of study intervention compliance and accountability	X	X	X	X	X	
Access IWRS	X	X	X	X	X	X
Dispense study intervention[j]	X	X	X	X		
Adverse events	X					
Concomitant medications/concurrent procedures	X					

[a] For participants who have a study visit replaced by a remote study visit, all missed in-person safety assessments (clinical laboratory determinations, vital signs, and ECGs) will be collected at the next in-person visit. To ensure participant safety, remote study visits can be performed for up to 8 weeks at the discretion of the investigator, after which, participants who cannot attend in-person for a study visit must be discontinued from the study.

[b] Effort should be made by site to not schedule Visit 7 earlier than 12 weeks after Day 1 (Day 84) to ensure that participants complete the full 12 weeks of treatment and have eDiary data through Day 84.

[c] If Visit 7 is conducted remotely, the participant will not be eligible to roll over into Study 3101-309-002, and Visit 8 should be performed in this study (3101-301-002).

[d] All participants who take at least one dose of study intervention must complete the follow-up period, except for participants rolling over into Study 3101-309-002 (longterm safety extension study). For these participants the Follow-up Visit will be performed in the longterm safety extension study.
During the COVID- 19 pandemic, Visit 8 (Follow-up/End of Study) should be conducted remotely for all participants in all cases.

[e] For women of childbearing potential only, a urine pregnancy test must be performed within 48 hours prior to the remote visits. Investigators/site staff will provide participants with study-supplied urine pregnancy tests and corresponding written instructions to be used at-home by participants for remote study visits. Sites are required to verbally review testing instructions with all participants.

[f] For participants who complete the double-blind treatment period only (Visit 2 to Visit 7/ET).

[g] For participants who terminate early from the double-blind treatment period only.

[h] "Since the Last Visit" C-SSRS will be completed.

[i] PRO measures should be administered prior to any evaluations.

[j] Study intervention for remote visits can be shipped to participants via an overnight courier or provided curbside. Study medication to cover 1 additional remote study visit may be dispensed.

1. Background and Clinical Rationale

1.1 Background

Migraine affects 18% of women and 6% of men in the United States with peak prevalence occurring between the ages of 25 to 55 years. Approximately one-third of patients with migraines have 3 or more migraine headaches per month, and over half report severe impairment or the need for bed rest (Lipton 2007). In the United States alone, work loss due to migraine is estimated to cost ~ $13 billion annually (Hu 1999). Prevalence is similar in Europe, with migraine headache affecting on average 17.6% of women and 8% of men (Stovner 2010). The Global Burden of Disease Survey 2010 (GBD2010) estimated the global prevalence of migraine to be 14.7%, making it the third most common disease in the world in both males and females. Migraine was ranked seventh highest among specific causes of disability globally (Steiner 2013).

Migraine is typically characterized by attacks of throbbing, unilateral headache of moderate or severe pain intensity, associated with nausea, vomiting, and/or sensitivity to light (photophobia), and sound (phonophobia). In about 25% of individuals, the migraine headache is preceded by focal neurological dysfunction (aura). Improving diagnosis and optimizing treatments for migraine have been recognized as critically important to overcoming current barriers to reduce the global burden of migraine.

Because there are no biological markers for migraine, diagnosis is based on clinical history, examination, and the exclusion of other headache disorders. Physicians apply clinical criteria to guide diagnoses and subsequent treatment. Episodic migraine is a syndrome diagnosis applied to patients with migraine (with or without aura) who have 1 to 14 headache days per month. Chronic migraine is a specific ICHD-3 diagnosis applied to a subset of patients with ≥ 15 headache days per month (Katsarava 2012; Olesen 2004; ICHD-3, 2018). This study will evaluate the efficacy, safety and tolerability of atogepant in participants with EM.

1.2 Overview of Atogepant

Atogepant is a potent, selective oral CGRP receptor antagonist being developed for migraine prevention. CGRP is a neuropeptide implicated in the pathophysiology of migraine. CGRP levels in the cranial venous outflow (ie, external jugular vein) are increased during a migraine attack and exogenously administered CGRP has been shown to trigger migraine-like headache in people with migraine. The majority (80 to 90%) of trigeminal Aδ fibers that innervate the dura contain CGRP, suggesting that these fibers may be involved in sterile neurogenic inflammation and migraine pain transmission. Furthermore, the CGRP

receptor is present on human meningeal and cerebral blood vessels. These observations suggest that activation of the trigeminovascular system, with release of CGRP, may play a key role in migraine pathogenesis and that inhibition of CGRP may yield a novel therapeutic approach to treating migraine.

The ability of CGRP inhibition to induce pain relief in the acute treatment of migraine was initially observed with an IV formulation of olcegepant (Olesen 2004), and replicated by Merck & Co., Inc with an oral formulation of MK-0974 (telcagepant), a highly selective CGRP receptor antagonist. In Phase 3 studies, telcagepant was superior to placebo in the primary endpoints of 2-hour pain freedom, 2-hour pain relief, and the absence of associated symptoms (photophobia, phonophobia, and nausea), as well as the key secondary endpoint of 24-hour sustained pain freedom (Connor 2009). However, serum ALT increases were observed with telcagepant. For this reason, the development of these oral CGRP receptor antagonists was stopped.

A Phase 2/3 clinical study (Study CGP-MD-01) was conducted, which compared atogepant 10 mg once a day, atogepant 30 mg once a day, atogepant 30 mg BID, atogepant 60 mg once a day and atogepant 60 mg BID to placebo in EM prevention. Overall, all the atogepant doses tested were well tolerated and the AE profile of all atogepant doses did not significantly differ from placebo. For the primary efficacy endpoint of change from baseline in mean monthly migraine days across the 12-week treatment period, all atogepant doses demonstrated a statistically significant reduction compared to placebo in patients with EM.

Additional information on non-clinical pharmacology, toxicology, and PK properties of atogepant can be found in the IB.

1.3 Study Rationale

Based on the results of the Phase 2/3 Study CGP-MD-01, the present study is being performed to prospectively assess the safety, tolerability and efficacy of atogepant 10 mg, atogepant 30 mg, and atogepant 60 mg compared with placebo in the prevention of EM. This randomized, double-blind, placebo-controlled Phase 3 study is designed to be a pivotal trial to confirm the efficacy of these doses and dose regimens and will be used to support registration applications.

1.4 Rationale for Doses and Dose Regimens Selected

This study will test 3 doses of atogepant, 10 mg, 30 mg, and 60 mg, which were selected based on the results from Study CGP-MD-01 in patients with EM. All atogepant doses

investigated in Study CGP-MD-01 demonstrated good safety and tolerability. While all atogepant doses also demonstrated a statistically significant reduction from baseline in mean monthly migraine days across the 12-week treatment period compared to placebo, there was no clear dose-response relationship. The current study will therefore investigate atogepant 10 mg, 30 mg and 60 mg, as a once-daily regimen during a 12-week treatment period.

2. Study Objectives and Clinical Hypotheses

2.1 Study Objectives

- To evaluate the safety and tolerability of atogepant 10 mg, atogepant 30 mg, and atogepant 60 mg for the prevention of migraine in participants with EM.
- To prospectively test for superiority of atogepant 10 mg, atogepant 30 mg, and atogepant 60 mg versus placebo for the prevention of migraine in participants with EM.

2.2 Clinical Hypothesis

In individuals with EM, at least one of the atogepant doses, 10 mg, 30 mg, and 60 mg, is superior to placebo as measured by the change from baseline in mean monthly migraine days across the 12-week treatment period.

Atogepant has an acceptable safety profile and is well tolerated in participants with EM.

3. Study Design

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study conducted at approximately 110 sites in the United States.

Approximately 872 participants will be randomized to one of 4 treatment arms (placebo, atogepant 10 mg, atogepant 30 mg, and atogepant 60 mg) in a 1:1:1:1 ratio as follows:

- Placebo (n = 218)
- Atogepant 10 mg (n = 218)
- Atogepant 30 mg (n = 218)
- Atogepant 60 mg (n = 218)

Approximately 70% of randomized participants will have taken at least 1 prior migraine prevention medication with proven efficacy (see Attachment 12.3). Randomization will be stratified based on prior exposure (yes/no) to a migraine prevention medication with proven efficacy (see Attachment 12.3).

Participant participation will begin with a 4-week screening/baseline period. Participants who complete the 4-week screening/baseline period and meet all entry criteria will be randomized to the double-blind treatment period of the study at Visit 2 (Randomization Visit). The double-blind treatment period will last 12 weeks, with a subsequent follow-up period of 4 additional weeks. There will be 8 scheduled clinic visits: Visit 1 (Screening/Baseline), Visit 2 (Randomization), Visit 3 (Week 2), Visit 4 (Week 4), Visit 5 (Week 6), Visit 6 (Week 8), Visit 7/ET (Week 12), and Visit 8 (Follow-up). For details, please see Table 1 (Schedule of Visit and Procedures for In-Person Visits Conducted Prior to or During the COVID-19 Pandemic). To eliminate immediate potential hazards to participants and study staff due to the COVID-19 pandemic while ensuring participant safety and maintaining data integrity, the protocol was updated to allow investigators/appropriately designated study staff to perform study visits remotely (as described in Table 2 Schedule of Visits and Procedures for Visits Conducted Remotely Due to the COVID-19 Pandemic).

Participants completing the double-blind treatment period in this study may be eligible to continue in Study 3101-309-002, a longterm extension safety study in participants with EM, if they are at a participating site. For these rollover participants, a Visit 8 is not required in the present study, as the Follow-up Visit will be performed in the longterm safety study. For participants who screen fail for the longterm safety study, the Follow-up Visit must be completed. If Visit 7 is conducted remotely due to the COVID-19 pandemic, the participant will not be eligible to roll over into Study 3101-309-002; therefore, Visit 8 (Follow-up/End of Study) should be conducted remotely as part of Study 3101-301-002.

3.1 Data Safety Monitoring Board

An independent DSMB will be established to review unblinded safety data and summary reports, identify any safety issues and trends, and make recommendations to Allergan, including modification or early termination of the trial, if emerging data show unexpected and clinically significant AEs of treatment.

Details of the DSMB memberships, standard operational procedures for data monitoring/review, frequency of review, and other pertinent details will be provided in a separate DSMB Charter.

3.2 Adjudication Committee

An Adjudication Charter will be established and will describe the process for the blinded surveillance, monitoring, and adjudication by the Clinical Adjudication Committee of events of post-treatment elevations of ALT and/or AST ≥ 3 × the ULN in the atogepant program. The purpose of this committee charter will be to provide a standardized process for the adjudication of data associated with these events in order to determine whether the elevation was related to atogepant.

4. Study Population and Entry Criteria

4.1 Number of Participants

Approximately 872 participants will be randomized at approximately 110 sites in the United States.

4.2 Inclusion Criteria

The following are requirements for entry into the study:

1. Written informed consent and participant privacy information (eg, written authorization for use and release of health and research study information) obtained from the participant prior to initiation of any study-specific procedures.
2. Male or female participants ages 18 to 80 years, inclusive, at Visit 1.
3. At least a 1-year history of migraine with or without aura consistent with a diagnosis according to the ICHD-3, 2018.
4. Age of the participant at the time of migraine onset < 50 years.
5. History of 4 to 14 migraine days per month (see Section 6.1 for definition) on average in the 3 months prior to Visit 1 in the investigator's judgment.
6. 4 to 14 migraine days in the 28-day baseline period per eDiary.
7. Completed at least 20 out of 28 days in the eDiary during baseline period and is able to read, understand, and complete the study questionnaires and eDiary per investigator's judgment.
8. Participants must be using a medically acceptable and effective method of birth control during the course of the entire study, as defined in Section 4.4.3.

4.3 Exclusion Criteria

The following are criteria for exclusion from participating in the study:

1. Difficulty distinguishing migraine headaches from tension-type or other headaches.
2. Has a history of migraine accompanied by diplopia or decreased level of consciousness or retinal migraine as defined by ICHD-3, 2018.
3. Has a current diagnosis of chronic migraine, new persistent daily headache, trigeminal autonomic cephalgia (eg, cluster headache), or painful cranial neuropathy as defined by ICHD-3, 2018.
4. Has ≥ 15 headache days per month (see Section 6.1 for definition of headache day) on average across the 3 months prior to Visit 1 in the investigator's judgment.
5. Has ≥ 15 headache days (see Section 6.1 for definition) in the 28-day baseline period per eDiary.
6. History of an inadequate response to > 4 medications (2 of which have different mechanisms of action) prescribed for the prevention of migraine (see Attachment 12.3 for classification of inadequate response to migraine-preventive medications).
7. Requirement for any medication, diet (ie, grapefruit juice), or non-pharmacological treatment that is on the list of prohibited concomitant medications or treatments that cannot be discontinued or switched to an allowable alternative medication or treatment (see Section 4.4.2 and Attachment 12.2). This includes concomitant medications with demonstrated efficacy for the prevention of migraine (eg, amitriptyline, topiramate, propranolol).
8. Usage of opioids or barbiturates > 2 days/month, triptans or ergots ≥ 10 days/month, or simple analgesics (eg, aspirin, NSAIDs, acetaminophen) ≥ 15 days/month in the 3 months prior to Visit 1 per investigator's judgment, or during the baseline period (barbiturates are excluded 30 days prior to screening and through the duration of the study) (see Attachment 12.2).
9. Female participant is pregnant, planning to become pregnant during the course of the study, or currently lactating. Women of childbearing potential must have a negative urine pregnancy test at Visit 1 and Visit 2.
10. An ECG with clinically significant abnormalities at Screening (Visit 1) as determined by the investigator.
11. QTcF > 450 msec for males and QTcF > 470 msec for females at Visit 1 based on the final ECG report.
12. Clinically significant cardiovascular or cerebrovascular disease per the investigator's opinion including, but not limited to:

- Clinically significant ischemic heart disease (eg, unstable angina pectoris).
- Clinically significant cardiac rhythm or conduction abnormalities (eg, atrial fibrillation, second- or third-degree heart block) or risk factors for Torsade de Pointes (eg, heart failure, hypokalemia, bradycardia).
- Myocardial infarction, transient ischemic attack, or stroke within 6 months prior to Visit 1.
- Heart failure defined as New York Heart Association functional classification system, Class III or IV.

13. Hypertension as defined by sitting systolic blood pressure > 160 mm Hg or sitting diastolic blood pressure > 100 mm Hg at Visits 1 or Visit 2. Vital sign measurements that exceed these limits may be repeated only once.

14. Clinically significant laboratory values OR any of the following laboratory values at Visit 1:

    - ALT or AST > 1 × ULN OR
    - Total bilirubin > 1 × ULN (except for participants with a diagnosis of Gilbert's disease) OR
    - Serum albumin < 2.8 g/dL.

15. Any clinically significant hematologic, endocrine, pulmonary, renal, hepatic, gastrointestinal, or neurologic disease:

    - If there is a history of such a disease, but the condition has been stable for more than 1 year prior to Visit 1, and is judged by the investigator as not likely to interfere with the participant's participation in the study, the participant may be included.
    - Participants on dialysis for renal failure are excluded.

16. History of acute hepatitis within 6 months of Screening (Visit 1); or chronic hepatitis (including nonalcoholic steatohepatitis); or a positive result on anti-hepatitis A IgM antibody, hepatitis B surface antigen, anti–hepatitis C antibody testing, or anti-hepatitis E IgM antibody.

17. In the opinion of the investigator, confounding psychiatric conditions, dementia, epilepsy or significant neurological disorders other than migraine.

18. Participant has any other concurrent pain condition that, in the opinion of the investigator, may significantly impact the current headache disorder (eg, fibromyalgia, facial pain).

19. Significant risk of self-harm based on clinical interview and responses on the C-SSRS, or of harm to others in the opinion of the investigator; participants must be excluded if they report suicidal ideation with intent, with or without a plan, (ie, Type 4 or 5 on the C-SSRS) in the past 6 months or report suicidal behavior in the 6 months prior to Visit 1 or Visit 2 assessments.

20. History of malignancy in the 5 years prior to Visit 1, except for adequately treated basal cell or squamous cell skin cancer, or in situ cervical cancer.

21. History of any GI prior procedures or GI conditions (eg, diarrhea syndromes, inflammatory bowel disease) that may affect the absorption or metabolism of study intervention; participants with prior gastric bariatric interventions (eg, Lap Band) which have been reversed are not excluded.

22. At Visit 1, a user of recreational or illicit drugs or has had a history within the past year of drug or alcohol abuse or dependence.

23. Positive result on the urine drug screen at Visit 1 unless explained by concomitant medication use (eg, opioids prescribed for migraine pain).

24. Currently participating or has participated in a study with an investigational compound or device within 30 days prior to Visit 1 (this includes studies using marketed compounds or devices).

25. Previous exposure to:

    - Atogepant (AGN-241689 or MK-8031)
    - Injectable monoclonal antibodies blocking the CGRP pathway within the last 6 months
    - Ubrogepant and took more than 3 doses of ubrogepant
    - Rimegepant and took more than 3 doses of rimegepant

26. History of hypersensitivity or clinically significant adverse reaction to a CGRP receptor antagonist.

27. Employed by or is an immediate family member (parents, spouses, siblings or children) of one of the investigators, study staff, or Allergan.

28. Participant has a condition or is in a situation which in the investigator's opinion may put the participant at significant risk, may confound the study results, or may interfere significantly with the participant’s participation in the study.

29. Any medical or other reasons (eg, unlikely to adhere to the study procedures, keep appointments, or is planning to relocate during the study) that, in the investigator’s opinion, might indicate that the participant is unsuitable for the study.

4.4 Permissible and Prohibited Medications/Treatments

4.4.1 Permissible Medications/Treatments

Medications that are not specifically prohibited in Section 4.4.2 are allowed, with the following clarifications and restrictions:

The following medications for the acute treatment of migraine are allowed during the study:

- Any triptan
- Any ergot derivative
- Any opioid
- Any other form of analgesic (including acetaminophen)
- Any NSAID agent
- Any antiemetic agent

Aspirin up to 325 mg/day is allowed for cardiac prophylaxis.

SSRI or SNRI will be permitted provided that treatment is stable for at least 60 days prior to screening (Visit 1) and continues without change in dose throughout the study.

Therapy considered necessary for the participant's welfare may be given at the discretion of the investigator. If the permissibility of a specific medication/treatment is in question, please contact Allergan.

4.4.2 Prohibited Medications/Treatments

The following medications are prohibited 30 days prior to Visit 1 (unless otherwise indicated) and throughout the study period:

- Strong and moderate CYP3A4 inhibitors, including but not limited to: systemic (oral/IV) itraconazole, ketoconazole, fluconazole; erythromycin, clarithromycin, telithromycin; diltiazem, verapamil; aprepitant, cyclosporine, nefazodone, cimetidine, quinine, and HIV protease inhibitors.

- Strong and moderate CYP3A4 inducers, including but not limited to: barbiturates (eg, phenobarbital and primidone), systemic (oral/IV) glucocorticoids, nevirapine, efavirenz, pioglitazone, carbamazepine, phenytoin, rifampin, rifabutin, and St. John's wort.

- Strong OATP1B1 inhibitors (eg, gemfibrozil).

- Drugs with narrow therapeutic margins with theoretical potential for CYP drug interactions (eg, warfarin).

- Medications with demonstrated efficacy for the prevention of migraine (eg, amitriptyline, topiramate, propranolol) (see Attachment 12.3).

- CBD oil.

- Injectable monoclonal antibodies blocking the CGRP pathway (eg, Aimovig™, Emgality™, Ajovy®) within 6 months prior to Visit 1 and through the study period.

- Therapeutic or cosmetic botulinum toxin injections (eg, Dysport®, BOTOX®, Xeomin®, Myobloc®, Jeuveau™) into areas of the head, face, or neck within 6 months prior to Visit 1 and throughout the study period.

- Acupuncture, non-invasive neuromodulation devices (eg, transcutaneous supraorbital neurostimulator, single-pulse transcranial magnetic stimulator, vagus nerve stimulator), cranial traction, nociceptive trigeminal inhibition, occipital nerve block treatments, or dental splints for headache, within 4 weeks prior to entry into the baseline phase at Week –4 or at any time during the study (including the Week –4 to Day 1 baseline phase).

The decision to administer a prohibited medication/treatment is done with the safety of the study participant as the primary consideration. When possible, Allergan should be notified before the prohibited medication/treatment is administered.

4.4.3 Definition of Women of (Non-)Childbearing Potential and/or Acceptable Contraceptive Methods

For the purposes of this study, women will be considered of childbearing potential unless they are naturally postmenopausal (ie, no menses for 2 years) or permanently sterilized (ie, bilateral tubal ligation, bilateral tubal occlusion [eg, Essure® placement with HSG confirmation], bilateral salpingectomy, bilateral oophorectomy, or hysterectomy). For women

of childbearing potential who may participate in the study, the following methods of contraception, if properly used, are generally considered highly effective:

- Combined (estrogen and progestogen containing) hormonal contraception such as oral, intravaginal, or transdermal (ie, pill, patch, vaginal ring)
- Progestogen-only hormonal contraception (with inhibition of ovulation) that are oral, injectable, or implantable
- IUD or IUS
- Vasectomized partner (provided that the partner is the sole sexual partner of study participant and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse for the duration of the study)

Acceptable birth control methods which may not be considered as highly effective:

- Progestogen-only oral hormonal contraception (where inhibition of ovulation is not the primary mode of action)
- Male or women condom with or without spermicide (women and male condoms should not be used together)
- Cap, diaphragm or sponge with spermicide
- A combination of male condom with either cap, diaphragm or sponge with spermicide (double-barrier methods) are also considered acceptable, but not highly effective, birth control methods.

For males who may participate in the study, the following methods of contraception, if properly used, are generally considered reliable: post-bilateral vasectomy, barrier contraception or sexual abstinence. Male participants must also refrain from donating sperm during the course of the study.

The investigator and each participant will determine the appropriate method of contraception for the participant during the participation in the study.

If a woman becomes pregnant during the study, the investigator will notify Allergan immediately after the pregnancy is confirmed and the participant will be exited from the study after appropriate follow-up. The investigator will (1) notify the participant's physician that the participant was being treated with an investigational drug atogepant and (2) follow the progress of the pregnancy. The investigator must document the outcome of the pregnancy and provide a copy of the documentation to Allergan.

4.4.4 Special Diet or Activities

Participants should refrain from consuming grapefruit or grapefruit juice from the time the consent form is signed until completion of the study. Participants should also refrain from making significant changes to their diet or caffeine intake during the study.

Alcohol intake should be limited to no more than 1 drink per day throughout the study. A drink is defined as a 12-ounce can/bottle of beer, a 4-ounce glass of wine, or 1 ounce of liquor.

4.5 Screen Failures

Screen failures are defined as participants who consent to participate in the study but are not subsequently randomized to treatment. Rescreening of screen failures is permitted in certain situations, with permission from Allergan. However, participants with clinically significant laboratory values at Visit 1 (including ALT or AST > 1 × ULN, total bilirubin > 1 × ULN or serum albumin < 2.8 g/dL), or those with a positive result on the Visit 1 urine drug screen for recreational (including marijuana regardless of legality) or illicit drugs, or nondisclosed concomitant medications, are not allowed to be rescreened.

5. Study Interventions

5.1 Study Interventions and Formulations

Tablets containing atogepant 10 mg (Formulation 11279X), atogepant 30 mg (Formulation Number 11280X), and atogepant 60 mg (Formulation Number 11281X).

5.2 Control Intervention

Atogepant 10 mg matching placebo (Formulation 011318X), atogepant 30 mg matching placebo (Formulation 011326X), and atogepant 60 mg matching placebo (Formulation 011317X).

5.3 Methods for Masking/Blinding

A double-dummy design will be used to maintain study blind. Atogepant tablets and matching placebo will be provided in identical blister cards to maintain masking of the study.

All participants will be instructed to take study intervention once a day (3 tablets) at approximately the same time each day. Participants will therefore, receive either placebo, atogepant 10 mg, atogepant 30 mg, or atogepant 60 mg once a day.

5.4 Intervention Allocation Ratio

Participants will be randomized to the following 4 arms in a 1:1:1:1 ratio:

- Placebo (n = 218)
- Atogepant 10 mg (n = 218)
- Atogepant 30 mg (n = 218)
- Atogepant 60 mg (n = 218)

Approximately 70% of randomized participants will have taken at least 1 prior migraine prevention medication with proven efficacy (see Attachment 12.3). Randomization will be stratified based on prior exposure (yes/no) to a migraine prevention medication with proven efficacy (see Attachment 12.3).

5.5 Method for Assignment to Intervention Groups/Randomization

Prior to initiation of study intervention, each participant who provides informed consent and/or assent will be assigned a participant number that will serve as the participant identification number on all study documents.

At randomization (Visit 2), eligible participants will be randomly assigned to 1 of 4 intervention arms in a 1:1:1:1 ratio to receive atogepant 10 mg, atogepant 30 mg, atogepant 60 mg, or placebo once a day.

All participants will be centrally assigned to randomized study intervention using an IWRS. Before the study is initiated, log in information and directions for the IWRS will be provided to each site.

Study intervention will be labeled with study intervention kit numbers. The IWRS system will provide the site with the specific medication kit number(s) for each randomized participant at the time of randomization. Sites will dispense study intervention according to the IWRS instructions. Sites will also log onto the IWRS at subsequent visits to obtain a kit number for dispensing study intervention. Sites will receive the IWRS confirmation notifications for each transaction. All notifications are to be maintained with the study source documents.

Study intervention will be dispensed at the study visits summarized in the schedule of activities. Returned study intervention should not be re-dispensed to the participants.

For study visits conducted remotely due to the COVID-19 pandemic (Table 2), study intervention, can be shipped to participants via an overnight courier or provided curbside. Study medication to cover 1 additional remote study visit may be dispensed.

5.6 Study Intervention Regimen and Dosing

Treatments to be used in this trial are listed in (Table 5-1). Participants who meet all of the study entry criteria at Visit 2 will be randomized and provided with study intervention to be taken on an outpatient basis. Sites will subsequently dispense study intervention to participants at Visits 3, 4, 5, and 6. Participants will take their first dose study intervention at the clinic at Visit 2 and will be instructed to take their study intervention at approximately the same time each day. Details of PK samples with respect to timing of study intervention are provided in Section 6.3. Study intervention will be administered orally for 12 weeks, and participants will be followed for 4 weeks following discontinuation of the study intervention.

Table 5-1 Study Interventions

Drug/Dose	Study Intervention Product	Study Intervention Frequency	Route of Administration
Placebo	Placebo 10 mg/ Placebo 30 mg/ Placebo 60 mg	Once daily	Oral
Atogepant 10 mg	Atogepant 10 mg/Placebo 30 mg/ Placebo 60 mg	Once daily	Oral
Atogepant 30 mg	Atogepant 30 mg/Placebo 10 mg/ Placebo 60 mg	Once daily	Oral
Atogepant 60 mg	Atogepant 60 mg/Placebo 10 mg/ Placebo 30 mg	Once daily	Oral

5.7 Storage of Study Interventions

The study intervention must be stored at room temperature in a securely locked cabinet. Further details regarding the storage of study intervention are in the Study Reference Manual.

6. Response Measures and Summary of Data Collection Methods

6.1 Efficacy Measures

Efficacy assessments will be based on information recorded by the participant. An eDiary will be used daily at home to collect data on headache duration, headache characteristics, symptoms, and acute medication use, which will be collectively applied to define migraine days per the criteria listed in Section 6.1.

The AIM-D, Activity Level, and Activity Limitation will also be collected daily via an eDiary. Additional health outcomes measures, namely, the Patient Satisfaction with Study Medication scale, HIT-6, MIDAS, PGIC, WPAI:MIGRAINE, EQ-5D-5L, PGI-S, MSQ v2.1, and PROMIS-PI will be administered in an eTablet at specified clinic visits. Health outcomes measures are described in Section 6.2.

6.1.1 Migraine Day

A migraine day is defined as any calendar day on which a headache occurs which meets criteria A, B, and C **OR** meets criteria D and E, as listed below, as per participant eDiary. Calendar days begin at midnight and last until 11:59 PM (23:59).

A. Headache has at least two of the following four characteristics:
   i. Unilateral location
   ii. Pulsating quality
   iii. Moderate or severe pain intensity
   iv. Aggravated by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
B. At least one of the following:
   i. Nausea and/or vomiting
   ii. Photophobia and phonophobia
   iii. Typical aura (ie, visual, sensory, or speech/language) accompanying or within 60 minutes before headache begins
C. Duration of headache lasting 2 hours or longer on a calendar day unless an acute, migraine-specific medication (ie, triptan or ergot derivative) was used after the start of the headache, in which case no minimum duration will be specified

OR

D. Any headache which fulfills one criterion from (1) and at least one criterion from (2) **OR** fulfills at least two criteria from (1) and no criteria from (2).

1) Headache characteristics:
    i. Unilateral location
    ii. Pulsating quality
    iii. Moderate or severe pain intensity
    iv. Aggravated by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
2) Symptoms:
    i. Nausea and/or vomiting
    ii. Photophobia and phonophobia
    iii. Typical aura (ie, visual, sensory, or speech/language) accompanying or within 60 minutes before headache begins

E. Duration of headache lasting 2 hours or longer on a calendar day unless an acute, migraine-specific medication (ie, triptan or ergot derivative) was used after the start of the headache, in which case no minimum duration will be specified.

6.1.2 Headache Day

A headache day is defined as any calendar day on which headache pain lasting 2 hours or longer occurs unless an acute headache medication (eg, ibuprofen, triptan) was used after the start of the headache, in which case no minimum duration will be specified. Calendar days begin at midnight and last until 11:59 PM (23:59).

6.1.3 Acute Medication Use Day and Triptan Use Day

An acute medication use day is defined as any day on which a participant reports, per eDiary, the intake of allowed medication(s) for the acute treatment of migraine. The allowed medications include the following categories of drugs: triptans, ergots, opioids, analgesics (including acetaminophen), NSAIDs (including aspirin), and antiemetics.

A triptan use day is defined as any day on which a participant reports intake of a triptan to treat a migraine per participant diary.

6.2 Health Outcomes Measures

6.2.1 Activity Impairment in Migraine – Diary (AIM-D)

The AIM-D is an 11-item daily diary measure that assesses the impact of migraine and is comprised of two domains that evaluate Performance of Daily Activities (7 items) and Physical Impairment (4 items). Participants are asked to rate the level of difficulty experienced in the past 24 hours with Performance of Daily Activities (ie, difficulty with

household chores, errands, leisure activities at home, leisure or social activities outside the home, strenuous physical activities, concentrating, and thinking clearly) and Physical Impairment (ie, difficulty walking, moving body, bending forward, moving head) using a 6-point rating scale ranging from "Not difficult at all," "A little difficult," "Somewhat difficult," "Very difficult," "Extremely difficult," and "I could not do it at all." Three items include a response of "I did not…," for example, "I did not have errands planned." The AIM-D was developed as an electronic daily diary with the same set of questions administered in headache and non-headache versions. The Headache version is administered on days when a participant reports a headache and the Non-Headache version is administered on days when a participant does not report having a headache. The AIM-D instructs participants to answer each question based on the level of difficulty experienced in the past 24 hours for both versions, with "during your headache" indicated for the AIM-D Headache version. In addition to the two domain scores, a total score using all 11 items can also be calculated. Each raw daily domain score, as well as the raw daily total score, are transformed to a 0-100 scale, with higher scores indicating greater impact of migraine (ie, higher disease burden).

6.2.2 Activity Level and Activity Limitation

Two items based on a 24-hour recall will be administered daily using Headache and Non-headache versions as additional health outcome measures and for evaluation of the AIM-D. The first item will be used to assess activity level within the past 24 hours with a 5-level response scale ranging from "No activity – Spent all day lying down" to "Exercised – Brisk walk, running, jogging, biking or other activity for 30 or more minutes." The second item will be used to evaluate activity limitation with a 5-level response scale ranging from "Not at all limited – I could do everything" to "Extremely limited".

6.2.3 Patient Satisfaction with Study Medication

Overall satisfaction with the study medication for prevention of migraine will be assessed using a single item and a 7-point rating scale ranging from extremely satisfied (0) to extremely dissatisfied (6).

6.2.4 Headache Impact Test (HIT-6)

The HIT is a 6-question assessment used to measure the impact headaches have on a participant's ability to function on the job, at school, at home and in social situations. It assesses the effect that headaches have on normal daily life and the participants' ability to function. Responses are based on frequency using a 5-point scale ranging from never to

always. The HIT-6 total score, which ranges from 36 to 78, is the sum of the responses – each of which is assigned a score ranging from 6 points (never) to 13 points (always).

6.2.5 Migraine Disability Assessment (MIDAS)

The MIDAS is a 7-item questionnaire designed to quantify headache-related disability over a 3-month period. The MIDAS score is the sum of missed work or school days, days at work or school plus days of household work where productivity was reduced by half or more, missed household work days, and missed non-work activity days due to headaches and in the last 3 months.

6.2.6 Patient Global Impression of Change (PGIC)

The PGIC is a single item used to measure the participant's impression of overall change in migraine since the first dose of study intervention. The measure uses a 7-point rating scale with responses ranging from "very much better" to "very much worse."

6.2.7 Work Productivity and Activity Impairment Questionnaire: Migraine v2.0 (WPAI:MIGRAINE)

The WPAI:MIGRAINE will be used to assess work productivity specific to migraine. The measure uses a 1-week recall and contains 6 questions related to work productivity. The WPAI measures both presenteeism and absenteeism. The measure yields four scores expressed as impairment percentages ranging from 0 to 100%: Percent work time missed, percent impairment while working, percent overall work impairment, and percent activity impairment due to migraine.

6.2.8 European Quality of Life - 5 Dimensional (EQ-5D-5L)

EQ-5D-5L is a generic instrument for use as a measure of health status. The EQ-5D-5L consists of 2 components – the EQ-5D descriptive system and the EQ visual analogue scale (VAS). The descriptive system comprises of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. The scoring range of the EQ-5D descriptive system is typically from 0 (dead) to 1 (full health). The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labelled "Best imaginable health state" and "Worst imaginable health state." The scoring range of the EQ VAS is from 0 (worst imaginable health) to 100 (best imaginable health).

6.2.9 Patient Global Impression – Severity (PGI-S)

The PGI-S is a single item used to measure the participant's impression of severity in relation to migraine symptoms overall at the time of administration of the measure. The measure uses a 5-point rating scale with responses ranging from "none" to "very severe."

6.2.10 Migraine Specific Quality of Life Questionnaire, Version 2.1 (MSQ v2.1)

The MSQ v2.1 is a 14-item questionnaire designed to measure health-related quality-of-life impairments attributed to migraine in the past 4 weeks. It is divided into three domains: Role Function-Restrictive assesses how migraines limit one's daily social and work-related activities; Role Function-Preventive assesses how migraines prevent these activities; and the Emotional Function domain assesses the emotions associated with migraines. Participants respond to items using a 6-point scale ranging from "none of the time" to "all of the time." Raw dimension scores are computed as a sum of item responses and rescaled to a 0 to 100 scale, where higher scores indicate better quality of life.

6.2.11 Patient-reported Outcomes Measurement Information System Pain Interference – Short Form 6a (PROMIS-PI)

The PROMIS-PI measures self-reported interference of pain on relevant aspects of daily life (ie, social, cognitive, emotional, physical, recreational) over the past 7 days. A 5-level response scale for all 6 items ranges from "Not at all" to "Very much." Scores range from 6 to 30, with higher scores indicating greater pain interference.

6.3 Pharmacokinetic Measures

A PK sample will be collected on site at Visits 2, 3, 4, 5, 6, and 7/ET from participants who consent to participate in the evaluation of the population pharmacokinetics of atogepant. Participants can withdraw consent at any time and should have no further PK samples collected. Each participant participating in the PK assessment will be asked to provide a total of 6 blood samples (1 per visit); at Visit 2 the sample should be collected prior to the initial dose of study intervention taken at the clinic. During 1 of the Visits 3 through 6, the sample should be collected prior to the daily dose of study intervention (the participant should wait to take the morning dose in the clinic after PK sample collection) and the samples collected at the remaining visits should be collected 1 to 10 hours post the daily dose.

The date and time of collection of each PK sample will be recorded in the eCRF. In addition, for each of the PK samples collected (except the Visit 2 sample) the date and time of the dose of study intervention prior to the PK sample should be recorded. PK samples will be collected, stored (frozen) and shipped according to instructions provided in the Study Reference Manual.

The treatment codes will be provided to the bioanalytical lab using a secure process ensuring no one outside the bioanalytical team is unblinded, to allow only atogepant-treated participant PK samples to be analyzed. The bioanalytical method for the determination of individual plasma concentrations of atogepant and the performance of the assay during validation and sample analysis will be summarized in a separate bioanalytical report, including the results obtained from analysis of the PK samples. The bioanalytical report will be appended to the integrated clinical trial report.

6.4 Future Biomedical Research

A blood sample will be collected from all participants who consent to participate in the substudy, for the purposes for Future Biomedical Research. The samples will be obtained at screening (Visit 1). All samples will be sent to the designated central laboratory and shipped to a biorepository for storage. Please refer to the Central Laboratory Manual for the genetic blood sampling procedures, shipping instructions, and contact information. Anonymized samples may be stored in the biorepository database for potential analysis under separate protocols for up to 15 years. Samples may be stored for a longer time if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, samples will be stored until these questions have been adequately addressed. The anonymized genetic material from the blood samples may also be used for future, unspecified research, not limited to the disease being studied in this particular clinical study.

All participants enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research substudy; however, participation is optional and will require a separate informed consent form. A participant who initially consents can withdraw that consent at any time and have his or her sample destroyed including any by-products of the sample whenever possible.

6.5 Safety Measures

6.5.1 Adverse Events

Subjective AEs will be collected from the time of consent through the last visit. For all AEs, the investigator must provide an assessment of the severity; causal relationship to study intervention; start and stop date, and seriousness of the event (eg, SAE); document all actions taken with regard to study intervention; and detail any other treatment measures taken for the AE. For events noted as SAEs, Allergan must be notified immediately to meet their reporting obligations to appropriate regulatory authorities.

6.5.2 Adverse Events of Special Interest

Selected nonserious and serious adverse events are of special interest and will require immediate reporting, recording, and follow-up. The following events will be closely monitored:

- Treatment-emergent suicidal ideations with intent, with or without a plan, (ie, Type 4 or 5 on the C-SSRS) or any suicidal behaviors.
- Treatment-emergent elevated ALT or AST lab value ≥ 3 × ULN.
- Potential Hy's law cases: elevated ALT or AST lab value that is ≥ 3 × ULN and an elevated total bilirubin lab value that is ≥ 2 × ULN and, at the same time, an alkaline phosphatase lab value that is < 2 × ULN.

Reporting requirements for ALT or AST elevations and potential Hy's law cases are outlined in Section 9.5 and Section 9.5.1. Responses to the C-SSRS that meet the above criterion will be captured in the eTablet and monitored by Allergan. These AEs or events determined to be SAEs must be reported appropriately via the designated eCRFs and safety forms.

6.5.3 Clinical Laboratory Determinations

Blood and urine samples for clinical laboratory tests will be collected at the visits outlined in Table 1. Hematology, chemistry, coagulation parameters (INR), and urinalysis will be conducted at these visits. Serology and the urine drug screen will be conducted at Screening (Visit 1). The investigator will assess the clinical significance of any values outside the reference ranges provided by the central laboratory. Participants with abnormalities judged to be clinically significant at Screening (Visit 1) or with positive results on the urine drug screen will be excluded from the study.

Women of childbearing potential will be required to have a urine pregnancy test at all visits. A positive pregnancy test at Visit 1 or Visit 2 will exclude the participant from participation in the study.

Investigators may also perform unscheduled clinical laboratory determinations at any time for the purpose of participant safety.

Participants are not required to fast overnight before coming in for their appointments.

The clinical laboratory parameters to be measured are shown in Table 6-1.

Table 6-1 Clinical Laboratory Parameters

Category	Parameter
Chemistry	Sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine kinase, total protein, albumin, calcium, phosphorus, uric acid, total cholesterol. The estimated glomerular filtration rate will be calculated by the central laboratory.
Hematology	Hemoglobin; hematocrit; red blood cell count; red blood cell indices (mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration); white blood cell count, including differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils); platelet count
Urinalysis	Urine dipstick for specific gravity, pH, protein, glucose, ketones, bilirubin, and blood; microscopic examination including red blood cells/high-power field, white blood cells/high-power field, and casts/low-power field.
Coagulation	International Normalized Ratio
Serology	At Visit 1 only: anti-hepatitis A IgM antibody, hepatitis B surface antigen, anti-hepatitis C antibody, or anti-hepatitis E IgM antibody.
Urine Drug Screen	Screening for drugs of abuse (eg, marijuana, cocaine, phencyclidine, amphetamines, benzodiazepines, barbiturates, opiates) will be conducted using a urine drug screen at Visit 1. Urine drug screens positive for recreational (including marijuana regardless of legality) or illicit drugs or non-disclosed concomitant medications are not allowed to be repeated. All other positive urine drug screens may be repeated with permission from Allergan; a negative result or an explanation of a positive result due to concomitant medication use (eg, opioids prescribed for migraine pain) will be required for randomization.

A central laboratory will be used to evaluate all urine and blood samples, which will be collected, processed, and stored according to the instructions provided by the laboratory.

6.5.4 Vital Signs

Vital sign measurements, including sitting and standing BP, sitting and standing pulse rate, respiratory rate, temperature, body weight, and height (at Visit 1 only), will be performed at every visit. Sitting and standing BP and pulse rate will be determined as follows: BP and pulse measurements will be performed after the participant sits quietly for 5 minutes,

followed by a second set of measurements taken after the participant stands for at least 3 minutes (but no longer than 10 minutes).

6.5.5 Physical Examination

A complete physical examination will be performed at the visits outlined in Table 1. A professionally trained physician or healthcare professional licensed to perform physical examinations will examine the participant for any detectable abnormalities of the following body systems: general appearance; neck (including thyroid); head, eyes, ears, nose, and throat; lungs; heart/cardiovascular; abdomen; neurologic; extremities; back; musculoskeletal; lymphatic; skin; and other. The neurologic examination should be conducted to detect the presence of any significant sensory/motor abnormalities.

6.5.6 Electrocardiograms (ECG)

A 12-lead ECG will be performed at the visits outlined in Table 1. All ECGs should be performed after the participant has been supine for at least 5 minutes. All ECGs performed will be saved as a source document. ECGs will be transmitted electronically to the central ECG laboratory for analysis according to the instructions provided by the laboratory to be centrally read by a cardiologist. The overall interpretation of the clinical significance of the ECG will be determined by the investigator and recorded in the participant's eCRF.

6.5.7 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a clinician-rated instrument that reports the severity of both suicidal ideation and behavior. Suicidal ideation is classified on a 5-item scale: 1 (wish to be dead), 2 (nonspecific active suicidal thoughts), 3 (active suicidal ideation with any methods [not plan] without intent to act), 4 (active suicidal ideation with some intent to act, without specific plan), and 5 (active suicidal ideation with specific plan and intent). The C-SSRS also captures information about the intensity of ideation, specifically the frequency, duration, controllability, deterrents, and reasons for the most severe types of ideation. Suicidal behavior is classified on a 5-item scale: 0 (no suicidal behavior), 1 (preparatory acts or behavior), 2 (aborted attempt), 3 (interrupted attempt), and 4 (actual attempt). More than 1 classification can be selected provided they represent separate episodes. For actual attempts only, the actual or potential lethality is classified for the initial, most lethal, and most recent attempts. The C-SSRS will be completed at all study visits. At Visit 1 (Screening), the C-SSRS will be completed for the participant's lifetime history and for the 6 months prior to screening. At all other visits the C-SSRS will be completed for ideation and behavior since the previous visit. The C-SSRS will be completed on the eTablet by the investigator or

designee with current and valid training in administering the assessment. A participant should not be released from the study center until the results of C-SSRS are reviewed and it is confirmed that the participant is not considered to be at risk. Participants who reply with "yes" to questions 4 or 5 in the suicidal ideation section or "yes" to any question in the suicidal behavior section of the C-SSRS at Visits 3 through 6 must be withdrawn from the study and should receive appropriate follow-up as in routine clinical practice, including the Early Termination Visit 7 and the Follow-up Visit 8. These participants must continue to complete their daily eDiary through Visit 8 Follow-up.

6.6 Other Study Supplies

The following will be provided by Allergan or Allergan designee:

- All supplies needed for blood and urine sampling (central laboratory analysis)
- All supplies needed for onsite urine pregnancy test
- All supplies needed for PK and future biomedical research sample collections
- Shipping materials for shipment of laboratory samples to central laboratory
- All supplies needed for ECG assessment including ECG machine
- Electronic diaries
- Electronic tablet(s)

6.7 Summary of Methods of Data Collection

An IWRS will be used to randomize participants and manage study intervention inventory. All office visit data (ie, non-diary data) for this study will be collected by either the eTablet (eg, questionnaires for participant reported outcomes) or eCRFs via an electronic data capture system. Source documents will be used at the sites and may include a participant's medical record, hospital charts, clinic charts, the investigator's participant study files, as well as the results of diagnostic tests such as laboratory tests, ECGs, etc. A centralized clinical laboratory will be used for the analysis of all blood and urine samples, and for ECG assessments. Additional information on the collection and handling of samples is detailed in the Laboratory Procedure Manual.

Participants will use an eDiary daily to record the daily total duration of headache, headache characteristics, associated symptoms, the worst pain severity, acute medication use, AIM-D, Activity Level, and Activity Limitation both in the screening/baseline period and double-blind treatment period until Visit 8. Training for the eDiary will be provided for qualified participants during the Screening/Baseline Visit (Visit 1).

7. Statistical Procedures

7.1 Analysis Populations

The ITT population will consist of all randomized participants. All efficacy analyses will be performed using the mITT population, consisting of all randomized participants who received at least 1 dose of study intervention, had an evaluable baseline period of eDiary data and had at least 1 evaluable post-baseline 4-week period (Weeks 1 to 4, 5 to 8, and 9 to 12) of eDiary data during the double-blind treatment period. All safety analyses will be performed using the safety population, consisting of all participants who received at least 1 dose of study intervention.

The primary efficacy analysis population in support of EU filing for off-treatment estimand (defined in Section 7.4.) includes all randomized participants who received at least 1 dose of study treatment, had an evaluable baseline period of eDiary data and had at least 1 evaluable post-baseline 4-week period (Weeks 1 to 4, 5 to 8, 9 to 12) of eDiary data during the double-blind treatment period and follow-up period, regardless of whether on study treatment or off study treatment.

7.2 Collection and Derivation of Efficacy Assessments

On a daily basis during the 28-day baseline period and throughout the study, participants are to record into an eDiary information on the daily total duration of headache, headache specific characteristics and symptoms, the worst pain severity, and use of any acute headache pain medication. Participants will be able to report headache data, including absence of headache, for the day of the eDiary report and for the day immediately prior to the day of the eDiary report, as long as information reported is for a time subsequent to the participant's most recent report. This is defined as a one-day "missing-recall" window.

Following randomization on Day 1, there are 4 visits at 2-week intervals, followed by 2 visits at 4-week intervals; altogether encompassing a 12-week double-blind treatment phase of the study and a 4-week follow-up phase. In practice, there may or may not be exact 2-week or 4-week durations between two consecutive visits and the visits might not align with each

28-day period recorded in the eDiary (ie, Weeks 1 to 4, 5 to 8 and 9 to 12, corresponding to Days 1 to 28, 29 to 56, and 57 to 84). Therefore, for data analysis purposes, the number of migraine days during the last 28 days prior to the randomization date, will serve as the "baseline", and change from baseline will be calculated for consecutive 28-day periods beginning with the date of first dose of study intervention.

In order to be randomized, a participant should be in the baseline phase for at least 28 days and must report eDiary data for at least 20 days (including missing recall) during the 28-day baseline period. If less than 28 days of baseline data are reported, the number of headache days and other such counting variables for "baseline" will be prorated to standardize the count to a 28-day equivalent. Subsequent to treatment start, the number of headache days will be counted in successive and non-overlapping 4-week (ie, 28-day) windows. Headaches that continue into a subsequent 4-week period will be counted (with recorded severity and duration) as occurring in each period.

If any postbaseline eDiary window for a participant has at least 14 but less than 28 days of reported data, the prorated approach will be used. If a participant reports less than 14 days of headache data, the participant's observed counts in that particular 28-day eDiary window will be set to missing for that window. These prorating rules will be applied to all efficacy analyses of eDiary data unless otherwise stated.

7.2.1 Primary Efficacy Variable

The primary efficacy variable is the change from baseline in mean monthly migraine days across the 12-week treatment period. Baseline is defined as the number of migraine days during the last 28 days of the baseline phase, ie, Day –28 to –1.

7.2.2 Secondary Efficacy Variables

The secondary efficacy variables for the United States and the EU:

- Change from baseline in mean monthly headache days across the 12-week treatment period.
- Change from baseline in mean monthly acute medication use days across the 12-week treatment period.
- At least a 50% reduction in 3-month average of monthly migraine days.

- Change from baseline in MSQ v2.1 Role Function-Restrictive domain score at Week 12

- Change from baseline in mean monthly Performance of Daily Activities domain score of the AIM-D across the 12-week treatment period.

- Change from baseline in mean monthly Physical Impairment domain score of the AIM-D across the 12-week treatment period.

7.2.3 Additional Efficacy Variables

Additional efficacy endpoints for the United States and the EU are provided below. Related analysis will be documented in the clinical study report SAP.

- ≥ 25%, ≥ 50%, ≥ 75%, 100% improvement (reduction) in monthly migraine days at Weeks 1-4, 5-8, and 9-12.
- ≥ 25%, ≥ 75%, 100% improvement (reduction) in 3-month average of monthly migraine days.
- Change from baseline in monthly migraine days at Weeks 1-4, 5-8, and 9-12.
- Change from baseline in monthly headache days at Weeks 1-4, 5-8, and 9-12.
- Change from baseline in monthly cumulative headache hours at Weeks 1-4, 5-8, 9-12, and average across the 12-week treatment period.
- Change from baseline in monthly acute medication use days at Weeks 1-4, 5-8, and 9-12.
- Change from baseline in monthly triptan use days at Weeks 1-4, 5-8, 9-12, and average across the 12-week treatment period.
- Change from baseline in monthly moderate/severe headache days at Weeks 1-4, 5-8, 9-12, and average across the 12-week treatment period.
- Change from baseline in monthly severe headache days at Weeks 1-4, 5-8, 9-12, and average across the 12-week treatment period.
- Change from baseline in weekly migraine days at Weeks 1-4.
- Participant having a migraine day on the day of initial dose and on each day of the 6 days post the initial dose.
- Change from baseline in the HIT-6 total score at Weeks 4, 8, and 12.
- At least a 5-point improvement (decrease) from baseline in HIT-6 total score at Weeks 4, 8, and 12.
- Participant assessed by the PGIC as “much better” or “very much better” at Week 12.

- Participant reporting "satisfied" or "extremely satisfied" with study medication for migraine prevention at Weeks 4, 8, and 12.
- Change from baseline in percent work time missed, percent impairment while working, percent overall impairment, and percent activity impairment due to migraine at Weeks 4, 8, and 12 as assessed by the WPAI:MIGRAINE.
- Change from baseline in the MIDAS total score at Week 12.
- Change from baseline in MIDAS absenteeism score (Questions 1, 3, and 5) at Week 12.
- Change from baseline in MIDAS presenteeism score (Questions 2 and 4) at Week 12.
- Change from baseline in PGI-S score at Weeks 4, 8, and 12.
- Change from baseline in the MSQ v2.1 Role Function-Preventive domain score at Weeks 4, 8, 12, and 16.
- Change from baseline in the MSQ v2.1 Role Function-Restrictive domain score at Weeks 4 and 8, and 16.
- Change from baseline in the MSQ v2.1 Emotional Function domain score at Weeks 4, 8, 12, and 16.
- Change from baseline in monthly Performance of Daily Activities domain score of the AIM-D at Weeks 1-4, 5-8, and 9-12.
- Change from baseline in monthly Physical Impairment domain score of the AIM-D at Weeks 1-4, 5-8, and 9-12.
- Change from baseline in monthly AIM-D total score at Weeks 1-4, 5-8, 9-12, and average across the 12-week treatment period.
- Change from baseline in monthly activity level at Weeks 1-4, 5-8, 9-12, and average across the 12-week treatment period.
- Change from baseline in monthly activity limitation at Weeks 1-4, 5-8, 9-12, and average across the 12-week treatment period.

7.2.3.1 Other Health Outcome Variables

Other health outcome endpoints are listed below. The related health outcome analyses will be documented in health economics and outcomes research SAP.

- Change from baseline in EQ-5D-5L descriptive system index score at Weeks 4, 8, 12, and 16.
- Change from baseline in the EQ-5D-5L VAS score at Weeks 4, 8, 12, and 16.
- Change from baseline in PROMIS-PI total score at Weeks 4, 8, and 12.

7.3 Hypothesis and Methods of Analysis

For efficacy analyses, data will be analyzed according to participants' randomization assignments, regardless of actual treatment received.

For safety data analyses, the participants will be analyzed according to actual treatment received (rather than as randomized).

7.3.1 Primary Efficacy Analyses

The primary efficacy endpoint is the change from baseline in mean monthly migraine days across the 12-week treatment period. The primary null hypothesis is that atogepant treatment doses (atogepant 10 mg, atogepant 30 mg, and atogepant 60 mg once a day) are each equally effective to placebo in mean change from baseline in mean monthly migraine days across the 12-week treatment period. The alternative hypothesis is that at least 1 of the 3 doses of atogepant has a different effect than placebo.

The primary comparison between treatment groups will be done by a mixed-effects model for repeated measures (MMRM) of the change from baseline. The statistical model will include treatment group, visit, prior exposure (yes/no) to a migraine prevention medication with proven efficacy, and treatment group by visit interaction as categorical fixed effects. It will also include the baseline score and baseline-by-visit interaction as covariates. An unstructured covariance matrix will be used to model the covariance of within-participant repeated measurements. The Kenward-Roger approximation (Kenward 1997) will be used to estimate the denominator degrees of freedom. The analysis will be performed based on all postbaseline values using only the observed cases without imputation of missing values. Pairwise contrasts in the MMRM model will be used to make the pairwise comparisons of each atogepant dose to placebo. This is the primary analysis method for the primary efficacy

endpoint in support of US filing. Only data collected during the double-blind period will be included in the analysis. Participants are always analyzed based on the treatment group assigned by randomization.

7.3.1.1 Sensitivity Analyses in Missing Data Handling

Multiple sensitivity analyses for missing data handling will be conducted and are summarized below. Details of the sensitivity analyses will be provided in the statistical analysis plan.

ANCOVA Model Based on 3-month Average of the Monthly Migraine Days

The response variable for the ANCOVA model is the change from baseline in 3-month average of monthly migraine days for each participant. The ANCOVA model includes terms for treatment, prior exposure (yes/no) to a migraine prevention medication with proven efficacy, and baseline score. The treatment difference for atogepant doses versus placebo will be estimated and reported along with the corresponding 95% CI and nominal p-value for superiority testing. This analysis is also termed as "supportive analysis".

Within-group Imputation Based on Observed Data

A sensitivity analysis will be performed based on imputation using participants from the same treatment group with observed data under the MAR assumption. Missing data for participants who prematurely discontinued are assumed to copy the profile of participants in the same treatment group with observed data.

Copy-reference Approach

The Copy-reference Approach will be performed on the primary endpoint to assess the robustness of the MMRM analysis to possible violation of the missing-at-random (MAR) assumption. This sensitivity analysis is one type of pattern-mixture models (PMM), under which data could be missing-not-at-random (MNAR), with repeated analyses combined via the reference based multiple imputation (MI) procedure. Participants who discontinued in the Atogepant groups are assumed to have no treatment effect after the discontinuation. Participants are assumed to copy the profile of placebo arm and missing values are imputed based on the distribution estimated from the placebo group under the MAR using copy-reference approach.

MMRM Based on Primary Measures Collected during the Double-blind and Follow-up Periods

The details for this analysis are provided in Section 7.4. The primary analysis in support of EU filing will serve as one sensitivity analysis in support of US filing.

7.3.1.2 Sensitivity Analysis for Possible Violation of Normality Assumption

The normality test is performed on the residuals which are generated by the same MMRM as used for the primary efficacy analysis. The residuals are scaled by the inverse Cholesky root of its estimated variance-covariance matrix. The Kolmogorov-Smirnov test for normality is applied to the de-correlated and scaled residuals and normality test is rejected if p-value from the Kolmogorov-Smirnov test is less than 0.01.

If the normality test is rejected, the sensitivity analysis uses MI in conjunction with robust regression to assess the robustness of the primary MMRM analysis to the possible violation of normality assumption. This method has been described and referred as ADAP [R] in Mehrotra 2012. The detail of the sensitivity analyses will be provided in the statistical analysis plan.

7.3.2 Secondary Efficacy Analyses

The secondary efficacy variables are identified in Section 7.2.2.

The secondary endpoints for headache days, acute medication use days, MSQ v2.1 Role Function-Restrictive domain score, Performance of Daily Activities domain score of the AIM-D, and Physical Impairment domain score of the AIM-D will be analyzed in the same manner as that used to analyze the primary endpoint.

The 50% responder, defined as a participant with at least a 50% reduction from baseline in the 3-month average of monthly migraine days, will be assessed for each individual. A logistic regression model will be used to analyze the 50% responders across the 12-week treatment period. This model assumes a binary distribution for the response and uses a logit link. The analysis model will include treatment group, prior exposure (yes/no) to a migraine prevention medication with proven efficacy, and baseline monthly migraine days. The treatment difference in terms of odds ratio between each atogepant dose group and placebo will be estimated and tested from this model.

The overall type I error rate for multiple comparisons across two atogepant doses and the primary and secondary efficacy endpoints will be controlled at the 0.05 level using a graphical approach by Bretz 2009. The primary endpoint will serve as the gatekeeper for the secondary endpoints. A complete graph and details of the graphical multiple comparison procedure will be presented in the statistical analysis plan of this study.

7.3.3 Additional Efficacy Analyses

In general, other efficacy analyses are performed at the nominal significance level, without adjusting for multiplicity.

Other efficacy variables will be analyzed as follows:

- For selected diary variables with a continuous response range, the baseline score will be included as a covariate in an MMRM analysis of the change from baseline. These analyses will be performed similarly to the primary MMRM, with focus again on the pairwise contrasts of each dose group to placebo.

- For weekly data analysis purposes, baseline is defined to be the baseline derived in monthly basis divided by 4, and change from baseline in the weekly migraine days will be calculated for consecutive 7-day periods beginning with Day 1. Subsequent to treatment start, the number of headache days will be counted in successive and non-overlapping 1-week (ie, 7-day) windows. Headaches that continue into a subsequent 1-week period will be counted (with recorded severity and duration) as occurring in each period. If any postbaseline eDiary window for a participant has at least 4, but less than 7 days, of reported data, the prorated approach will be used. If a participant reports less than 4 days of headache data, the participant's observed counts in that particular 7-day eDiary window will be set to missing for that window.

- For variables where the data are essentially binary, comparisons between treatment groups will be done with logistic regression for variables with only one postbaseline assessment or using a generalized linear mixed model for variables with multiple postbaseline assessments.

Descriptive statistics will be provided by visit for each efficacy variable by treatment group. Analysis of some variables will be limited to descriptive summary statistics.

Details will be specified in the statistical analysis plan.

7.3.4 Safety Analyses

MedDRA nomenclature will be used to code TEAEs. Incidence will be tabulated by primary SOC and by specific event within each primary SOC. TEAEs will be analyzed after treatment start on Day 1 through the end of the study. TEAEs will also be summarized separately for the double-blind treatment and follow-up phases of the study.

7.4 Off-treatment Hypothetical Estimand

This section defines an estimand, termed as off-treatment hypothetical estimand, which will be the primary estimand in support of EU filing and serve as one sensitivity analysis in support of US filing.

7.4.1 Treatment Condition of Interest

Participants take assigned treatment by randomization during the double-blind treatment period. In addition, permissible and prohibited mediations are described below:

- Participants are allowed to take acute migraine medications (Protocol Section 4.4.1) to keep the participants in the study.
- The protocol prohibits patients from starting any new migraine preventive treatments (Protocol Section 4.4.2) during the study (including the double-blind treatment period and the follow-up period).

7.4.2 Population

The target population is patients suffering from migraine with aura or migraine without aura satisfying the inclusion and exclusion criteria as specified in Section 4.

The analysis population is defined to be all randomized participants who received at least 1 dose of study treatment, had an evaluable baseline period of eDiary data and had at least 1 evaluable post-baseline 4-week period (Weeks 1 to 4, 5 to 8, 9 to 12) of eDiary data, regardless of whether on study treatment or off study treatment.

7.4.3 Variable

The variable is the same as the primary efficacy endpoint defined in Section 7.2.1, which is the change from baseline in the participant's mean monthly (4-weeks) migraine days across the 12-week treatment period as derived from the eDiary data.

7.4.4 Accounting of Intercurrent Events

Intercurrent events and their handling rules are as follows:

- Participants who started a new migraine prophylaxis treatment during the double-blind or safety follow-up period will have their data during the safety follow-up period after starting the new migraine prophylaxis treatment excluded from the analysis.
- Participants who discontinue study treatment due to all reasons other than starting a new migraine prophylaxis treatment will have their data collected after discontinuation of study treatment, and those off-treatment data will be included in the analysis.

Detailed methods and procedures will be documented in the statistical analysis plan prior to study completion.

7.4.5 Population-level Summary

The population-level summary for the primary endpoint is the difference in primary variable means between each atogepant group and placebo.

Participants are always analyzed based on their treatment assignment by randomization. To obtain the estimate of treatment effect defined in the off-treatment hypothetical estimand, a MMRM similar to the primary analysis specified in Section 7.3.1 will be performed on observed data including both on-treatment and off-treatment monthly migraine days.

7.4.6 Off-treatment Hypothetical Estimand Approach for the Secondary Endpoints

Continuous secondary endpoints will be handled using the same estimand approach defined above for the primary endpoint.

The secondary endpoint of 50% responders will be derived using both on-treatment and off-treatment observed data as defined in the primary endpoint above. The population-level summary for this endpoint is the odds ratio for each atogepant group relative to placebo.

7.5 Subgroup Analyses

Subgroup analysis based on prior exposure (yes/no) to a migraine prevention medication with proven efficacy will be performed for the following efficacy endpoints:

- Change from baseline in mean monthly migraine days across the 12-week treatment period.
- Change from baseline in mean monthly headache days across the 12-week treatment period.
- Change from baseline in mean monthly acute medications use days across the 12-week treatment period.
- ≥ 50% reduction in 3-month average of monthly migraine days
- ≥ 75% reduction in 3-month average of monthly migraine days
- 100% reduction in 3-month average of monthly migraine days

Subgroup analyses for primary efficacy endpoint based on demographic factors (age, sex, race) will be provided in the integrated summary of efficacy to facilitate the comparison across pivotal studies.

7.6 Sample Size Calculation

A total sample size of 218 participants will be randomized per treatment group and that will provide at least 98% power to detect the treatment difference between each of the 3 atogepant doses (assumed equally effective) and placebo for the primary efficacy endpoint. The sample size of this study was selected to provide sufficient power for the primary efficacy endpoint and the first 3 secondary endpoints as shown in Table 7-1. The power calculations are based on the following assumptions:

1) The treatment difference from placebo will be similar to the average value across the migraine prevention studies for atogepant (Phase 2/3 Study CGP-MD-01), telcagepant (Ho 2014) and monoclonal antibodies (Dodick 2014a; Dodick 2014b; Bigal 2015). The standard deviation of each endpoint was estimated from an internal study that randomized approximately 800 participants. In particular, the assumed treatment difference from placebo in change from baseline in mean monthly migraine days across the 12-week treatment period is -1.5 days, and the standard deviation is 3.5 days. Detailed treatment difference and standard deviation assumptions are listed in Table 7-1.

2) The study statistical testing plan controls the overall type I error at 5%. The power calculations of the primary and secondary endpoints have taken the multiple comparisons into consideration by testing each dose versus placebo at a 0.0167 significance level, 2-sided.

A detailed graphical multiple comparison procedure will be presented in the statistical analysis plan.

Table 7-1 Statistical Power for Primary and the First Three Secondary Endpoints

Hypothesis Testing	Endpoint	Treatment Difference from Placebo	Standard Deviation	Statistical Power
Primary	Change from baseline in mean monthly migraine days across the 12-week treatment period	–1.5	3.5[a]	98%
Secondary 1	Change from baseline in mean monthly headache days across the 12-week treatment period	–1.5	3.8[a]	95%[b]
Secondary 2	Change from baseline in mean monthly acute medication use days across the 12-week treatment period	–1.2	3.2[a]	93%[b]
Secondary 3	≥ 50% reduction in 3-month average of monthly migraine days	33% Placebo rate	50% Atogepant rate	89%[b]

[a] Standard deviations observed in an internal study that randomized approximately 800 participants

[b] Statistical power for secondary endpoints are conditional on success of prior endpoints (assuming independence among the endpoints) in the sequence for the comparisons of each dose versus placebo.

7.7 Pharmacokinetics and Exposure-response Analyses

A graphical evaluation of the PK and PD data of atogepant will be performed for the identification of possible trends. The pharmacokinetics will be evaluated using the existing population PK model, updated with data from this study. Individual predictions of atogepant exposure (including but not limited to steady state $AUC_{0\text{-}Tau}$ and C_{min}) will be evaluated graphically for potential relationships with efficacy and/or safety endpoints. If graphical evaluation identifies possible trends, exploratory PK/PD analyses will be performed for the evaluation and quantification of potential relationships via nonlinear mixed effects modeling. Efficacy endpoints to be evaluated will include migraine days and responder rates. A standalone pharmacometric analysis plan will be written, and the analyses results will be reported separately from the integrated clinical study report.

7.8 Interim Analyses

No interim analysis is planned.

8. Study Visit Schedule and Procedures

Please see Table 1 for a schematic of the schedule of visits and procedures (for in-person visits conducted prior to or during the COVID-19 pandemic) and Figure 1 for a study visit flowchart. Refer to Table 2 for assessments to be performed at study visits conducted remotely due to the COVID-19 pandemic.

8.1 Participant Entry Procedures

8.1.1 Overview of Entry Procedures

Prospective participants as defined by the criteria in Sections 4.2 and 4.3 (inclusion/exclusion criteria) will be considered for entry into this study.

8.1.2 Informed Consent and Participant Privacy

The study will be discussed with the participant and those wishing to enter the study must give informed consent prior to any study-related procedures or change in treatment. The participant must also give authorization and other written documentation in accordance with local privacy requirements (where applicable) prior to any study-related procedures or change in treatment.

Each participant who provides informed consent and/or assent will be assigned a participant identification number that will be used on participant documentation throughout the study.

The investigator or qualified designee will explain the PK and future biomedical research substudy consents to the participant and answer all of his/her questions. Participants will sign separate consent forms to participate in the PK substudy and future biomedical research before performing any procedure related to the substudies, respectively.

8.1.3 Procedures for Duplicate Participant Identification – Verified Clinical Trials (VCT)

A central vendor will be used to verify participants current and past research study status in order to mitigate safety concerns associated with duplicate enrollment and protocol deviations associated with multiple trial enrollment. The use of this central vendor will be mandatory for US sites. Following proper informed consent and after issuing a participant number, each participant will be checked in the VCT database, indicated in the Schedule of Visits and Procedures (Table 1). Partial identifiers will be utilized. Participants who are

identified as verification failures by VCT should not be enrolled without documented approval from Allergan.

8.2 Washout Intervals

This study will not include a washout period.

8.3 Procedures for Final Study Entry

At the Screening and Randomization Visits (Visits 1 and 2), participants must meet all of the inclusion criteria and must not meet any of the exclusion criteria. Rescreening of participants may be considered with permission from Allergan (Section 4.5). Also, all women of childbearing potential must have negative results on the urine pregnancy test at the Screening and Randomization Visits (Visits 1 and 2, prior to the first administration of study intervention).

Prior to randomization, it must be confirmed that the participant had 4 to 14 migraine days and < 15 headache days during the 28-day baseline period (see Section 6.1.1 for definition) and completed the eDiary for at least 20 of the 28 days.

See Section 5.5 for the method for assignment to treatment groups/randomization.

8.4 Visits and Associated Procedures

There will be 8 scheduled clinic visits: Visit 1 (Screening/Baseline), Visit 2 (Randomization), Visit 3 (Week 2), Visit 4 (Week 4), Visit 5 (Week 6), Visit 6 (Week 8), Visit 7/ET (Week 12), and Visit 8 (Follow-up). For details, please see Table 1 Schedule of Visits and Procedures for In-Person Visits Conducted Prior to or During the COVID-19 Pandemic. Refer to Table 2 for assessments to be performed at study visits conducted remotely due to the COVID-19 pandemic.

8.4.1 Visit 1 (Screening/Baseline) Day -35 to Day -28

- Obtain informed consent and participant privacy
- Obtain informed consent for future biomedical research (optional)
- Obtain informed consent for PK substudy (optional)
- Register participant in IWRS

- Obtain VCT consent and perform verification (if applicable)
- Collect demographic information
- Collect medical history
- Collect start date (first day) of last menstrual cycle for women having menstrual cycles
- Collect ASC-12
- Collect migraine history (3-month retrospective) and confirm diagnosis
- Review and record prior medications taken in the past 6 months, and all prior headache medications and concomitant medications.
- Collect vital sign measurements (height, weight, pulse rate, respiratory rate, blood pressure, and body temperature). Height will be measured only at Visit 1.
- Perform and transmit ECG
- Perform physical examination
- Collect blood and urine samples for clinical laboratory determinations (chemistry, hematology, INR, urinalysis, and serology).
- Perform urine pregnancy test for women of childbearing potential. Discuss the method of contraception with women of childbearing potential and document this method. Counsel participants on the importance of maintaining their agreed upon method of contraception throughout the study.
- Collect urine sample for drug screen
- Collect blood for future biomedical research. Informed consent for optional future biomedical research samples must be obtained before the sample for DNA analysis.
- Assess C-SSRS on eTablet (the 'Screening/Baseline' assessment of the C-SSRS will be completed).
- Verify if the participant meets inclusion/exclusion criteria at this point

- Provide eDiary, along with training and instructions. Participants to bring eDiary to all visits.
- Review and assess AEs

8.4.2 Double-blind Treatment Phase (12 Weeks)

8.4.2.1 Visit 2 (Randomization) Day 1

- Review eDiary data and compliance (Participants should bring eDiary to visits).
- Perform urine pregnancy test for women of childbearing potential.
- Collect vital sign measurements (sitting and standing systolic and diastolic BP, pulse rate, respiration rate, temperature, and weight).
- Collect start date (first day) of last menstrual cycle for women having menstrual cycles.
- Assess C-SSRS on eTablet (the "Since Last Visit" assessment of the C-SSRS will be completed).
- Verify if participant meets inclusion/exclusion criteria and is eligible for the study at this point.

If the participant continues to meet study entry criteria, including acceptable results from Visit 1 clinical laboratory tests, pregnancy tests and the urine drug screen (see Section 6.5.3) the following procedures will be carried out at the Randomization Visit (Visit 2):

- Prior to any other test or evaluations, administer PRO measures including: HIT-6, PGI-S, WPAI:MIGRAINE, EQ-5D-5L, MIDAS, MSQ v2.1, and PROMIS-PI.
- Update concomitant medications and concurrent procedures (including all prior headache medications).
- Review and assess AEs.
- Randomize the participant in IWRS and obtain the kit number for study intervention.
- Collect pre-treatment blood and urine samples for chemistry, hematology, INR, and urinalysis.

- Collect pre-treatment PK sample (for participants who consented).
- Dispense study intervention. Participants must take their first dose of study intervention at the clinic on this day.

8.4.2.2 Visits 3 to 6 (Weeks 2 to 8)

Refer to Table 2 for assessments to be performed at study visits conducted remotely due to the COVID-19 pandemic.

- Prior to any other test or evaluations, administer PRO measures, including: HIT-6, PGI-S, WPAI:MIGRAINE, Patient Satisfaction with Study Medication, EQ-5D-5L, MSQ v2.1, and PROMIS-PI, as outlined in Table 1, Schedule of Visits and Procedures for In-Person Visits Conducted Prior to or During the COVID-19 Pandemic.
- Assess C-SSRS on eTablet (the "Since Last Visit" assessment of the C-SSRS will be completed).
- Collect vital sign measurements (weight, pulse rate, respiratory rate, blood pressure, and body temperature).
- Collect start date (first day) of last menstrual cycle for women having menstrual cycles.
- Review and assess AEs.
- Update concomitant medications and concurrent procedures.
- Perform and transmit ECG (Visit 5 only).
- Perform urine pregnancy test for women of childbearing potential.
- Collect blood and urine samples for chemistry, hematology, INR, and urinalysis.
- Collect PK sample (for participants who consented).
- Collect previous visit study intervention, review participant compliance, and perform accountability.
- Review eDiary data and compliance (participants should bring eDiary to visits).

- Access IWRS to dispense study intervention and enter accountability.

8.4.2.3 Visit 7/Early Termination (Week 12)

Refer to Table 2 for assessments to be performed at study visits conducted remotely due to the COVID-19 pandemic. If Visit 7 is conducted remotely, the participant will not be eligible to roll over into Study 3101-309-002.

Effort should be made by the site to not schedule Visit 7 earlier than 12 weeks after Day 1 to ensure participants complete the full 12 weeks of treatment and have eDiary data through Day 84.

- Prior to any other test or evaluations, administer PRO measures, including: HIT-6, PGIC, PGI-S, WPAI:MIGRAINE, Patient Satisfaction with Study Medication, EQ-5D-5L, MIDAS, MSQ v2.1, and PROMIS-PI.
- Perform physical examination.
- Collect vital sign measurements (weight, pulse rate, respiratory rate, blood pressure, and body temperature).
- Collect start date (first day) of last menstrual cycle for women having menstrual cycles.
- Perform urine pregnancy test for women of childbearing potential.
- Perform and transmit ECG.
- Collect blood and urine samples for chemistry, hematology, INR, and urinalysis.
- Collect post-dose PK sample (for participants who consented).
- Assess C-SSRS on eTablet (the "Since Last Visit" assessment of the C-SSRS will be completed).
- Collect previous visit study intervention, review participant compliance, and perform accountability.
- Review eDiary data and compliance (participants should bring eDiary to visits).
- Review and assess AEs.

- Update concomitant medications and procedures.
- Collect eDiary only for the participants who completed the double-blind treatment period (Visit 2 to Visit 7/ET), review eDiary data and compliance.
- Advise participants who early terminated from the double-blind treatment period to continue completing their eDiary through the Follow-up Visit.
- Access IWRS and enter accountability.

8.4.3 Follow-up Period (4 weeks)

8.4.3.1 Visit 8 (End of Study) Week 16 Conducted Remotely (Due to the COVID-19 Pandemic)

During the COVID-19 pandemic, Visit 8 (Follow-up/End of Study) should be conducted remotely for all participants in all cases. Refer to Table 2 for assessments to be performed at study visits conducted remotely due to the COVID-19 pandemic.

8.4.3.2 Visit 8 (End of Study) Week 16 Conducted During In-Person Visit (Prior to the COVID-19 Pandemic)

- Prior to any other test or evaluations, administer PRO measures, including: EQ-5D-5L and MSQ v2.1.
- Perform physical examination.
- Collect vital sign measurements (weight, pulse rate, respiratory rate, blood pressure, and body temperature).
- Perform urine pregnancy test for women of childbearing potential.
- Collect blood and urine samples for chemistry, hematology, INR, and urinalysis.
- Assess C-SSRS on eTablet (the “Since Last Visit” assessment of the C-SSRS will be completed).
- Review and assess AEs.
- Update concomitant medications and procedures.

- Collect eDiary for participants who early terminated from the double-blind treatment period, review eDiary data and compliance.
- Access IWRS to enter study visit.

8.5 Instructions for the Participants

Section 4.4.4 provides diet and activity instructions for participants enrolled in the study.

Participants will be provided with instructions on daily completion of the eDiary. A practice session with a hypothetical scenario should be administered to ensure the participant's comprehension of the questions and the information to be entered. In addition, prohibited medications should be reviewed with the participants. Participants will be instructed to bring their eDiary to each clinic visit and return their study intervention (used and unused).

Participants should be instructed to take study intervention once daily at approximately the same time each day. For dosing on Day 1 (Visit 2), the first dose is to be taken at the study site.

Participants should use appropriate contraceptive measures for the duration of their participation in the study (See Section 4.4.3).

8.6 Unscheduled Visits

Additional examinations and laboratory assessments may be performed as necessary to ensure the safety and wellbeing of the participants during the study period. Unscheduled visit eCRFs should be completed for each unscheduled visit.

8.7 Compliance with Protocol

All assessments will be conducted at the appropriate visits as outlined in Table 1 (or Table 2 if conducted remotely due to the COVID-19 pandemic) and the timing of the visits should occur as close as possible to the day specified. At each visit, the participant will be asked if they changed the dose/regimen of any existing concomitant medications or initiated the use of any new concomitant medications since the last visit to ensure compliance with the protocol.

Study intervention compliance during any period will be closely monitored by counting the number of tablets dispensed and returned. Every effort will be made to collect all unused study intervention.

8.8 Early Discontinuation of Participants

A premature discontinuation will occur when a participant who signed the ICF and has been randomized ceases participation in the study, regardless of circumstances, before completion of the study. Participants can be prematurely discontinued from the study for one of the following reasons:

- AE
- Lack of efficacy
- Lost to follow-up
- Non-compliance with study intervention
- Other
- Pregnancy
- Protocol deviation
- Site terminated by Allergan
- Study terminated by Allergan
- Withdrawal by participant

Participants may voluntarily withdraw from the study at any time. Notification of early participant discontinuation from the study and the reason for discontinuation will be made to Allergan and will be documented on the appropriate case report form. All randomized participants who prematurely discontinue from the study, regardless of cause, should be seen for final study assessments. The final assessments will be defined as completion of the evaluations scheduled for Visit 7/ET and Visit 8 Follow-up, 4 weeks post the last dose of study intervention. These participants must continue to complete their eDiary through Visit 8 Follow-up.

8.9 Withdrawal Criteria

Women who become pregnant (Section 9.4) and participants who meet study intervention discontinuation criteria related to abnormal liver function tests (Section 9.5) and advised not to be rechallenged will be withdrawn from the study and should refrain from taking study

intervention. The participant should return to the clinic for early termination procedures (Visit 7) and the Follow-up Visit 8. Participants who reply with “yes” to questions 4 or 5 in the suicidal ideation section or “yes” to any question in the suicidal behavior section of the C-SSRS at Visits 3 through 6 must be withdrawn from the study and should receive appropriate follow-up as in routine clinical practice, including the Early Termination Visit 7 and the Follow-up Visit 8. These participants must continue to complete their daily eDiary through Visit 8 Follow-up.

A participant with a condition and/or a situation that, in the investigator's opinion, may put the participant at significant risk, may confound the study results, or may interfere significantly with the participant's participation in the study must be withdrawn from treatment.

8.10 Withdrawal from Future Biomedical Research

A participant who initially consents can withdraw that consent at any time and have his or her sample destroyed, including any by-products of the sample whenever possible. If a participant withdraws consent, their physical sample will be destroyed and no new health information identifying the participant will be gathered after that date. However, once the genetic data is anonymized and placed into the biorepository database after study database lock, the information cannot be withdrawn.

8.11 Study Termination

The study may be stopped at his/her study site at any time by the site investigator. Allergan may stop the study (and/or the study site) for any reason with appropriate notification.

9. Adverse Events

AEs occurring during the study will be recorded on an AE eCRF. If AEs occur, the first concern will be the safety of the study participants.

9.1 Definitions

9.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical study participant associated with the use of study intervention, whether or not considered related to the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally

associated with the use of study intervention. In addition, during the screening period, AEs will be assessed regardless of the administration of a study intervention.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or study (Section 8.8).

All AEs must be collected once informed consent has been obtained, regardless of whether or not the participant has been administered study intervention, until the Follow-up Visit (Visit 8) or 30 days after the last dose of study intervention if the Follow-up Visit is not done. These will be collected at the timepoints specified in the schedule of visits and procedures (Table 1 [or Table 2 if conducted remotely due to the COVID-19 pandemic]), and as observed or reported spontaneously by study participants. Investigators are not obligated to actively seek AE information after conclusion of the study participation.

AEs will be assessed, documented, and recorded in the eCRF throughout the study (ie, after informed consent has been obtained). At each visit, the investigator will begin by querying for AEs by asking each participant a general, non-directed question such as 'How have you been feeling since the last visit?' Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences. Care will be taken not to introduce bias when detecting AEs and/or SAEs. All reported AEs will be documented on the appropriate eCRF.

9.1.2 Serious Adverse Event (SAE)

SAEs must meet both the AE criteria described above and the seriousness criteria listed below:

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life threatening The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually

involving at least an overnight stay) at the hospital or emergency ward for observation and/or intervention that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective intervention of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive intervention in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Allergan considers all cancer AEs as SAEs. Allergan considers any spontaneous abortion as an SAE. Elective abortions can be SAEs or AEs depending on the reason for the elective abortion (eg, fetal death, still birth, congenital anomalies, ectopic pregnancy, which would make the elective abortion an SAE).

Pre-planned surgeries or procedures for pre-existing, known medical conditions for which a participant requires hospitalization is not reportable as an SAE.

Any pre-planned surgery or procedure should be clearly documented in the site source documents by the medically qualified investigator at the time of the participant's entry into the study. If it has not been documented at the time of the participant's entry into the study, then it should be documented as an SAE and reported to Allergan.

9.1.3 Intensity

The intensity assessment for a clinical AE must be completed using the following definitions as guidelines:

MILD	A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
MODERATE	A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
SEVERE	A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

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

9.1.4 Assessment of Causality

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

9.1.5 Follow-up of Adverse Events and Serious Adverse Events

- After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs/SAEs (and nonserious AEs of special interest, as defined in Section 6.5.2) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.8).

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Allergan to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- Prior to database lock, new or updated information will be recorded in the originally completed eCRF. If the event is an SAE, it will also need to be reported on the SAE reporting form. Post database lock, new or updated SAE information will only be reported on the SAE reporting form.

- The investigator will submit any updated SAE data to Allergan within 24 hours of receipt of the information.

9.2 Procedures for Reporting Adverse Events

Any AE must be recorded on the appropriate eCRF.

All AEs that are related to study intervention and are unexpected (not listed as treatment-related in the current IB) must be reported to the governing IRB/IEC as required by the IRB/IEC, local regulations, and the governing health authorities. Any AE that is marked 'ongoing' at the exit visit must be followed-up as appropriate.

9.3 Procedures for Reporting a Serious Adverse Event

Any SAE occurring during the study period (beginning with informed consent) until the Follow-up Visit (Visit 8) or 30 days after the last dose of study intervention if the Follow-up Visit is not done must be immediately reported but no later than 24 hours after learning of an SAE. SAEs must be reported to Allergan as listed on the Allergan Study Contacts Page and recorded on the SAE form. All participants with an SAE must be followed up and the outcomes reported. The investigator must supply Allergan and the IRB/IEC with any additional requested information (eg, autopsy reports and discharge summaries).

9.3.1 Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to Allergan of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

- Allergan has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. Allergan will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Allergan's policy and forwarded to investigators as necessary.

- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from Allergan will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

9.4 Exposure to Study Intervention During Pregnancy

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until the Follow-up Visit (Visit 8) or 30 days after the last dose of study intervention if the Follow-up Visit is not done. Study center personnel must report every pregnancy on the pregnancy form within 24 hours of learning of the pregnancy to the **SAE/pregnancy fax number, 1-714-796-9504**, even if no AE has occurred. The pregnancy must be followed to term and the outcome reported by completing a follow-up pregnancy form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs. Elective abortions can be SAEs or AEs depending on the reason for the elective abortion (eg, fetal death, still birth, congenital anomalies, ectopic pregnancy, which would make the elective abortion an SAE). For pregnancy-related SAEs, in addition to the pregnancy form, a separate SAE form must be filed as described in Section 9.3 with the appropriate serious criterion (eg, hospitalization) indicated.

9.5 ALT or AST Elevations

A treatment-emergent ALT ≥ 3 × ULN and/or AST ≥ 3 × ULN is considered an AE of special interest. Any participant with this laboratory result after study intervention was taken must have repeat testing within 48 to 72 hours to confirm the abnormality. For this repeat testing, the following laboratory tests must be drawn: hematology and chemistry panels, INR, serum acetaminophen level, urine drugs of abuse screen, and blood alcohol level. An extra blood serology sample must be collected and sent to the central laboratory for further diagnostic testing at a later date if needed. In addition, the investigator will perform a complete history and examination to evaluate the participant for possible liver disease.

All AEs of special interest must be reported to Allergan within 24 hours of the time the investigator becomes aware of the event using the abnormal liver function reporting form and the AE eCRF. All new elements of history, physical examination, diagnostic testing results, and other relevant medical reports are to be reported for each AE of special interest.

If an ALT or AST ≥ 3 × ULN is confirmed, close medical follow-up is required: For these participants, the following laboratory tests must be performed: anti-hepatitis A IgM, hepatitis B surface antigen, anti-hepatitis B core IgM, hepatitis C antibody, hepatitis C quantitative RNA by polymerase chain reaction, anti-hepatitis E IgM, anti-hepatitis E IgG, Cytomegalovirus IgM antibody and Epstein-Barr Virus IgM antibody. The participant must be followed clinically and further medical evaluation (for other causes of acute hepatic injury) should be done per the judgment of the investigator and in conjunction with medical personnel at Allergan. In general, the chemistry panel should be repeated 1 to 2 times per week to follow the course of ALT/AST elevation.

Study intervention must be discontinued if any of the following criteria are met:

- ALT or AST ≥ 3 × ULN and the participant is symptomatic with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> 5%)
- ALT or AST ≥ 3 × ULN and total bilirubin > 2 × ULN
- ALT or AST ≥ 3 × ULN and INR > 1.5
- ALT or AST ≥ 5 × ULN for more than 2 weeks
- ALT or AST ≥ 8 × ULN

The participant may be rechallenged with study intervention only after consultation with the Allergan Medical Monitor. For participants who are not rechallenged with study intervention, they should be discontinued from the study and complete an ET visit (Visit 7/ET assessments) and 4-week Follow-up Visit. Participants should receive appropriate follow-up as per standard of care.

The investigator must contact the Allergan Medical Monitor to discuss all cases of confirmed ALT/AST elevation ≥ 3 × ULN. All ALT/AST elevations must be followed until ALT and AST return to < 1.5 × ULN and there is full clinical resolution.

9.5.1 Potential Hy's Law Cases

Sites must report every participant who meets the following potential Hy's law criteria if this occurs within the time the participant signs the ICF until 30 days after the last dose of study intervention:

- ALT or AST ≥ 3 x ULN **AND**
- Total bilirubin ≥ 2 x ULN **AND**
- Alkaline phosphatase < 2 x ULN

Study site personnel must report every participant who meets these criteria. Typically, all 3 analytes will be obtained from the same sample, but they may come from multiple samples taken within a 24-hour period. This requirement applies from the time the participant signs the ICF for the study until 30 days after the final protocol-defined study visit or the last known dose of study intervention (if the final visit does not occur).

A laboratory alert for possible Hy's law cases will be in place, and must notify investigators and Allergan immediately when the above criteria have been met. A possible Hy's law case must be faxed to Allergan on an abnormal liver function reporting form as soon as possible (within 24 hours of learning of the possible Hy's law case) to the fax number on the form or the SAE fax number, even if no AE has occurred. If the event is serious, please complete the SAE form. The eCRF for possible Hy's law cases must be completed within 7 calendar days. Every effort to determine the cause of the liver enzyme abnormalities must be made, and close monitoring should be initiated in conjunction with the medical monitor and medical safety physician and in accordance with the FDA Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009. The participant should return to the study site and be evaluated as soon as possible, preferably within 48 hours from the time the investigator becomes aware of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

9.6 Procedures for Unmasking of Study Intervention

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Allergan Medical Monitor

prior to unblinding a participant's study intervention assignment unless this could delay emergency treatment of the participant. If a participant's study intervention assignment is unblinded, the Allergan Medical Monitor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation.

10. Administrative Items

10.1 Protection of Human Participants

10.1.1 Compliance with Informed Consent Regulations (US 21 CFR Part 50) and Relevant Country Regulations

Written informed consent is to be obtained from each participant prior to any study-related activities or procedures in the study, and/or from the participant's legally authorized representative.

The following process will be followed:

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study if required by the IRB.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

10.1.2 Compliance with IRB or IEC Regulations

This study is to be conducted in accordance with IRB regulations (US 21 CFR Part 56.103) or applicable IEC regulations. The investigator must obtain approval from a properly constituted IRB/IEC prior to initiating the study and re-approval or review at least annually. Allergan is to be notified immediately if the responsible IRB/IEC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/IEC correspondence with the investigator should be provided to Allergan.

10.1.3 Compliance with Good Clinical Practice

This protocol is to be conducted in accordance with the applicable GCP regulations and guidelines.

10.1.4 Compliance with Electronic Records; Electronic Signatures Regulations (US 21 CFR Part 11)

This study is to be conducted in compliance with the regulations on electronic records and electronic signature.

10.2 Financial Disclosure

Investigators and subinvestigators will provide Allergan with sufficient, accurate financial information as requested to allow Allergan to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.3 Changes to the Protocol

The investigator must not implement any deviation from or changes of the protocol without approval by Allergan and prior review and documented approval/favorable opinion from the IRB/IEC of a protocol amendment, except where necessary to eliminate immediate hazards to study participants, or when the changes involve only logistical or administrative aspects of the study (eg, change in monitors, change of telephone numbers).

10.4 Data Protection

Participants will be assigned a unique identifier. Any participant records or datasets that are transferred to Allergan will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by Allergan in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Allergan, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.5 Participant Confidentiality

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study intervention may ultimately be marketed, but the participant’s name will not be disclosed in these documents. The participant's name may be disclosed to the sponsor of the study, Allergan, or the governing health authorities or the FDA if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

10.5.1 Participant Privacy

Written authorization and other documentation in accordance with local privacy requirements (where applicable) is to be obtained from each participant prior to enrollment into the study, and/or from the participant's legally authorized representative in accordance with the applicable privacy requirements (eg, HIPAA).

In accordance with HIPAA requirements, additional purposes of this study may include publishing of anonymous participant data from the study.

10.6 Documentation

10.6.1 Source Documents

Source documents may include a participant's medical records, hospital charts, clinic charts, the investigator's participant study files, the eDiary, as well as the results of diagnostic tests

such as laboratory tests and electrocardiograms. The investigator's copy of the case report forms serves as part of the investigator's record of a participant's study-related data.

The following information should be entered into the participant's medical record:

- Participant’s name
- Participant’s contact information
- The date that the participant entered the study, participant number, study intervention kit numbers
- The study title and/or the protocol number of the study and the name of Allergan
- A statement that informed consent was obtained (including the date). A statement that written authorization or other local participant privacy required documentation for this study has been obtained (including the date).
- Dates of all participant visits
- Participant’s medical history
- Information regarding participant’s diagnosis of migraine headache
- All concurrent medications. (List all prescription and non-prescription medications being taken at the time of enrollment. At each subsequent visit, changes to the list of medications should be recorded).
- Occurrence and status of any AEs
- The date the participant exited the study, and a notation as to whether the participant completed the study or reason for discontinuation
- The results of laboratory tests performed by the site (eg, results of urine pregnancy tests)
- Key study variables

Source documentation practices must follow Section 4.0 of ICH E6, Good Clinical Practice: Consolidated Guidance and ALCOA, ie, records must be attributable, legible, contemporaneous, original and accurate.

10.6.2 Case Report Form Completion

The investigator is responsible for ensuring that data are properly recorded on each participant's eCRF and related documents. An investigator who has signed the protocol signature page should personally sign for the case report forms (as indicated in the case report forms) to ensure that the observations and findings are recorded on the case report forms correctly and completely. The eCRFs are to be submitted to Allergan in a timely manner at the completion of the study, or as otherwise specified by Allergan and will be maintained in a central data repository.

10.6.3 Study Summary

An investigator's summary will be provided to Allergan within a short time after the completion of the study, or as designated by Allergan. A summary is also to be provided to the responsible IRB/IEC.

10.6.4 Retention of Documentation

All study related correspondence, participant records, consent forms, participant privacy documentation, records of the distribution and use of all study interventions, and copies of eCRFs should be maintained on file.

For countries falling within the scope of the ICH guidelines, Allergan-specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by Allergan.

In addition, for countries not falling within the scope of the ICH guidelines, local regulatory requirements should be followed regarding the retention of clinical study documentation.

Allergan requires that it be notified in writing if the investigator wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

10.7 Labeling, Packaging, and Return or Disposal of Study Interventions

10.7.1 Labeling/Packaging

Study intervention will be supplied in blister cards and will be labeled with the protocol number, storage information, warning language, and instructions to take the tablets as directed. The card will also include the study intervention number. Immediately before dispensing the blister card, the investigator or designee will write the study center number, participant's initials and participant number, and date on the blister card.

10.7.2 Clinical Supply Inventory

The investigator must keep an accurate accounting of the number of intervention units received from Allergan, dispensed or administered to the participants, the number of units returned to the investigator by the participant (if applicable), and the number of units returned to Allergan during and at the completion of the study. A detailed inventory must be completed for the study intervention. The study intervention must be dispensed or administered only by an appropriately qualified person to participants in the study. The medication is to be used in accordance with the protocol for participants who are under the direct supervision of a study investigator.

10.7.3 Return or Disposal of Study Intervention and/or Supplies

All clinical study intervention and/or supplies will be returned to Allergan or Allergan designee for destruction.

10.8 Monitoring by the Sponsor

A representative of Allergan will monitor the study on a periodic basis. The determination of the extent and nature of monitoring will be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the study.

Authorized representatives of Allergan or regulatory authority representatives will conduct on-site visits to review, audit and copy study-related documents. These representatives will meet with the investigator(s) and appropriate staff at mutually convenient times to discuss study-related data and questions.

10.9 Handling of Biological Specimens

Urine pregnancy test kits will be provided by the central laboratory; all urine pregnancy testing will be administered on site according to instructions in the central laboratory manual.

Samples of blood and urine for evaluation of urine drug screen, hematology, blood chemistry, INR, urinalysis, and serology will be analyzed at a centralized clinical laboratory with certification from a recognized accreditation agency (eg, College of American Pathology or Clinical Laboratory Improvement Amendments certification).

Samples obtained from participants in the PK substudy will be stored at the centralized clinical laboratory until ready for PK analyses by Allergan or Allergan's designee using a validated method. This laboratory meets GLP requirements.

All samples will be returned to Allergan or Allergan's designee for destruction. Allergan shall have full ownership rights to any biological specimens/samples derived from the study. For additional details regarding handling of biological specimens please refer to the Study Reference Manual.

10.10 Publications

Allergan as the sponsor, has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allergan.

10.11 Coordinating Investigator

A signatory coordinating investigator will be designated prior to the writing of the clinical study report.

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12. Attachments

12.1 International Classification of Headache Disorders, 3rd Edition

1. Migraine
1.1 Migraine without aura
1.2 Migraine with aura
1.2.1 Migraine with typical aura
1.2.1.1 Typical aura with headache
1.2.1.2 Typical aura without headache
1.2.2 Migraine with brainstem aura
1.2.3 Hemiplegic migraine
1.2.3.1 Familial hemiplegic migraine (FHM)
1.2.3.1.1 Familial hemiplegic migraine type 1 (FHM1)
1.2.3.1.2 Familial hemiplegic migraine type 2 (FHM2)
1.2.3.1.3 Familial hemiplegic migraine type 3 (FHM3)
1.2.3.1.4 Familial hemiplegic migraine, other loci
1.2.3.2 Sporadic hemiplegic migraine (SHM)
1.2.4 Retinal migraine
1.3 Chronic migraine
1.4 Complications of migraine
1.4.1 Status migrainosus
1.4.2 Persistent aura without infarction
1.4.3 Migrainous infarction
1.4.4 Migraine aura-triggered seizure
1.5 Probable migraine
1.5.1 Probable migraine without aura
1.5.2 Probable migraine with aura
1.6 Episodic syndromes that may be associated with migraine
1.6.1 Recurrent gastrointestinal disturbance
1.6.1.1 Cyclical vomiting syndrome
1.6.1.2 Abdominal migraine
1.6.2 Benign paroxysmal vertigo
1.6.3 Benign paroxysmal torticollis

Coded elsewhere:

Migraine-like headache secondary to another disorder (*symptomatic migraine*) is coded as a secondary headache attributed to that disorder.

General comment

Primary or secondary headache or both? Three rules apply to migraine-like headache, according to circumstances.

1. When a *new headache with the characteristics of migraine* occurs for the first time in close temporal relation to another disorder known to cause headache, or fulfils other criteria for causation by that disorder, the new headache is coded as a secondary headache attributed to the causative disorder.
2. When *pre-existing migraine* becomes *chronic* in close temporal relation to such a causative disorder, both the initial migraine diagnosis and the secondary diagnosis should be given. 8.2 *Medication-overuse headache* is a particularly important example of this: both the migraine diagnosis (episodic or chronic) and the diagnosis 8.2 *Medication-overuse headache* should be given when medication overuse is present.
3. When *pre-existing migraine* is made *significantly worse* (usually meaning a twofold or greater increase in frequency and/or severity) in close temporal relation to such a causative disorder, both the initial migraine diagnosis and the secondary headache diagnosis should be given, provided that there is good evidence that the disorder can cause headache.

Introduction

Migraine is a common disabling primary headache disorder. Many epidemiological studies have documented its high prevalence and socio-economic and personal impacts. In the *Global Burden of Disease Study 2010* (GBD2010), it was ranked as the third most prevalent disorder in the world. In GBD2015, it was ranked the third-highest cause of disability worldwide in both males and females under the age of 50 years.

Migraine has two major types: 1.1 Migraine without aura is a clinical syndrome characterized by headache with specific features and associated symptoms; 1.2 *Migraine with aura* is primarily characterized by the transient focal neurological symptoms that usually precede or sometimes accompany the headache. Some patients also experience a prodromal phase, occurring hours or days before the headache, and/or a postdromal phase following headache resolution. Prodromal and postdromal symptoms include hyperactivity, hypoactivity, depression, cravings for particular foods, repetitive yawning, fatigue and neck stiffness and/or pain.

When a patient fulfils criteria for more than one type, subtype or subform of migraine, all should be diagnosed and coded. For example, a patient who has frequent attacks with aura but also some attacks without aura should be coded as 1.2 *Migraine with aura* and 1.1 *Migraine without aura*. However, since the diagnostic criteria for 1.3 *Chronic migraine* subsume attacks of all types, subtypes or subforms, additional coding is unnecessary for episodic subtypes of migraine.

1.1 Migraine without aura

Previously used terms: Common migraine; hemicrania simplex

Description: Recurrent headache disorder manifesting in attacks lasting 4–72 hours Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia.

Diagnostic criteria:

A. At least five attacks[1] fulfilling criteria B–D
B. Headache attacks lasting 4–72 hours (when untreated or unsuccessfully treated)[2,3]
C. Headache has at least two of the following four characteristics:
   1. unilateral location
   2. pulsating quality
   3. moderate or severe pain intensity
   4. aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
D. During headache at least one of the following:
   1. nausea and/or vomiting
   2. photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis.

Notes:

1. One or a few migraine attacks may be difficult to distinguish from symptomatic migraine-like attacks. Furthermore, the nature of a single or a few attacks may be difficult to understand. Therefore, at least five attacks are required. Individuals who otherwise meet criteria for 1.1 *Migraine without aura* but have had fewer than five attacks should be coded 1.5.1 *Probable migraine without aura*.
2. When the patient falls asleep during a migraine attack and wakes up without it, duration of the attack is reckoned until the time of awakening.
3. In children and adolescents (aged under 18 years), attacks may last 2–72 hours (the evidence for untreated durations of less than two hours in children has not been substantiated).

Comments: Migraine headache in children and adolescents (aged under 18 years) is more often bilateral than is the case in adults; unilateral pain usually emerges in late adolescence or early adult life. Migraine headache is usually frontotemporal. Occipital headache in *children* is rare and calls for diagnostic caution. A subset of otherwise typical patients have facial location of pain, which is called 'facial migraine' in the literature; there is no evidence that these patients form a separate subgroup of migraine patients. Prodromal symptoms may begin hours or a day or two before the other symptoms of a migraine attack without aura. They include various combinations of fatigue, diffculty in concentrating, neck stiffness, sensitivity to light and/or sound, nausea, blurred vision, yawning and pallor. Postdromal symptoms, most commonly feeling tired or weary, difficulty with concentration and neck stiffness, may follow resolution of the headache, persisting for up to 48 hours; these are less well studied.

Migraine attacks can be associated with cranial autonomic symptoms and symptoms of cutaneous allodynia.
In young children, photophobia and phonophobia may be inferred from their behaviour.
A minority (<10%) of women have attacks of migraine in association with the majority of their menstrual cycles; most of such attacks are without aura. Attacks during menstruation tend to be longer and accompanied by more severe nausea than attacks outside the menstrual cycle. ICHD-3 offers criteria for A1.1.1 *Pure menstrual migraine without aura*, A1.1.2 *Menstrually related migraine without aura* and A1.1.3 *Non-menstrual migraine without aura*, but in the Appendix because of uncertainty over whether they should be regarded as separate entities. Criteria are also offered for A1.2.0.1 *Pure menstrual migraine with aura*, A1.2.0.2 *Menstrually related migraine with aura* and A1.2.0.3 *Non-menstrual migraine with aura* to encourage better characterization of these uncommon subforms if they are separate entities.

Very frequent migraine attacks are distinguished as 1.3 *Chronic migraine*. When there is associated medication overuse, both of the diagnoses 1.3 *Chronic migraine* and 8.2 *Medication-overuse headache* should be applied. 1.1 *Migraine without aura* is the disease most prone to accelerate with frequent use of symptomatic medication. Regional cerebral blood flow imaging shows no changes suggestive of cortical spreading depression (CSD) during attacks of 1.1 *Migraine without aura*, although blood flow changes in the brainstem may occur, as may cortical changes secondary to pain activation. This contrasts with the pathognomonic spreading oligaemia of 1.2 *Migraine with aura*. While the bulk of the literature suggests that CSD does not occur in 1.1 *Migraine without aura*, some recent studies disagree. Furthermore, it has been suggested that glial waves or other cortical phenomena may be involved in 1.1 *Migraine without aura*. The messenger molecules nitric oxide (NO), serotonin (5-hydroxytryptamine;5-HT) and calcitonin gene-related peptide (CGRP) are involved. While the disease was previously regarded as primarily vascular, the importance of sensitization of pain pathways, and the possibility that attacks may originate in the central nervous system, have gained increasing attention over the last decades.

At the same time, the circuitry of migraine pain, the trigeminovascular system, and several aspects of its neurotransmission peripherally and in the trigeminal nucleus caudalis, central mesencephalic grey and thalamus, have been recognized. Highly receptor- specific acute medications including 5-$HT_{1B/D}$ receptor agonists

(triptans), 5-HT_{1F} receptor agonists and CGRP receptor antagonists have demonstrated efficacy in the acute treatment of migraine attacks. Because of their high receptor-specificity, their mechanisms of action provide new insight into migraine mechanisms. It is now clear that 1.1 *Migraine without aura* is a neurobiological disorder, while clinical as well as basic neuroscience studies continue to advance our knowledge of migraine mechanisms.

1.2 Migraine with aura

Previously used terms: Classic or classical migraine; ophthalmic, hemiparaesthetic, hemiplegic or aphasic migraine; migraine accompagnee; complicated migraine.

Description: Recurrent attacks, lasting minutes, of unilateral fully reversible visual, sensory or other central nervous system symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms.

Diagnostic criteria:

A. At least two attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura symptoms:
   1. visual
   2. sensory
   3. speech and/or language
   4. motor
   5. brainstem
   6. retinal
C. At least three of the following six characteristics:
   1. at least one aura symptom spreads gradually over ≥5 minutes
   2. two or more aura symptoms occur in succession
   3. each individual aura symptom lasts 5–60 minutes[1]
   4. at least one aura symptom is unilateral[2]
   5. at least one aura symptom is positive[3]
   6. the aura is accompanied, or followed within 60 minutes, by headache
D. Not better accounted for by another ICHD-3 diagnosis.

Notes:

1. When, for example, three symptoms occur during an aura, the acceptable maximal duration is 3 x 60 minutes. Motor symptoms may last up to 72 hours.
2. Aphasia is always regarded as a unilateral symptom; dysarthria may or may not be.
3. Scintillations and pins and needles are positive symptoms of aura.

Comments: Many patients who have migraine attacks with aura also have attacks without aura; they should be coded as both 1.2 *Migraine with aura* and 1.1 *Migraine without aura*.

Field testing has compared the diagnostic criteria for 1.2 *Migraine with aura* in the main body of ICHD-3 beta with those for A1.2 *Migraine with aura* in the Appendix. The latter performed better in distinguishing migraine with aura from transient ischaemic attacks. These are now adopted in ICHD-3, which no longer has Appendix criteria for this disorder.

The aura is the complex of neurological symptoms that occurs usually before the headache of 1.2 *Migraine with aura*, but it may begin after the headache phase has commenced or continue into the headache phase.
Visual aura is the most common type of aura, occurring in over 90% of patients with 1.2 *Migraine with aura*, at least in some attacks. It often presents as a fortification spectrum: a zigzag figure near the point of fixation that may gradually spread right or left and assume a laterally convex shape with an angulated scintillating edge, leaving absolute or variable degrees of relative scotoma in its wake. In other cases, scotoma without positive phenomena may occur; this is often perceived as being of acute onset but, on scrutiny, usually enlarges gradually. In children and adolescents, less typical bilateral visual symptoms occur that may represent an aura. A visual aura rating scale with high specificity and sensitivity has been developed and validated.
Next in frequency are sensory disturbances, in the form of pins and needles moving slowly from the point of origin and affecting a greater or smaller part of one side of the body, face and/or tongue. Numbness may occur in its wake, but numbness may also be the only symptom.
Less frequent are speech disturbances, usually aphasic but often hard to categorize.
Systematic studies have demonstrated that many patients with visual aura occasionally have symptoms in the extremities and/or speech symptoms. Conversely, patients with symptoms in the extremities and/or speech or language symptoms almost always also experience visual aura symptoms at least during some attacks. A distinction between migraine with visual aura, migraine with hemiparaesthetic aura and migraine with speech and/or language aura is probably artificial, and therefore not recognized in this classification: they are all coded as 1.2.1 *Migraine with typical aura.*

When aura symptoms are multiple, they usually follow one another in succession, beginning with visual, then sensory, then aphasic; but the reverse and other orders have been noted. The accepted duration for most aura symptoms is one hour, but motor symptoms are often longer lasting.

Patients with aura symptoms arising from the brainstem are coded as 1.2.2 *Migraine with brainstem aura*, but they almost always have additional typical aura symptoms. When the aura includes motor weakness, the disorder should be coded as 1.2.3 *Hemiplegic migraine* or one of its subforms. 1.2.3 *Hemiplegic migraine* is classified as a separate subtype because of genetic and pathophysiological differences from 1.2.1 *Migraine with typical aura*. Patients with 1.2.3 *Hemiplegic migraine* often have brainstem symptoms in addition.

Patients often find it hard to describe their aura symptoms, in which case they should be instructed to time and record them prospectively. The clinical picture then becomes clearer. Common mistakes are incorrect reports of lateralization, of sudden rather than gradual onset and of monocular rather than homonymous visual disturbances, as well as of duration of aura and mistaking sensory loss for weakness. After an initial consultation, use of an aura diary may clarify the diagnosis.

Migraine aura is sometimes associated with a headache that does not fulfill criteria for 1.1 *Migraine without aura*, but this is still regarded as a migraine headache because of its relation to the aura. In other cases, migraine aura may occur without headache.

Before or simultaneously with the onset of aura symptoms, regional cerebral blood flow is decreased in the cortex corresponding to the clinically affected area and often over a wider area. Blood flow reduction usually starts posteriorly and spreads anteriorly, and is usually above the ischaemic threshold. After one to several hours, gradual transition into hyperaemia occurs in the same region. Cortical spreading depression of Leao is the likely underlying mechanism.

The previously defined syndromes, *migraine with prolonged aura* and *migraine with acute-onset aura*, have been abandoned. It is not rare for aura to last more than one hour but, in most such cases, patients have at least two of the other characteristics of criterion C. Even when most of a patient's attacks do not fulfil criterion C, it is usual that other attacks fulfil criteria for one of the recognized subtypes or subforms of 1.2 *Migraine with aura*, and this should be the diagnosis. The few other cases should be coded to 1.5.2 *Probable migraine with aura*, specifying the atypical feature (prolonged aura or acute-onset aura) in parenthesis. The diagnosis is usually evident after a careful history alone, although there are rare secondary mimics including carotid dissection, arteriovenous malformation and seizure.

Prodromal symptoms may begin hours or a day or two before the other symptoms of a migraine attack with aura. They include various combinations of fatigue, difficulty in concentrating, neck stiffness, sensitivity to light and/or sound, nausea, blurred vision, yawning and pallor. The term 'prodrome', which has replaced 'premonitory phase' or 'premonitory symptoms', does not include aura. Postdromal symptoms, most commonly feeling tired or weary, difficulty with concentration and neck stiffness, may follow resolution of the headache, persisting for up to 48 hours; these are less well studied.

1.2.1 Migraine with typical aura

Description: Migraine with aura, in which aura consists of visual and/or sensory and/or speech/language symptoms, but no motor weakness, and is characterized by gradual development, duration of each symptom no longer than one hour, a mix of positive and negative features and complete reversibility

Diagnostic criteria:

A. Attacks fulfilling criteria for 1.2 *Migraine with aura* and criterion B below
B. Aura with both of the following:
   1. fully reversible visual, sensory and/or speech/ language symptoms
   2. no motor, brainstem or retinal symptoms.

1.2.1.1 Typical aura with headache

Description: Migraine with typical aura in which aura is accompanied or followed within 60 minutes by headache with or without migraine characteristics.

Diagnostic criteria:

A. Attacks fulfilling criteria for 1.2.1 *Migraine with typical aura* and criterion B below
B. Headache, with or without migraine characteristics, accompanies or follows the aura within 60 minutes.

1.2.1.2 Typical aura without headache

Description: Migraine with typical aura in which aura is neither accompanied nor followed by headache of any sort.

Diagnostic criteria:

A. Attacks fulfilling criteria for 1.2.1 *Migraine with typical aura* and criterion B below
B. No headache accompanies or follows the aura within 60 minutes.

Comments: In some patients, a typical aura is always followed by migraine headache, but many patients have, in addition, attacks with aura followed by a less distinct headache or even without headache. A number of patients have, exclusively, 1.2.1.2 *Typical aura without headache*.

In the absence of headache fulfilling criteria for 1.1 *Migraine without aura*, the precise diagnosis of aura and its distinction from mimics that may signal serious disease (e.g. transient ischaemic attack) becomes more difficult and often requires investigation. When aura occurs for the first time after age 40, when symptoms are exclusively negative (e.g. hemianopia) or when aura is prolonged or very short, other causes, particularly transient ischaemic attacks, should be ruled out.

1.2.2 Migraine with brainstem aura

Previously used terms: Basilar artery migraine; basilar migraine; basilar-type migraine.

Description: Migraine with aura symptoms clearly originating from the brainstem, but no motor weakness.

Diagnostic criteria:

A. Attacks fulfilling criteria for 1.2 *Migraine with aura* and criterion B below
B. Aura with both of the following:
    1. at least two of the following fully reversible brainstem symptoms:
        a. dysarthria[1]
        b. vertigo[2]
        c. tinnitus
        d. hypacusis[3]
        e. diplopia[4]
        f. ataxia not attributable to sensory deficit
        g. decreased level of consciousness (GCS ≤13)[5]
    2. no motor[6] or retinal symptoms.

Notes:

1. Dysarthria should be distinguished from aphasia.
2. Vertigo does not embrace and should be distinguished from dizziness.
3. This criterion is not fulfilled by sensations of ear fullness.
4. Diplopia does not embrace (or exclude) blurred vision.
5. The Glasgow Coma Scale (GCS) score may have been assessed during admission; alternatively, deficits clearly described by the patient allow GCS estimation.
6. When motor symptoms are present, code as 1.2.3 *Hemiplegic migraine*.

Comments: Originally the terms *basilar artery migraine* or *basilar migraine* were used but, since involvement of the basilar artery is unlikely, the term *migraine with brainstem aura* is preferred.

There are typical aura symptoms in addition to the brainstem symptoms during most attacks. Many patients who have attacks with brainstem aura also report other attacks with typical aura and should be coded for both 1.2.1 *Migraine with typical aura* and 1.2.2 *Migraine with brainstem aura*.
Many of the symptoms listed under criterion B1 may occur with anxiety and hyperventilation, and are therefore subject to misinterpretation.

1.2.3 Hemiplegic[1] migraine

Description: Migraine with aura including motor weakness.

Diagnostic criteria:

A. Attacks fulfilling criteria for 1.2 *Migraine with aura* and criterion B below
B. Aura consisting of both of the following:
    1. fully reversible motor weakness[2]
    2. fully reversible visual, sensory and/or speech/ language symptoms.

Notes:

1. The term *plegic* means paralysis in most languages, but most attacks are characterized by motor weakness.
2. Motor symptoms generally last less than 72 hours but, in some patients, motor weakness may persist for weeks.

Comment: It may be difficult to distinguish weakness from sensory loss.

1.2.3.1 Familial hemiplegic migraine (FHM)

Description: Migraine with aura including motor weakness, and at least one first- or second-degree relative has migraine aura including motor weakness.

Diagnostic criteria:

A. Attacks fulfilling criteria for 1.2.3 *Hemiplegic migraine*
B. At least one first- or second-degree relative has had attacks fulfilling criteria for 1.2.3 *Hemiplegic migraine*.

Comments: New genetic data have allowed a more precise definition of 1.2.3.1 *Familial hemiplegic migraine* than was previously possible. Specific genetic subforms have been identified: in FHM1 there are mutations in the *CACNA1A* gene (coding for a calcium channel) on chromosome 19; in FHM2 there are mutations in the *ATP1A2* gene (coding for a K/Na-ATPase) on chromosome 1; and in FHM3 there are mutations in the *SCN1A* gene (coding for a sodium channel) on chromosome 2. There may be other loci not yet identified. When genetic testing is done, the genetic subform (if discovered) should be specified at the fifth digit.

It has been shown that 1.2.3.1 *Familial hemiplegic migraine* very often presents with brainstem symptoms in addition to the typical aura symptoms, and that headache almost always occurs. Rarely, during FHM attacks, disturbances of consciousness (sometimes including coma), confusion, fever and cerebrospinal fluid (CSF) pleocytosis can occur. 1.2.3.1 *Familial hemiplegic migraine* may be mistaken for epilepsy and treated (unsuccessfully) as such. FHM attacks can be triggered by (mild) head trauma. In approximately 50% of FHM families, chronic progressive cerebellar ataxia occurs independently of the migraine attacks.

1.2.3.1.1 Familial hemiplegic migraine type 1 (FHM1)

Diagnostic criteria:

A. Attacks fulfilling criteria for 1.2.3.1 *Familial hemiplegic migraine*
B. A mutation on the *CACNA1A* gene has been demonstrated.

1.2.3.1.2 Familial hemiplegic migraine type 2 (FHM2)

Diagnostic criteria:

A. Attacks fulfilling criteria for 1.2.3.1 *Familial hemiplegic migraine*
B. A mutation on the *ATP1A2* gene has been demonstrated.

1.2.3.1.3 Familial hemiplegic migraine type 3 (FHM3)

Diagnostic criteria:

A. Attacks fulfilling criteria for 1.2.3.1 *Familial hemiplegic migraine*
B. A mutation on the *SCN1A* gene has been demonstrated.

1.2.3.1.4 Familial hemiplegic migraine, other loci

Diagnostic criteria:

A. Attacks fulfilling criteria for 1.2.3.1 *Familial hemiplegic migraine*
B. Genetic testing has demonstrated no mutation on the *CACNA1A*, *ATP1A2* or *SCN1A* genes.

1.2.3.2 Sporadic hemiplegic migraine (SHM)

Description: Migraine with aura including motor weakness, and no first- or second-degree relative has migraine aura including motor weakness.

Diagnostic criteria:

A. Attacks fulfilling criteria for 1.2.3 *Hemiplegic migraine*
B. No first- or second-degree relative fulfils criteria for 1.2.3 *Hemiplegic migraine.*

Comments: Epidemiological studies have shown that sporadic cases occur with approximately the same prevalence as familial cases.

The attacks in 1.2.3.2 *Sporadic hemiplegic migraine* have the same clinical characteristics as those in 1.2.3.1 *Familial hemiplegic migraine*. Some apparently sporadic cases have known FHM mutations and, in some, a first- or second-degree relative later develops hemiplegic migraine, thus completing fulfilment of the

criteria for 1.2.3.1 *Familial hemiplegic migraine* and requiring a change of diagnosis.

Sporadic cases usually require neuroimaging and other tests to rule out other causes. A lumbar puncture may be necessary to rule out 7.3.5 *Syndrome of transient headache and neurological deficits with cerebrospinal fluid lymphocytosis (HaNDL)*.

1.2.4 Retinal migraine

Description: Repeated attacks of monocular visual disturbance, including scintillations, scotomata or blindness, associated with migraine headache.

Diagnostic criteria:

A. Attacks fulfilling criteria for 1.2 *Migraine with aura* and criterion B below

B. Aura characterized by both of the following:
   1. fully reversible, monocular, positive and/or negative visual phenomena (e.g. scintillations, scotomata or blindness) confirmed during an attack by either or both of the following:
      a. clinical visual field examination
      b. the patient's drawing of a monocular field defect (made after clear instruction)
   2. at least two of the following:
      a. spreading gradually over ≥5 minutes
      b. symptoms last 5–60 minutes
      c. accompanied, or followed within 60 minutes, by headache

C. Not better accounted for by another ICHD-3 diagnosis, and other causes of amaurosis fugax have been excluded.

Comments: Some patients who complain of monocular visual disturbance in fact have hemianopia. Some cases without headache have been reported, but migraine as the underlying aetiology cannot be ascertained.

1.2.4 *Retinal migraine* is an extremely rare cause of transient monocular visual loss. Cases of permanent monocular visual loss associated with migraine have been described. Appropriate investigations are required to exclude other causes of transient monocular blindness.

1.3 Chronic migraine

Description: Headache occurring on 15 or more days/ month for more than three months, which, on at least eight days/month, has the features of migraine headache.

Diagnostic criteria:

A. Headache (migraine-like or tension-type-like[1]) on ≥15 days/month for >3 months, and fulfilling criteria B and C

B. Occurring in a patient who has had at least five attacks fulfilling criteria B–D for 1.1 *Migraine without aura* and/or criteria B and C for 1.2 *Migraine with aura*

C. On ≥8 days/month for >3 months, fulfilling any of the following[2]:
   1. criteria C and D for 1.1 *Migraine without aura*
   2. criteria B and C for 1.2 *Migraine with aura*
   3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative

D. Not better accounted for by another ICHD-3 diagnosis.[3–5]

Notes:

1. The reason for singling out 1.3 *Chronic migraine* from types of episodic migraine is that it is impossible to distinguish the individual episodes of headache in patients with such frequent or continuous headaches. In fact, the characteristics of the headache may change not only from day to day but even within the same day. Such patients are extremely difficult to keep medication-free in order to observe the natural history of the headache. In this situation, attacks with and those without aura are both counted, as are both migraine-like and tension-type-like headaches (but not secondary headaches).
2. Characterization of frequently recurring headache generally requires a headache diary to record information on pain and associated symptoms day by day for at least one month.
3. Because tension-type-like headache is within the diagnostic criteria for 1.3 *Chronic migraine*, this diagnosis excludes the diagnosis of 2. *Tension-type headache* or its types.
4. 4.10 *New daily persistent headache* may have features suggestive of 1.3 *Chronic migraine*. The latter disorder evolves over time from 1.1 *Migraine without aura* and/ or 1.2 *Migraine with aura*; therefore, when these criteria A–C are fulfilled by headache that, unambiguously, is daily and unremitting from <24 hours after its first onset, code as 4.10 *New daily persistent headache*. When the manner of onset is not

remembered or is otherwise uncertain, code as 1.3 *Chronic migraine*.

5. The most common cause of symptoms suggestive of chronic migraine is medication overuse, as defined under 8.2 *Medication-overuse headache*. Around 50% of patients apparently with 1.3 *Chronic migraine* revert to an episodic migraine type after drug withdrawal; such patients are in a sense wrongly diagnosed as 1.3 *Chronic migraine*. Equally, many patients apparently overusing medication do not improve after drug withdrawal; the diagnosis of 8.2 *Medication-overuse headache* may be inappropriate for these (assuming that chronicity induced by drug overuse is always reversible). For these reasons, and because of the general rule to apply all relevant diagnoses, patients meeting criteria for 1.3 *Chronic migraine* and for 8.2 *Medication-overuse headache* should be coded for both. After drug withdrawal, migraine will either revert to an episodic type or remain chronic and should be re-diagnosed accordingly; in the latter case, the diagnosis of 8.2 *Medication-overuse headache* may be rescinded.

1.4 Complications of migraine

Comment: Code separately for both the migraine type, subtype or subform and for the complication.

1.4.1 Status migrainosus

Description: A debilitating migraine attack lasting for more than 72 hours.

Diagnostic criteria:

A. A headache attack fulfilling criteria B and C

B. Occurring in a patient with 1.1 *Migraine without aura* and/or 1.2 *Migraine with aura*, and typical of previous attacks except for its duration and severity

C. Both of the following characteristics:
   1. unremitting for >72 hours[1]
   2. pain and/or associated symptoms are debilitating[2]

D. Not better accounted for by another ICHD-3 diagnosis.

Notes:

1. Remissions of up to 12 hours due to medication or sleep are accepted.
2. Milder cases, not meeting criterion C2, are coded 1.5.1 *Probable migraine without aura*.

Comment: Headache with the features of 1.4.1 *Status migrainosus* may often be caused by medication overuse. When headache in these circumstances meets the criteria for 8.2 *Medication-overuse headache*, code for this disorder and the relevant type or subtype of migraine but not for 1.4.1 *Status migrainosus*. When overuse of medication is of shorter duration than three months, code for the appropriate migraine type or subtype(s) only.

1.4.2 Persistent aura without infarction

Description: Aura symptoms persisting for one week or more without evidence of infarction on neuroimaging.

Diagnostic criteria:

A. Aura fulfilling criterion B

B. Occurring in a patient with 1.2 *Migraine with aura* and typical of previous auras except that one or more aura symptoms persists for ≥1 week

C. Neuroimaging shows no evidence of infarction

D. Not better accounted for by another ICHD-3 diagnosis.

Comments: Persistent aura symptoms are rare but well documented. They are often bilateral and may last for months or years. The one-week minimum in criterion B is based on the opinion of experts and should be formally studied.
Diagnostic work-up must distinguish 1.4.2 *Persistent aura without infarction* from 1.4.3 *Migrainous infarction* and exclude symptomatic aura due to cerebral infarction of other causes. Attacks with prolonged aura lasting less than one week and not fulfilling criteria for 1.2.1 *Migraine with typical aura* are coded 1.5.2 *Probable migraine with aura.*

1.4.3 Migrainous infarction

Description: One or more migraine aura symptoms occurring in association with an ischaemic brain lesion in the appropriate territory demonstrated by neuroimaging, with onset during the course of a typical migraine with aura attack.

Diagnostic criteria:

A. A migraine attack fulfilling criteria B and C
B. Occurring in a patient with 1.2 *Migraine with aura* and typical of previous attacks except that one or more aura symptoms persists for >60 minutes[1]
C. Neuroimaging demonstrates ischaemic infarction in a relevant area
D. Not better accounted for by another ICHD-3 diagnosis.

Note:

1. There may be additional symptoms attributable to the infarction.

Comments: Ischaemic stroke in a migraine sufferer may be categorized as cerebral infarction of other cause coexisting with 1. *Migraine*, cerebral infarction of other cause presenting with symptoms resembling 1.2 *Migraine with aura*, or cerebral infarction occurring during the course of a typical attack of 1.2 *Migraine with aura.* Only the last fulfils criteria for 1.4.3 *Migrainous infarction*.
1.4.3 Migrainous infarction mostly occurs in the posterior circulation and in younger women. A twofold increased risk of ischaemic stroke in patients with 1.2 *Migraine with aura* has been demonstrated in several population-based studies. However, it should be noted that these infarctions are not migrainous infarctions. The mechanisms of the increased risk of ischaemic stroke in migraine sufferers remain unclear; likewise, the relationship between increased risk and frequency of aura and the nature of aura symptoms denoting the increase in risk are unknown. Most studies have shown a lack of association between 1.1 *Migraine without aura* and ischaemic stroke.

1.4.4 Migraine aura-triggered seizure

Description: A seizure triggered by an attack of migraine with aura.

Diagnostic criteria:

A. A seizure fulfilling diagnostic criteria for one type of epileptic attack, and criterion B below
B. Occurring in a patient with 1.2 *Migraine with aura*, and during or within one hour after an attack of migraine with aura
C. Not better accounted for by another ICHD-3 diagnosis.

Comment: Migraine and epilepsy are prototypical examples of paroxysmal brain disorders. While migraine-like headaches are quite frequently seen in the epileptic post-ictal period, sometimes a seizure occurs during or following a migraine attack. This phenomenon, sometimes referred to as *migralepsy*, is a rare event, originally described in patients with 1.2 *Migraine with aura*. Evidence of an association with 1.1 *Migraine without aura* is lacking.

1.5 Probable migraine

Previously used term: Migrainous disorder.

Coded elsewhere: Migraine-like headache secondary to another disorder (*symptomatic migraine*) is coded according to that disorder.

Description: Migraine-like attacks missing one of the features required to fulfil all criteria for a type or subtype of migraine coded above, and not fulfilling criteria for another headache disorder.

Diagnostic criteria:

A. Attacks fulfilling all but one of criteria A-D for 1.1 *Migraine without aura*, or all but one of criteria A–C for 1.2 *Migraine with aura*
B. Not fulfilling ICHD-3 criteria for any other headache disorder
C. Not better accounted for by another ICHD-3 diagnosis.

Comment: In making a headache diagnosis, attacks that fulfil criteria for both 2. *Tension-type headache* and 1.5 *Probable migraine* are coded as the former in accordance with the general rule that a definite diagnosis always trumps a probable diagnosis. However, in patients who already have a migraine diagnosis, and where the issue is to count the number of attacks they are having (e.g. as an outcome measure in a drug trial), attacks fulfilling criteria for 1.5 *Probable migraine* should be counted as migraine. The reason for this is that mild migraine attacks, or attacks treated early, often do not achieve all characteristics necessary for a migraine attack diagnosis but nevertheless respond to specific migraine treatments.

1.5.1 Probable migraine without aura Diagnostic criteria:

A. Attacks fulfilling all but one of criteria A-D for 1.1 *Migraine without aura*
B. Not fulfilling ICHD-3 criteria for any other headache disorder

C. Not better accounted for by another ICHD-3 diagnosis.

1.5.2 Probable migraine with aura

Diagnostic criteria:

A. Attacks fulfilling all but one of criteria A–C for 1.2 *Migraine with aura* or any of its subtypes
B. Not fulfilling ICHD-3 criteria for any other headache disorder
C. Not better accounted for by another ICHD-3 diagnosis.

1.6 Episodic syndromes that may be associated with migraine

Previously used terms: Childhood periodic syndromes; periodic syndromes of childhood.

Comments: This group of disorders occurs in patients who also have 1.1 *Migraine without aura* or 1.2 *Migraine with aura*, or who have an increased likelihood to develop either of these disorders. Although historically noted to occur in childhood, they may also occur in adults.

Additional conditions that may also occur in these patients include episodes of motion sickness and periodic sleep disorders including sleep walking, sleep talking, night terrors and bruxism.

1.6.1 Recurrent gastrointestinal disturbance

Previously used terms: Chronic abdominal pain; functional abdominal pain; functional dyspepsia; irritable bowel syndrome; functional abdominal pain syndrome.

Description: Recurrent episodic attacks of abdominal pain and/or discomfort, nausea and/or vomiting, occurring infrequently, chronically or at predictable intervals, that may be associated with migraine.

Diagnostic criteria:

A. At least five attacks with distinct episodes of abdominal pain and/or discomfort and/or nausea and/or vomiting
B. Normal gastrointestinal examination and evaluation
C. Not attributed to another disorder.

1.6.1.1 Cyclic vomiting syndrome

Description: Recurrent episodic attacks of intense nausea and vomiting, usually stereotypical in the individual and with predictable timing of episodes. Attacks may be associated with pallor and lethargy. There is complete resolution of symptoms between attacks.

Diagnostic criteria:

A. At least five attacks of intense nausea and vomiting, fulfilling criteria B and C
B. Stereotypical in the individual patient and recurring with predictable periodicity
C. All of the following:
   1. nausea and vomiting occur at least four times per hour
   2. attacks last for ≥1 hour, up to 10 days
   3. attacks occur ≥1 week apart
D. Complete freedom from symptoms between attacks
E. Not attributed to another disorder.[1]

Note:

1. In particular, history and physical examination do not show signs of gastrointestinal disease.

Comments: 1.6.1.1 *Cyclic vomiting syndrome* is typically a self-limiting episodic condition occurring in childhood, with periods of complete normality between episodes. The cyclic nature is the hallmark, and attacks are predictable.

This disorder was first included as a childhood periodic syndrome in ICHD-II. The clinical features of this syndrome resemble those found in association with migraine headaches, and multiple threads of research over the last years have suggested that 1.6.1.1 *Cyclic vomiting syndrome* is a condition related to migraine.

1.6.1.2 Abdominal migraine

Description: An idiopathic disorder seen mainly in children as recurrent attacks of moderate to severe midline abdominal pain, associated with vasomotor symptoms, nausea and vomiting, lasting 2–72 hours and with normality between episodes. Headache does not occur during these episodes.

Diagnostic criteria:

A. At least five attacks of abdominal pain, fulfilling criteria B–D
B. Pain has at least two of the following three characteristics:
   1. midline location, periumbilical or poorly localized
   2. dull or 'just sore' quality
   3. moderate or severe intensity
C. At least two of the following four associated symptoms or signs:
   1. anorexia
   2. nausea
   3. vomiting
   4. pallor
D. Attacks last 2–72 hours when untreated or unsuccessfully treated
E. Complete freedom from symptoms between attacks
F. Not attributed to another disorder.[1]

Note:

1. In particular, history and physical examination do not show signs of gastrointestinal or renal disease, or such disease has been ruled out by appropriate investigations.

Comments: Pain of 1.6.1.2 *Abdominal migraine* is severe enough to interfere with normal daily activities.
In young children, the presence of headache is often overlooked. A careful history of presence or absence of headache must be taken and, when headache or head pain during attacks is identified, a diagnosis of 1.1 *Migraine without aura* should be considered.
Children may find it difficult to distinguish anorexia from nausea. Pallor is often accompanied by dark shadows under the eyes. In a few patients, flushing is the predominant vasomotor phenomenon.
Most children with abdominal migraine will develop migraine headache later in life.

1.6.2 Benign paroxysmal vertigo

Description: A disorder characterized by recurrent brief attacks of vertigo, occurring without warning and resolving spontaneously, in otherwise healthy children.

Diagnostic criteria:

A. At least five attacks fulfilling criteria B and C
B. Vertigo[1] occurring without warning, maximal at onset and resolving spontaneously after minutes to hours without loss of consciousness
C. At least one of the following five associated symptoms or signs:
   1. nystagmus
   2. ataxia
   3. vomiting
   4. pallor
   5. fearfulness
D. Normal neurological examination and audiometric and vestibular functions between attacks
E. Not attributed to another disorder.[2]

Notes:

1. Young children with vertigo may not be able to describe vertiginous symptoms. Parental observation of episodic periods of unsteadiness may be interpreted as vertigo in young children.
2. In particular, posterior fossa tumours, seizures and vestibular disorders have been excluded.

Comment: The relationship between 1.6.2 *Benign paroxysmal vertigo* and A1.6.6 *Vestibular migraine* (see Appendix) needs to be further examined.

1.6.3 Benign paroxysmal torticollis

Description: Recurrent episodes of head tilt to one side, perhaps with slight rotation, which remit spontaneously. The condition occurs in infants and small children, with onset in the first year.

Diagnostic criteria:

A. Recurrent attacks[1] in a young child, fulfilling criteria B and C
B. Tilt of the head to either side, with or without slight rotation, remitting spontaneously after minutes to days
C. At least one of the following five associated symptoms or signs:
   1. pallor
   2. irritability
   3. malaise
   4. vomiting
   5. ataxia[2]
D. Normal neurological examination between attacks
E. Not attributed to another disorder.[3]

Notes:

1. Attacks tend to recur monthly.
2. Ataxia is more likely in older children within the affected age group.
3. The differential diagnosis includes gastro-oesophageal reflux, idiopathic torsional dystonia and complex partial seizure, but particular attention must be paid to the posterior fossa and craniocervical junction where congenital or acquired lesions may produce torticollis.

Comments: The child's head can be returned to the neutral position during attacks: some resistance may be encountered but can be overcome.
These observations need further validation by patient diaries, structured interviews and longitudinal data collection.
1.6.3 *Benign paroxysmal torticollis* may evolve into 1.6.2 *Benign paroxysmal vertigo* or 1.2 *Migraine with aura* (particularly 1.2.2 *Migraine with brainstem aura*) or cease without further symptoms.

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12.2 Examples of Prohibited Medications

The following medications are prohibited 30 days prior to screening and throughout the study period:

- Strong OATP1B1 inhibitors eg, Gemfibrozil (Lopid™)
- CBD oil

	Strong/moderate CYP3A4 inducers	Strong/moderate CYP3A4 inhibitors
Anti-depressants/ Anti-anxiety	Barbiturates: Amobarbital (Amytal™) Aprobarbital (Alurate™) Butalbital (Fiorinal™, Fioricet™) Butabarbital (Busodium™ Butisol™) Mephobarbital (Mebaral™) Pentobarbital (Nembutal™) Phenobarbital (Luminal™ Solfoton™) Secobarbital (Seconal™)	Nefazodone (Serzone™)
Anti-seizure	Carbamazepine (Atretol™, Carbatrol™, Epitol™, Equetro™, Tegretol™) Oxcarbazepine (Trileptal™) Phenytoin (Dilantin™, Phenytek™) Primidone (Myidone™, Mysoline™)	
Diabetes	Pioglitazone (Actos™) Troglitazone (Rezulin™, Resulin™)	
Antiemetic		Aprepitant (Emend™)
Anti-hypertension		Diltiazem (Cardizem™) Verapamil (Calan™, Calan SR™)
Glucocorticoid (Systemic)	Betamethasone (Celestone™) Dexamethasone (Baycadron™, DexPak™) Hydrocortisone (Cortef™) Methylprednisolone (Medrol™) Prednisolone (Prelone™) Prednisone (Deltasone™) Triamcinolone (Kenalog™)	
Antibiotics	Rifabutin (Mycobutin™) Rifampicin/ Rifampin (Rifadin™, Rifater™, Rimactane™)	Erythromycin (Benzamycin™, EryTab™) Clarithromycin (Biaxin™) Telithromycin (Ketek™)
Anti-fungal		Fluconazole (Diflucan™, Trican™) Itraconazole (Sporanox™) Ketoconazole (Nizoral™)

	Strong/moderate CYP3A4 inducers	Strong/moderate CYP3A4 inhibitors
Anti-HIV	Efavirenz (Stocrin™, Sustiva™) Nevirapine (Viramune™)	Indinavir (Crixivan™) Nelfinavir (Viracept™) Ritonavir (Norvir™) Saquinavir (Fortovase™, Invirase™)
Immune Suppressant		Cyclosporine - Oral/IV only (Neoral™, Sandimmune™)
Others	St. John's Wort Enzalutamide (Xtandi™) Modafinil (Provigil™) Armodafinil (Nuvigil™)	Buprenorphine (Cizol™, Subutex™, Suboxone™) Quinine

Drugs with narrow therapeutic margins with potential for CYP drug interactions	Warfarin (Coumadin™) Digoxin (Digitek™, Lanoxin™, Digox™) Cisapride (Prepulsid™, Propulsid™) Pimozide (Orap™)
Drugs with demonstrated efficacy for the prevention of migraine	Topiramate (Topamax™) Valproic acid, sodium valproate, divalproex sodium (Depakote™) Amitriptyline (Elavil™) Nortriptyline (Pamelor™) Metoprolol (Lopressor™, Toprol™) Atenolol (Tenormin™) Nadolol (Corgard™) Propranolol (Inderal™) Timolol (Apo-Timol™) Flunarizine (Sibelium™) Candesartan (Atacand™) Lisinopril (Zestril™, Prinivil™) Desvenlafaxine (Pristiq™) Venlafaxine (Effexor™)
Non-pharmacologic headache interventions	Acupuncture Non-invasive neuromodulation devices (eg, transcutaneous supraorbital neurostimulator, single-pulse transcranial magnetic stimulator, vagus nerve stimulator). Cranial traction Nociceptive trigeminal inhibition Occipital nerve block treatments Dental splints for headache

The following treatments are prohibited 6 months prior to screening and throughout the study period:

- Therapeutic or cosmetic botulinum toxin injections (eg, Dysport®, BOTOX®, Xeomin®, Myobloc®, Jeuveau™) into areas of the head, face, or neck.
- Injectable monoclonal antibodies blocking the CGRP pathway (eg, Aimovig™, Emgality™, Ajovy®).

12.3 List of Migraine-preventive Medications with Proven Efficacy and Criteria for Determining Inadequate Response to a Prior Migraine-preventive Medication

12.3.1 List of Migraine-preventive Medications with Proven Efficacy

Below is a list of migraine-preventive medications considered effective or probably effective sorted by mechanism of action. Of note, topiramate and valproic acid derivatives are considered separate categories. A history of inadequate response to greater than 4 of these medications (2 of which have different mechanisms of action) will exclude the participant from the study.

Pharmacologic Category	**Drug Name**
Antiepileptic	Divalproex sodium (valproic acid, sodium valproate) Topiramate
Tricyclin antidepressant	Amitriptyline Nortriptyline
Beta-blockers	Metoprolol Bisoprolol Atenolol Nadolol Propranolol Timolol
Calcium channel blocker	Flunarizine
Angiotensin receptor blocker (ARB)	Candesartan
Angiotensin converting enzyme (ACE) inhibitor	Lisinopril
Serotonin-norepinephrine reuptake inhibitor (SNRI)	Desvenlafaxine Venlafaxine
Miscellaneous (non-US only)	Country approved products for migraine prevention (eg, oxetrone, pizotifen)

Source: Evers 2009, Hoffmann 2014, Schürks 2008, Silberstein 2012, Steiner 2007

12.3.2 Criteria for Determining Inadequate Response to a Prior Migraine Preventive Medication

Failure of a migraine-preventive medication can be assessed on the basis of efficacy or tolerability and is based on investigator judgment. The criteria below should be used to determine eligibility related to the number of prior failed migraine-preventive medications with unique mechanisms of action.

For efficacy:

- Failure is defined as a < 50% reduction in migraine days per month per investigator judgment and participant interview.
- Medications must have been started within the past 7 years.

For tolerability:

- Failure is defined as discontinuation of a drug treatment due to adverse effects.
- In assessing failure of a migraine preventive drug on the basis of inadequate tolerability, the entire medical history can be considered. For example, a participant who tried and discontinued topiramate 10 years ago for cognitive clouding should be considered to have failed this treatment.

12.4 Glossary of Abbreviations

Term/ Abbreviation	Definition
ACE	angiotensin-converting enzyme
AE	adverse event
AIM-D	Activity Impairment in Migraine – Diary
ALT	alanine aminotransferase
ARB	angiotensin receptor blocker
ASC-12	Allodynia Symptom Checklist
AST	aspartate aminotransferase
$AUC_{0\text{-}Tau}$	area under the concentration-time curve over the dosing interval
BID	twice-daily
BP	blood pressure
CBD	cannabidiol
CFR	Code of Federal Regulations
CGRP	calcitonin gene-related peptide
C_{min}	minimum plasma drug concentration
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
CYP3A4	cytochrome P450 3A4
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
EM	episodic migraine
EMA	European Medicines Agency
EQ-5D-5L	European Quality of Life – 5-Dimensional – 5-Level
ET	early termination
eTablet	electronic tablet
EU	European Union
FDA	Food and Drug Administration
GBD2010	Global Burden of Disease Survey 2010
GCP	Good Clinical Practices
GI	gastrointestinal
GLP	Good Laboratory Practice
HIPAA	Health Insurance Portability and Accountability Act
HIT-6	Headache Impact Test
HIV	human immunodeficiency virus
HSG	hysterosalpingogram
IB	investigators brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ICHD-3	International Classification of Headache Disorders criteria, 3rd edition
IEC	Independent Ethics Committee

Term/ Abbreviation	Definition
IgG	immunoglobulin G
IgM	immunoglobulin M
IHS	International Headache Society
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine system
IV	intravenous
IWRS	interactive web response system
MAR	missing-at-random
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MIDAS	Migraine Disability Assessment
mITT	modified intent-to-treat
MMRM	mixed-effects model for repeated measures
MNAR	missing-not-at-random
MSQ v2.1	Migraine Specific Quality of Life Questionnaire, version 2.1
NA	not applicable
NSAID	nonsteroidal anti-inflammatory drug
OATP1B1	organic-anion-transporting polypeptide 1B1
PD	pharmacodynamic
PGIC	Patient Global Impression of Change
PGI-S	Patient Global Impression - Severity
PK	pharmacokinetic
PMM	pattern-mixture model
PRO	Patient-Reported Outcome
PROMIS-PI	Patient-Reported Outcomes Measurement Information System Pain Interference-Short Form 6a
QTcF	QT interval corrected for heart rate using the Fridericia formula
SAE	serious adverse event
SAP	statistical analysis plan
SNRI	serotonin–norepinephrine reuptake inhibitors
SOC	system organ class
SSRI	selective serotonin reuptake inhibitors
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
VAS	visual analogue scale
VCT	Verified Clinical Trials
WPAI:MIGRAINE	Work Productivity and Activity Impairment Questionnaire: Migraine v2.0.

12.5 Protocol Amendment 1 Summary

Title: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-group Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Atogepant for the Prevention of Migraine in Participants With Episodic Migraine (Advance)

Protocol 3101-301-002

Date of Amendment: 30 November 2018

Amendment Summary

This amendment includes changes made to Protocol 3101-301-002 dated 25 September 2018. The protocol was amended to:

- Add an atogepant treatment 10 mg arm
- Increase the sample size of each treatment arm to 218 participants per arm
- Change the MSQ Role-Function-Restrictive domain score at Week 12 from an additional efficacy endpoint to a secondary efficacy endpoint
- Modify the e-Diary prorating rules
- Clarification of exclusion criterion related to Visit 1 laboratory results
- Added injectable monoclonal antibodies to the list of prohibited medications
- Clarification of the primary efficacy analyses
- Added Week 16 assessments to specified Additional Efficacy Variables of EQ-5D-5L and MSQ v2.1
- Defined criteria for determining inadequate response to prior migraine-preventive medication

The table below provides details related to content changes that were made in the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
Global Protocol Addition	Added the atogepant 10 mg arm	To reflect the addition of the atogepant 10 mg treatment arm
Protocol Title Page	Added "Protocol Amendment 1 Date" to the title page	To reflect the approval date of Amendment 1
Protocol Summary, Study Design; Section 3, Study Design; Section 5.4, Intervention Allocation Ratio; Section 5.5 Method for Assignment to Intervention Groups/Randomization	Updated the study randomization ratio to 1:1:1:1	To reflect the addition of the atogepant 10 mg treatment arm
Protocol Summary, Study Design; General Statistical Methods and Types of Analyses. Section 3, Study Design; Section 5.4, Intervention Allocation Ratio; Section 7.6, Sample Size Calculation	Revised the planned sample size for each treatment arm from 200 to 218	To provide sufficient power for secondary endpoints
Protocol Summary, Study Population Characteristics; Section 3, Study Design; Section 4.1, Number of Participants	Increased the number of planned participants to 872 and the number of study sites to approximately 110 sites in the United States.	To provide sufficient power for secondary endpoints
Protocol Summary, General Statistical Methods and Types of Analyses; Section 7.3.1, Primary Efficacy Analyses	Updated the primary comparison between treatment groups to include prior exposure to migraine medication as a categorical fixed effect: The primary comparison between treatment groups will be done by a mixed effects model for repeated measures (MMRM) of the change from baseline. The statistical model will include treatment group, visit, ***prior exposure (yes/no) to a migraine prevention medication with proven efficacy***, and treatment group by visit interaction as categorical fixed effects.	Clarification
Section 7.3.1, Primary Efficacy Analyses	Updated information regarding the supportive primary analysis: ***A supportive analysis will be performed on the primary endpoint using an analysis of covariance (ANCOVA) model. The response variable for the ANCOVA model is the change from baseline in the calculated average monthly migraine days during the 12-week treatment period for each participant. The ANCOVA model includes terms for treatment, prior exposure (yes/no) to a migraine prevention medication with proven efficacy,***	Clarification

Section	Revision	Rationale
	and baseline score. The treatment difference for atogepant doses versus placebo will be estimated and reported along with the corresponding 95% CI and nominal p-value for superiority testing. Details of the sensitivity ***and supportive analyses*** will be provided in the statistical analysis plan.	
Protocol Summary, General Statistical Methods and Types of Analyses; Section. 7.2.2 Secondary Efficacy Variables; Section 7.3.2 Secondary Efficacy Analyses	Changed the endpoint of change from baseline in mean MSQ v2.1 Role Function-Restrictive subscale score of at Week 12 from an additional efficacy endpoint to a secondary efficacy endpoint: • ***Change from baseline in mean MSQ v2.1 Role Function-Restrictive subscale score at Week 12***	Per Regulatory Agency feedback
Protocol Summary, General Statistical Methods and Types of Analyses; Section 7.3.2 Secondary Efficacy Analyses	Revised the responder analysis for the secondary endpoint: A generalized linear mixed model will be used to analyze the proportion of 50% responders as repeated measures across the 12-week treatment period. This model assumes a binary distribution for the response and uses a logit link. The analysis model will include treatment group, visit, ***prior exposure (yes/no) to a migraine prevention medication with proven efficacy, and*** treatment group by visit interaction as categorical fixed effects...	Clarification
Protocol Summary, General Statistical Methods and Types of Analyses; Section 7.3.2 Secondary Efficacy Analyses	Updated responder analysis to note that an unstructured covariance matrix will be used in the model: Participants will be included as random effects ***with unstructured covariance matrix*** in the model to account for the correlation among repeated measurements.	Clarification
Protocol Summary, General Statistical Methods and Types of Analyses; Section 7.3.2 Secondary Efficacy Analyses	Updated responder analysis to include prior migraine medication exposure as a categorical fixed effect: The analysis model will include treatment group, visit, ***prior exposure (yes/no) to a migraine prevention medication with proven efficacy***, and treatment group-by-visit interaction as categorical fixed effects; baseline value and baseline-by-visit interaction will be included as covariates.	Clarification
Section 7.3.3, Additional Efficacy Analyses	Removed analysis related to variables with ordered response categories: Other efficacy variables will be analyzed as follows: • ~~For variables with ordered response categories, the baseline score will be included as a covariate in an MMRM analysis of the ranked changes from baseline. These analyses will be performed similarly to the primary MMRM, with focus again on the pairwise contrasts of each dose group to placebo.~~	Clarification

Section	Revision	Rationale
Protocol Summary, Sample Size Calculation; Section 7.6 Sample Size Calculation, Table 7-1	Revised the sample size calculation as follows: A sample size of ***218***~~00~~ randomized participants per treatment group will provide at least 9~~8~~***7***% power to detect the treatment difference between each of the **3**~~2~~ atogepant doses (assumed equally effective) and placebo for the primary efficacy endpoint. This sample size was selected to provide sufficient power for the primary efficacy endpoint and the first 3 secondary endpoints.	To provide power to detect treatment differences and reflect the addition of the atogepant 10 mg arm
Protocol Summary, Sample Size Calculation; Section 7.6 Sample Size Calculation	Modified the assumptions for power calculations: ...In particular, the assumed treatment difference from placebo in change from baseline in mean monthly migraine days across the 12 week treatment period is -1.5 days, and the standard deviation is 3.5 days; and 2) ***the study statistical testing plan controls the overall type I error at 5%. The power calculations of the primary and secondary endpoints have taken the multiple comparisons into consideration by testing each dose versus placebo at a 0.0167 significance level, 2-sided. Once the primary endpoint for each dose is significant at 0.0167, 2-sided, the secondary endpoints will be tested sequentially***.~~the test is 2-sided and at overall significance level of 0.05. Simulation was used to estimate the power of the primary and secondary endpoints adjusting for the multiple comparisons based on a graphical approach.~~	Clarification
Section 4.3, Exclusion Criteria	Exclusion Criterion 14 was revised as follows: 14. Clinically significant laboratory values ~~at Visit 1 including but not limited to~~ OR any of the following laboratory values at Visit 1: o ALT or AST > 1 × ULN OR o Total bilirubin > 1 × ULN (except for participants with a diagnosis of Gilbert's disease) OR o Serum albumin < 2.8 g/dL.	Clarification
Section 4.4.2, Prohibited Medications/Treatments; Attachment 12.2, Examples of Prohibited Medications	Added the following to the list of medications prohibited during the study: ***Injectable monoclonal antibodies blocking the CGRP pathway (eg, Aimovig™, Emgality™, Ajovy®)***	Per Expert Consultant feedback
Section 5.1, Study Interventions and Formulations	Added formulation information for the atogepant 10 mg intervention	To reflect the addition of the atogepant 10 mg treatment arm
Section 5.2, Control Intervention	Added formulation information for the atogepant-10-mg-matching placebo intervention	To reflect the addition of the atogepant 10 mg matching placebo
Section 5.3, Methods for Masking/Blinding	Added the following paragraph: ***All participants will be instructed to take study intervention once a day (3 tablets) at approximately the same time each day. Participants will therefore, receive either placebo, atogepant 10 mg, atogepant 30 mg, or atogepant 60 mg once a day.***	Clarification

Section	Revision	Rationale
Section 7.2 Collection and Derivation of Primary and Secondary Efficacy Assessments (last paragraph)	Modified prorating rules for eDiary information: ...If any postbaseline eDiary window for a participant has at least ***14*** ~~2~~ but less than 28 days of reported data, the prorated approach will be used. If a participant reports less than ***14*** ~~2~~ days of headache data...	Clarification
Section 7.2.3, Additional Efficacy Variables	Added Week 16 endpoint to: • Change from baseline in EQ-5D-5L descriptive system index score • Change from baseline in EQ-5D-5L VAS score • Change from baseline in MSQ v2.1 Role Function Preventive domain score • Change from baseline in the MSQ v2.1 Role Function Restrictive domain score Change from baseline in MSQ v2.1 Emotional-Function domain score	For consistency with the Schedule of Assessments
Attachment 12.3.2, Criteria for Determining Inadequate Response to a Prior Migraine-Preventive Medication	Added new attachment detailing the criteria used to determine eligibility related to the number of prior failed migraine-preventive medications	Clarification

12.6 Protocol Amendment 2 Summary

Title: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-group Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Atogepant for the Prevention of Migraine in Participants With Episodic Migraine (ADVANCE)

Protocol 3101-301-002

Date of Amendment: 25 February 2019

Amendment Summary

This amendment includes changes made to Protocol 3101-301-002 Amendment 1 dated 30 November 2018. The protocol was amended to:

- Update the study number for the rollover study
- Update the subgroup analysis
- Correct the number of migraine preventative medications which would be exclusionary and update the prohibited medications
- To add an additional efficacy variable
- To clarify how efficacy variables will be analyzed

The table below provides details related to content changes that were made in the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
Protocol Title Page	Added "Amendment 2 Date"	To reflect the approval date of Amendment 2
Protocol Summary	Updated study number and name for rollover study: Study 3101-30~~2~~9-002 (longterm **extension** study).	To clarify that participants will rollover into Study 3101-309-002
Protocol Summary, Table 1 Schedule of Visits and Procedures	Deleted footnote j from C-SSRS (eTablet)	For clarity
Protocol Summary, Table 1 Schedule of Visits and Procedures, footnote b	Updated study number and name for rollover study: Study 3101-30~~2~~9-002 (longterm **extension** study).	To clarify that participants will rollover into Study 3101-309-002
Section 3 Study Design, paragraph 5	Updated study number and name for rollover study: Study 3101-30~~2~~9-002 (longterm **extension** study).	To clarify that participants will rollover into Study 3101-309-002
Section 4.4.2 Prohibited Medications/Treatments	Updated prohibited medications list: • **CBD oil.** • Injectable monoclonal antibodies blocking the CGRP pathway (eg, Aimovig™, Emgality™, Ajovy®) **within 6 months prior to Visit 1 and through the study period**. • Therapeutic or cosmetic botulinum toxin injections (eg, Dysport®, BOTOX®, Xeomin®, **Myobloc®, Jeuveau™**) into areas of the head, face, or neck within 6 months prior to Visit 1 and throughout the study period.	For clarity
Section 6.5.1 Adverse Events	Deleted: For events noted as SAEs, Allergan must be notified immediately to meet their reporting obligations to appropriate regulatory authorities. ~~For participants who will rollover to Study 3101-302-002, AEs will be collected until participants sin the ICF for Study 3101-302-002.~~	For clarity, since participants will no longer rollover into Study 3101-302-002, and AEs are collected differently
Section 7.2.3 Additional Efficacy Variables	Added: • **Change from baseline in weekly migraine days at Weeks 1-4.**	To add an efficacy variable added

Section	Revision	Rationale
Section 7.3.3 Additional Efficacy Analyses	Added: • **For weekly data analysis purposes, baseline is defined to be the baseline derived in monthly basis divided by 4, and change from baseline in the weekly migraine days will be calculated for consecutive 7-day periods beginning with Day 1. Subsequent to treatment start, the number of headache days will be counted in successive and non-overlapping 1-week (ie, 7-day) windows. Headaches that continue into a subsequent 1-week period will be counted (with recorded severity and duration) as occurring in each period. If any postbaseline eDiary window for a participant has at least 4, but less than 7 days, of reported data, the prorated approach will be used. If a participant reports less than 4 days of headache data, the participant's observed counts in that particular 7-day eDiary window will be set to missing for that window.**	For clarity

Section	Revision	Rationale
Section 7.5 Subgroup Analyses	Updated how subgroups will be defined: Subgroup analysis based on prior exposure **(yes/no)** to a migraine prevention medication with proven efficacy **will be performed for the following efficacy endpoints:** • **Change from baseline in mean monthly migraine days across the 12-week treatment period.** • **Change from baseline in mean monthly headache days across the 12-week treatment period.** • **Change from baseline in mean monthly acute medications use days across the 12-week treatment period.** • **Proportion of participants with at least a 50% reduction in mean monthly migraine days across the 12-week treatment period.** • **Proportion of participants with at least a 75% reduction in mean monthly migraine days across the 12-week treatment period.** • **Proportion of participants with 100% reduction in mean monthly migraine days across the 12-week treatment period.** **Additional subgroup analyses for primary efficacy endpoint will be performed by the presence of allodynia based on the ASC-12 sum score (absence: 0 to 2, presence: > 2) and by the number of failed prior migraine prevention medication of proven efficacy (failed 1 or more medications, failed no medications, or no prior exposure).**	For clarity

Section	Revision	Rationale
Section 8.4.2.2 Visits 3 to 6 (Weeks 2 to 8)	Added: • Prior to any other test or evaluations, administer PRO measures, including: HIT-6, PGI-S, WPAI:MIGRAINE, Patient Satisfaction with Study Medication, EQ-5D-5L, MSQ v2.1, and PROMIS-PI**, as outlined in Table 1, Schedule of Visits and Procedures**.	For clarity
Section 9.1.1 Adverse Event (AE), paragraph 4	Deleted: These will be collected at the timepoints specified in the schedule of visits and procedures (Table 1), and as observed or reported spontaneously by study participants. ~~For participants who will rollover to Study 3101-302-002, AEs will be collected until the participant signs the ICF for Study 3101-302-002.~~ Investigators are not obligated to actively seek AE information after conclusion of the study participation.	For clarity, since participants will no longer rollover into Study 3101-302-002, and AEs are collected differently
9.1.5 Follow-up of Adverse Events and Serious Adverse Events	Updated bullet 3 • **Prior to database lock, new or updated information will be recorded in the originally completed eCRF. If the event is an SAE, it will also need to be reported on the SAE reporting form. Post database lock, new or updated SAE information will only be reported on the SAE reporting form.** ~~New or updated information will be recorded in the originally completed eCRF.~~	For clarity
Section 12.2 Examples of Prohibited Medications	Added CBD oil	For clarity and internal consistency
Section 12.2 Examples of Prohibited Medications	Aligned examples with the body of the protocol: • **Therapeutic or cosmetic botulinum toxin injections (eg, Dysport®, BOTOX®, Xeomin®, Myobloc®, Jeuveau™)** into areas of the head, face, or neck. • **Injectable monoclonal antibodies blocking the CGRP pathway (eg, Aimovig™, Emgality™, Ajovy®)**	
Section 12.3.1 List of Migraine-preventative Medications with Proven Efficacy	Corrected the number of migraine-preventative medications a participant may use before being excluded from the study: A history of inadequate response to **greater than** 4 ~~or more~~ of these medications (2 of which have different mechanisms of action) will exclude the participant from the study.	For clarity and internal consistency
Section 12.3.1 List of Migraine-preventative Medications with Proven Efficacy	Added language to clarify that miscellaneous referred to non-US countries only.	For clarity

Section	Revision	Rationale
Section 12.4 Glossary of Abbreviations	Added CBD.	CBD added to protocol

12.7 Protocol Amendment 3 Summary

Title: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-group Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Atogepant for the Prevention of Migraine in Participants With Episodic Migraine (ADVANCE)

Protocol 3101-301-002

Date of Amendment: 14 May 2020

Amendment Summary

This amendment includes changes made to Protocol 3101-301-002 Amendment 2 dated 25 February 2019. The protocol was amended to:

- To eliminate immediate potential hazards to participants and study staff due to the COVID-19 pandemic while ensuring participant safety and maintaining data integrity, the protocol was updated to allow investigators/appropriately designated study staff to perform study visits remotely (as described in Table 2 Schedule of Visits and Procedures for Visits Conducted Remotely Due to the COVID-19 Pandemic), as follows:
    - Visits 3-6 can be conducted remotely if participants are unable to attend in-person due to the COVID-19 pandemic.
    - Visit 7/ET can be conducted remotely if participants are unable to attend in-person due to the COVID-19 pandemic. If Visit 7/ET is conducted remotely, the participant will not be eligible to roll over into Study 3101-309-002; therefore, Visit 8 (Follow-up/End of Study) should be conducted remotely as part of Study 3101-301-002.
    - Visit 8/Follow-up/End of Study should be conducted remotely for all participants in all cases.
    - Safety assessments to be completed at remote study visits include assessment of AEs, concomitant medications, pregnancy test results review, and the C-SSRS. For participants who have a study visit replaced by a remote study visit, all missed in-person safety assessments (clinical laboratory determinations, vital signs, and ECGs) will be collected at the next in-person visit.

  - To ensure patient safety, remote study visits can be performed for up to 8 weeks at the discretion of the Investigator after which, participants who cannot attend in-person for a study visit must be discontinued from the study.

- Update statistical analyses based on feedback from and discussion with FDA.
- Update Section 7.4 Off-treatment Hypothetical Estimand
- Clarify the definition of mITT population
- Separate the efficacy variables and other health outcome variables into two subsections.
- Update description of the AIM-D health outcomes measure and endpoints

The table below provides details related to content changes that were made in the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	**Revision**	**Rationale**
Protocol Title Page	Added Amendment 3 date Updated USA agent address	To reflect the approval of Amendment 3 Update
Table 1 Schedule of Visits and Procedures for In-Person Visits Conducted Prior to or During the COVID-19 Pandemic	Added "for In-Person Visits Conducted Prior to or During the COVID-19 Pandemic" to table title. Footnote "b" clarifies that during the COVID-19 pandemic, Visit 8 (Follow-up/End of Study) should be conducted remotely for all participants in all cases.	Clarification
Protocol Summary Table 2 Schedule of Visits and Procedures for Visits Conducted Remotely Due to the COVID-19 Pandemic Section 3 Study Design Section 8 Study Visit Schedule and Procedures Section 8.4 Visits and Associated Procedures Section 8.4.2.2 Visits 3 to 6 (Weeks 2 to 8) Section 8.4.2.3 Visit 7/Early Termination (Week 12)	New tabular summary of visits and procedures added to describe assessments/procedures to be performed at study visits conducted remotely due to the COVID-19 pandemic, as follows: Visits 3-6 and Visit 7/ET can be conducted remotely if participants are unable to attend in-person due to the COVID-19 pandemic. If Visit 7/ET is conducted remotely, the participant will not be eligible to roll over into Study 3101-309-002; therefore, Visit 8 (Follow-up/End of Study) should be conducted as part of Study 3101-301-002 Visit 8/Follow-up/End of Study should be conducted remotely for all participants in all cases. Safety assessments to be completed at remote study visits include assessment of AEs, concomitant medications, pregnancy test results review, and the C-SSRS. To ensure patient safety, remote study visits can be	To eliminate immediate potential hazards to participants and study staff due to the COVID-19 pandemic while ensuring participant safety and maintaining data integrity.

Section	Revision	Rationale
Section 8.4.3.1 Visit 8 (End of Study) Week 16 Conducted Remotely (Due to the COVID-19 Pandemic) Section 8.4.3.2 Visit 8 (End of Study) Week 16 Conducted During In-Person Visit (Prior to the COVID-19 Pandemic)	performed for up to 8 weeks at the discretion of the Investigator after which, participants who cannot attend in-person for a study visit must be discontinued from the study.	
Section 5.5 Method for Assignment to Intervention Groups/Randomization	Added bolded text: **For study visits conducted remotely due to the COVID-19 pandemic (Table 2), study intervention, can be shipped to participants via an overnight courier or provided curbside. Study medication to cover 1 additional remote study visit may be dispensed.**	To provide instructions for shipment of study intervention for study visits conducted remotely due t the COVID-19 pandemic.
Protocol Summary Table 1 Section 6.1 Efficacy Measures Section 6.2.1 Activity Impairment in Migraine – Diary (AIM-D) Section 6.2.2 Activity Level and Activity Limitation Section 6.7 Summary of Methods of Data Collection Section 7.2.3 Additional Efficacy Variables	Updated description of AIM-D Patient Difficulty in Concentrating and Difficulty in Thinking Clearly items are no longer considered stand-alone items but part of the AIM-D, thus these endpoints were removed	Based on psychometric (quantitative) analyses, AIM-D consists of two domains, performance of daily activities (7 items including patient difficulty in concentrating and difficulty in thinking clearly) and physical impairment (4 items).
Protocol Summary Section 7.1 Analysis Population	Added bolded text: All efficacy analyses will be performed using the mITT population, consisting of all randomized participants who received at least 1 dose of study intervention, had an evaluable baseline period of eDiary data and had at least 1 evaluable post-baseline 4-week period (Weeks 1 to 4, 5 to 8, and 9 to 12) of eDiary data **during the double-blind treatment period.** Added the detailed definition of primary efficacy analysis population for off-treatment estimand in support of EU filing	To clarify the definition of the mITT population. To clarify the primary efficacy analysis population in support of EU filing.
Section 7.2 Collection and Derivation of Efficacy Assessments	Added bolded text: Change from baseline will be calculated for consecutive 28-day periods beginning with **the date of first dose of study intervention.**	To clarify the starting day for postbaseline month calculation

Section	Revision	Rationale
Protocol Summary Section 7.2.2. Secondary Efficacy Variables	Elevated the endpoint "Change from baseline in MSQ v2.1 Role Function-Restrictive domain score at Week 12" above the AIM-D related endpoints Updated: ~~Proportion of participants with a~~ **A**t least a 50% reduction in **3-month average of** ~~mean~~ monthly migraine days ~~across the 12-week treatment period.~~	Update the order for secondary efficacy variables To clarify that 50% responder will be assessed for each individual. The related summary statistics are unchanged.
Section 7.2.3 Additional Efficacy Variables	Added bolded text: Additional efficacy endpoints for the United States and the EU **are provided below. Related analysis will be documented in the clinical study report SAP**. Updated 25%, 75% and 100% responders in 3-month average of monthly migraine days Modified multiple endpoint names by removing "Proportion of participants" Added Section 7.2.3.1 to classify other health outcome variables Removed the following endpoints: Change from baseline in monthly headache-free days at Weeks 1-4, 5-8, 9-12, and average across the 12-week treatment period. Change from baseline in monthly headache day pain intensity at Weeks 1-4, 5-8, 9-12, and average across the 12-week treatment period. Added endpoint: • **Participant having a migraine day on the day of initial dose and on each day of the 6 days post the initial dose**	Clarification To clarify that responder will be defined for each individual. To clarify the corresponding endpoints will be assessed for each individual. To classify other health outcomes together because related analyses will be described in the health economics and outcomes research SAP To remove redundancy because monthly headache free days will be complementary to monthly headache day, and headache pain intensity can be interpreted using monthly moderate/severe days. To evaluate onset of effect
Section 7.3.1 Primary Efficacy Analyses	Added bolded text: • **This is the primary analysis method for the primary efficacy endpoint in support of US filing. Only data collected during the double-blind period will be included in the analysis. Participants are always analyzed based on the treatment group assigned by randomization.**	Clarification
7.3.1.1 Sensitivity Analyses in Missing Data Handling 7.1.3.2 Sensitivity Analysis for Possible Violation of Normality Assumption	Reorganized section and added subsections 7.3.1.1 and 7.1.3.2 Added 2 sensitivity analyses (bolded text): • **Within-group Imputation Based on Observed Data** • **MMRM Based on Primary Measures Collected during the Double-blind and Follow-up Periods** Provided more detail for pattern-mixture model and renamed it "Copy-reference Approach".	Clarification of sensitivity analyses Added additional sensitivity analyses based on the feedback from a Type C meeting with FDA.

Section	Revision	Rationale
Protocol Summary Section 7.3.2 Secondary Efficacy Analyses	The analysis method for 50% responder was updated from generalized linear- mixed model to logistic regression model. Updated the reference	The logistic regression model is valid for one-time assessment (3-month average of 12 weeks) on each participant. Clarification
Section 7.3.3 Additional Efficacy Analysis	Removed text in strikethrough font: Descriptive statistics will be provided by visit for each efficacy variable by treatment group. Analysis of some variables will be limited to descriptive summary statistics. ~~For ASC-12, the number and percentage of randomized participants will be summarized by the presence of allodynia as measured by the sum of score (absence: 0 to 2, presence: > 2).~~	Clarification
Section 7.4 Off-treatment Hypothetical Estimand	Section name updated: **Off-treatment Hypothetical** Estimand ~~Framework for EMA~~ Added bolded text: **This section defines an estimand, termed as off-treatment hypothetical estimand, which will be the primary estimand in support of EU filing and serve as one sensitivity analysis in support of US filing.**	Clarification
7.4.1 Treatment Condition of Interest	Added subsection. The subsequent subsection numbers were updated.	To align with ICH E9R1 (issued on Nov 20, 2019) Section A.3.3.
7.4.4 Accounting of Intercurrent Events	Updated section, as follows: • **Participants who started a new migraine prophylaxis treatment during the double-blind or safety follow-up period will have their data during the safety follow-up period after starting the new migraine prophylaxis treatment excluded from the analysis.** • Participants who discontinue study treatment due to all reasons other than **starting a new migraine** prophylaxis ~~switching~~ treatment will have their data collected after discontinuation of study treatment, and those off-treatment data will be included in the analysis. ~~Participants with missing data up to the 12-week treatment period will have their data imputed using participants in the same treatment group who provide data while off study treatment.~~ Detailed methods and procedures will be documented in the statistical analysis plan prior to study completion.	Clarified accounting of intercurrent events. Proposal deleted due to infeasibility for the following reasons: 1) Data exploration revealed a relative low dropout rate (10%); 2) there are insufficient patients with observations during the follow-up period.

Section	Revision	Rationale
7.4.5 Population-level Summary	Added bolded text: **Participants are always analyzed based on their treatment assignment by randomization. To obtain the estimate of treatment effect defined in the off-treatment hypothetical estimand, a MMRM similar to the primary analysis specified in Section 7.3.1 will be performed on observed data including both on-treatment and off-treatment monthly migraine days.**	To propose the analysis method to obtain the population-level summary for the primary endpoint.
Section 7.4.6: **Off-treatment Hypothetical** Estimand Approach for the Secondary Endpoints	Updated section title and text: The secondary endpoint of 50% responders will be derived using ~~the imputed~~ **both on-treatment and off-treatment observed** data as defined in the primary endpoint above. The population-level summary for this endpoint is the odds ratio for each atogepant group relative to placebo.	Clarification
7.5 Subgroup Analyses	Updated 3 bullets as follows: • P~~roportion of participants with at least a~~ ≥50% reduction in **3-month average of** ~~mean~~ monthly migraine days ~~across the 12-week treatment period.~~ • P~~roportion of participants with at least a~~ ≥75% reduction in **3-month average of** ~~mean~~ monthly migraine days ~~across the 12-week treatment period.~~ • P~~roportion of participants with at least a~~ ≥ 100% reduction in **3-month average of** ~~mean~~ monthly migraine days ~~across the 12-week treatment period.~~ **Subgroup analyses for primary efficacy endpoint based on demographic factors (age, sex, race) will be provided in the integrated summary of efficacy to facilitate the comparison across pivotal studies.** ~~Additional subgroup analyses for primary efficacy endpoint will be performed by the presence of allodynia based on the ASC-12 sum score (absence: 0 to 2, presence: > 2) and by the number of failed prior migraine prevention medication of proven efficacy (failed 1 or more medications, failed no medications, or no prior exposure).~~	Modified the description of responders to be consistent with Sections 7.2.2 and 7.2.3 To clarify the location of subgroup analyses on age, gender and race. Clarification

1 Title Page

STATISTICAL ANALYSIS PLAN

A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF ORAL ATOGEPANT FOR THE PREVENTION OF MIGRAINE IN PARTICIPANTS WITH EPISODIC MIGRAINE (ADVANCE)

Final SAP Date: 13 MAR 2019

Amendment 1: 25 JUN 2020

Protocol Number:	3101-301-002
Development Phase:	3
Product Name:	AGN-241689
Study Statistician:	[redacted]
Sponsor Name and Legal Registered Address:	Allergan Pharmaceuticals International Limited [redacted]

2 Table of Contents

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3 List of Abbreviations and Definition of Terms

Table 3–1 Abbreviations and Definitions of Terms

Abbreviation/Term	Definition
AE	adverse event
AIM-D	Activity Impairment in Migraine - Diary
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
C-SSRS	Columbia–Suicide Severity Rating Scale
DB	double-blind
eCRF	electronic case report form
ePRO	electronic patient report outcome
ECG	electrocardiogram, electrocardiographic
ET	early termination
HIT-6	Headache Impact Test
INR	international normalized ratio
ITT	intent-to-treat
IWRS	interactive web response system
mITT	modified intent-to-treat
MedDRA	Medication Dictionary for Regulatory Activities
MIDAS	Migraine Disability Assessment
MMRM	mixed-effects model for repeated measures
MSQ	Migraine Specific Quality of Life Questionnaire
PCS	potentially clinically significant
PDRS	protocol deviation requirement specification
PGIC	Patient Global Impression of Change
PGI-S	Patient Global Impression - Severity
PID	participant identification
PT	preferred term
Q1	first quartile (25th percentile of the data)
Q3	third quartile (75th percentile of the data)
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula (QTcB = QT/(RR)½)
QTcF	QT interval corrected for heart rate using the Fridericia formula (QTcF = QT/(RR)⅓)
SAE	serious adverse event
SAP	statistical analysis plan
SI	Le Système International d'Unités (International System of Units)
SOC	standard of care
TBL	total bilirubin
TEAE	treatment-emergent adverse event
WHO	World Health Organization
WPAI-MIGRAINE	Work Productivity and Activity Impairment Questionnaire: Migraine v2.0

4 Introduction

This statistical analysis plan (SAP) details comprehensive, technical specifications of the statistical analyses of the efficacy and safety data outlined and/or specified in the protocol amendment #3 (dated 14 May 2020) of Study 3101-301-002. Specifications of tables, figures, and data listings are contained in a separate document.

This study is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study conducted in the United States and will enroll approximately 872 participants from approximately 110 sites. Participants will be randomized to one of four treatment arms (placebo, atogepant 10 mg, atogepant 30 mg, and atogepant 60 mg) in a 1:1:1:1 ratio. Approximately 70% of randomized participants will have taken at least 1 prior migraine prevention medication with proven efficacy. Randomization will be stratified based on prior exposure (yes/no) to a migraine prevention medication with proven efficacy.

The study will consist of a 4-week screening and baseline period, a 12-week double-blind treatment period, and a follow up period of 4 additional weeks, for a total duration of 20 weeks. Participant participation will begin with a 4-week screening/baseline period. Participants who complete the 4-week screening/baseline period and meet all entry criteria will be randomized to the double-blind treatment period of the study at Visit 2 (Randomization Visit). The double-blind treatment period will last 12 weeks, with a subsequent follow-up period of 4 additional weeks. There will be 8 scheduled clinic visits: Visit 1 (Screening/Baseline), Visit 2 (Randomization), Visit 3 (Week 2), Visit 4 (Week 4), Visit 5 (Week 6), Visit 6 (Week 8), Visit 7/ET (Week 12), and Visit 8 (Follow-up). The Visit 8 (Follow-up) must be completed for all participants who take at least one dose of study intervention, except for participants rolling over into Study 3101-309-002 (long-term safety extension study). For these participants Visit 8 is not required, as the Follow-up Visit will be performed in the long-term safety study. For participants who screen fail for the long-term safety, the Follow-up Visit must be completed.

Per study design (Protocol Sections 8.4.3.2 and 8.8), eDiary data will be collected for participants who early terminated from the double-blind treatment period during the 4 weeks between V7 (Early termination visit) and V8 (Follow-up Visit).

After the last patient first visit on January 31,2020, COVID-19 pandemic emerged. The Section 0 is added to specify analyses for evaluating the impact of COVID-19.

Figure 4-1 Study Design

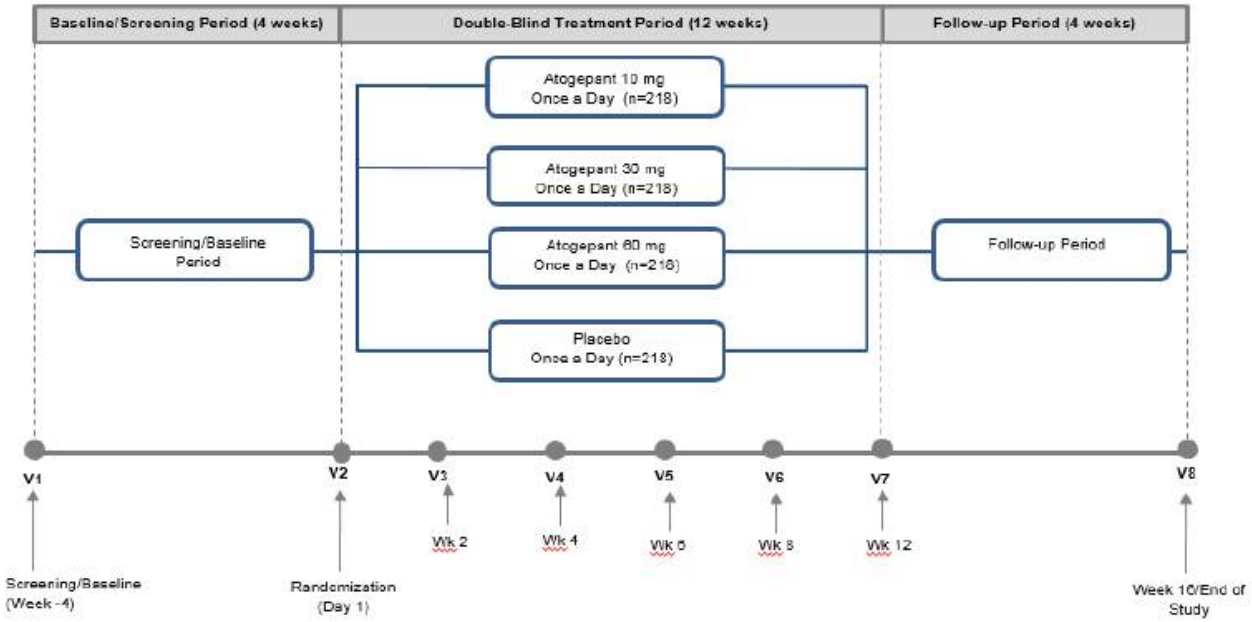


Table 4–1 Schedule of Visits and Procedures for In-Person Visits Conducted Prior to or During the COVID-19 Pandemic

Study Period	**Screening Period (4 weeks)**	**Double-blind Treatment Period (12 weeks)**						**Follow-up Period (4 weeks)**
Visit #	**Visit 1 (Screening/ Baseline)**	**Visit 2 (Randomization)**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7/ET[a]**	**Visit 8 (End of Study)[b]**
Day/Week	***Week -4***	***Day 1***	***Week 2 (Day 14)***	***Week 4 (Day 28)***	***Week 6 (Day 42)***	***Week 8 (Day 56)***	***Week 12 (Day 84)***	***Week 16 (Day 112)***
Visit Windows	Day -35 to Day -28	NA	± 3 day	± 3 day	± 3 day	± 3 days	+ 3 days	± 3 days
Obtain informed consent and participant privacy	X							
Obtain informed consent for future biomedical research (optional)	X							
Obtain informed consent for PK (optional)	X							
Access IWRS	X	X	X	X	X	X	X	X
Obtain VCT consent and perform verification	X							
Assess inclusion/exclusion criteria	X	X						
Collect demographic information	X							
Collect medical history	X							
Collect migraine headache history	X							
Review prior medications including all migraine prophylactic medication use	X							
Perform physical examination	X						X	X
Collect vital sign measurements[c]	X	X	X	X	X	X	X	X
Perform and transmit ECG	X				X		X	
Perform urine pregnancy test[d]	X	X	X	X	X	X	X	X
Perform urine drug screen	X							
Clinical laboratory determinations[e]	X	X	X	X	X	X	X	X
PK sample collection (for those participating)[f]		X	X	X	X	X	X	
Collect blood for future biomedical research (for those participating)	X							

Study Period	**Screening Period (4 weeks)**	**Double-blind Treatment Period (12 weeks)**						**Follow-up Period (4 weeks)**
Visit #	**Visit 1 (Screening/ Baseline)**	**Visit 2 (Randomization)**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7/ET[a]**	**Visit 8 (End of Study)[b]**
Day/Week	***Week -4***	***Day 1***	***Week 2 (Day 14)***	***Week 4 (Day 28)***	***Week 6 (Day 42)***	***Week 8 (Day 56)***	***Week 12 (Day 84)***	***Week 16 (Day 112)***
Visit Windows	Day -35 to Day -28	NA	± 3 day	± 3 day	± 3 day	± 3 days	+ 3 days	± 3 days
Provide eDiary, and eDiary instructions and training[g]	X							
Participant eDiary data collection (eg, daily entries for headache frequency, duration, characteristics, symptoms, and acute medication use)	X	X	X	X	X	X	X[l]	X[m]
AIM-D (eDiary)	X	X	X	X	X	X	X[l]	X[m]
Activity Level and Activity Limitation (eDiary)	X	X	X	X	X	X	X[l]	X[m]
Review eDiary data (eg, headache duration, frequency, characteristics and symptoms, acute medication use, compliance)[h]		X	X	X	X	X	X[l]	X[m]
C-SSRS (eTablet)[i]	X	X	X	X	X	X	X	X
ASC-12 (eTablet)[j]	X							
HIT-6 (eTablet)[j,k]		X		X		X	X	
PGIC (eTablet)[j,k]							X	
PGI-S (eTablet)[j,k]		X		X		X	X	
WPAI:MIGRAINE (eTablet)[j,k]		X		X		X	X	
Patient Satisfaction with Study Medication (eTablet)[j,k]				X		X	X	
EQ-5D-5L (eTablet)[j,k]		X		X		X	X	X
MIDAS (eTablet)[j,k]		X					X	
MSQ v2.1 (eTablet)[j,k]		X		X		X	X	X
PROMIS-PI (eTablet)[j,k]		X		X		X	X	
Collect eDiary		X[n]					X[o]	X[p]

Study Period	**Screening Period (4 weeks)**	**Double-blind Treatment Period (12 weeks)**						**Follow-up Period (4 weeks)**
Visit #	**Visit 1 (Screening/ Baseline)**	**Visit 2 (Randomization)**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7/ET[a]**	**Visit 8 (End of Study)[b]**
Day/Week	***Week -4***	***Day 1***	***Week 2 (Day 14)***	***Week 4 (Day 28)***	***Week 6 (Day 42)***	***Week 8 (Day 56)***	***Week 12 (Day 84)***	***Week 16 (Day 112)***
Visit Windows	Day -35 to Day -28	NA	± 3 day	± 3 day	± 3 day	± 3 days	+ 3 days	± 3 days
Review of study intervention compliance and accountability			X	X	X	X	X	
Dispense study intervention		X	X	X	X	X		
Adverse events	X							
Concomitant medications/concurrent procedures	X							

[a] Effort should be made by site to not schedule Visit 7 earlier than 12 weeks after Day 1 (Day 84) to ensure that participants complete the full 12 weeks of treatment and have eDiary data through Day 84.

[b] All participants who take at least one dose of study intervention must complete the follow-up period, except for participants rolling over into Study 3101-309-002 (longterm safety extension study). For these participants the Follow-up Visit will be performed in the longterm safety extension study.
During the COVID- 19 pandemic, Visit 8 (Follow-up/End of Study) should be conducted remotely for all participants in all cases.

[c] Vital sign measurements: height, weight, sitting and standing pulse rate, respiratory rate, sitting and standing blood pressure, and body temperature. Height will be measured only at Visit 1.

[d] For women of childbearing potential only, a urine pregnancy test will be performed at all visits.

[e] Clinical laboratory determinations include chemistry, hematology, coagulation parameters (INR) and urinalysis to be collected for all visits. Samples for serology and the urine drug screen will be collected only at Screening (Visit 1).

[f] PK sample should be collected prior to the initial dose at Visit 2, 1 sample should be collected prior to the daily dose during one of the Visits 3 to 6, and the remaining samples should be collected 1 to 10 hours post the daily dose.

[g] Participants should begin using the eDiary as soon as it is dispensed. If it is subsequently determined that the participant has failed entry criteria, the eDiary should be returned to site.

[h] Participants should bring the eDiary to all visits and review with site personnel.

[i] At Visit 1, the "Screening/Baseline" assessment of the C-SSRS will be completed. At all other visits, the "Since the Last Visit" C-SSRS will be completed.

[j] Participants will complete on eTablet.

[k] PRO measures should be administered prior to any tests and/or evaluations unless indicated otherwise in the protocol (eg, during Randomization Visit, some tests will be conducted prior to PROs for eligibility).

[l] For participants who complete the double-blind treatment period only (Visit 2 to Visit 7/ET).

[m] For participants who terminate early from the double-blind treatment period only.

[n] Collected at Visit 2 only for participants who fail screening.

[o] Collected at Visit 7/ET only for participants who complete the double-blind treatment period.

[p] Collected at Visit 8/Follow-up only for participants who discontinue from the double-blind treatment period.

Table 4–2 Schedule of Visits and Procedures for Visits Conducted Remotely Due to the COVID-19 Pandemic

Study Period	**Double-blind Treatment Period (12 weeks)[a]**					**Follow-up Period (4 weeks)**
Visit #	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7/ET[b,c]**	**Visit 8 (End of Study)[d]**
Day/Week	***Week 2 (Day 14)***	***Week 4 (Day 28)***	***Week 6 (Day 42)***	***Week 8 (Day 56)***	***Week 12 (Day 84)***	***Week 16 (Day 112)***
Visit Windows	± 3 day	± 3 day	± 3 day	± 3 days	+ 3 days	± 3 days
Provide urine pregnancy test and instructions[e]	X	X	X	X	X	X
Participant eDiary data collection	X	X	X	X	X[f]	X[g]
Review eDiary data	X	X	X	X	X[f]	X[g]
C-SSRS[h]	X	X	X	X	X	X
HIT-6[i]					X	
PGIC[i]					X	
PGI-S[i]					X	
WPAI: MIGRAINE[i]					X	
Patient Satisfaction with Study Medication[i]					X	
EQ-5D-5L[i]					X	
MIDAS[i]					X	
MSQ v2.1[i]					X	
PROMIS-PI[i]					X	
Review of study intervention compliance and accountability	X	X	X	X	X	
Access IWRS	X	X	X	X	X	X
Dispense study intervention[j]	X	X	X	X		
Adverse events	X					
Concomitant medications/concurrent procedures	X					

[a] For participants who have a study visit replaced by a remote study visit, all missed in-person safety assessments (clinical laboratory determinations, vital signs, and ECGs) will be collected at the next in-person visit. To ensure participant safety, remote study visits can be performed for up to 8 weeks at the discretion of the investigator, after which, participants who cannot attend in-person for a study visit must be discontinued from the study.

[b] Effort should be made by site to not schedule Visit 7 earlier than 12 weeks after Day 1 (Day 84) to ensure that participants complete the full 12 weeks of treatment and have eDiary data through Day 84.

[c] If Visit 7 is conducted remotely, the participant will not be eligible to roll over into Study 3101-309-002, and Visit 8 should be performed in this study (3101-301-002).

[d] All participants who take at least one dose of study intervention must complete the follow-up period, except for participants rolling over into Study 3101-309-002 (longterm safety extension study). For these participants the Follow-up Visit will be performed in the longterm safety extension study.
During the COVID- 19 pandemic, Visit 8 (Follow-up/End of Study) should be conducted remotely for all participants in all cases.

[e] For women of childbearing potential only, a urine pregnancy test must be performed within 48 hours prior to the remote visits. Investigators/site staff will provide participants with study-supplied urine pregnancy tests and corresponding written instructions to be used at-home by participants for remote study visits. Sites are required to verbally review testing instructions with all participants.

[f] For participants who complete the double-blind treatment period only (Visit 2 to Visit 7/ET).

[g] For participants who terminate early from the double-blind treatment period only.

[h] "Since the Last Visit" C-SSRS will be completed.

[i] PRO measures should be administered prior to any evaluations.

[j] Study intervention for remote visits can be shipped to participants via an overnight courier or provided curbside. Study medication to cover 1 additional remote study visit may be dispensed.

5 Study Objectives

- To evaluate the safety and tolerability of atogepant 10 mg, atogepant 30 mg and 60 mg for the prevention of migraine in participants with EM.
- To prospectively test for superiority of atogepant 10 mg, atogepant 30 mg and 60 mg versus placebo for the prevention of migraine in participants with EM.

6 Analysis Populations

The analysis populations will consist of participants as defined below.

The Intent-to-Treat (ITT) Population includes all randomized participants.

The Safety Population includes all participants who received at least 1 dose of study intervention. All safety analyses will be performed using the Safety Population and based on the treatment actually received, regardless of assigned treatment according to the planned randomization. Participants will be summarized according to the study treatment received for the majority of treatment period.

The Modified Intent-to-Treat (mITT) Population includes all randomized participants who received at least 1 dose of study intervention, had an evaluable baseline period of eDiary data and had at least 1 evaluable post-baseline 4-week period (Weeks 1 to 4, 5 to 8, and 9 to 12) of eDiary data during the double-blind treatment period. All efficacy analyses described in Sections 10.2 - 10.4 will be performed using the mITT population and based on the randomization assignment, regardless of the actual treatment received. All efficacy analyses will be conducted using mITT population unless specified otherwise.

The analysis population for Off-treatment Hypothetical Estimand includes all randomized participants who received at least 1 dose of study treatment, had an evaluable baseline period of eDiary data and had at least 1 evaluable post-baseline 4-week period (Weeks 1 to 4, 5 to 8, 9 to 12) of eDiary data during the DB treatment period and follow-up period, regardless of whether on study treatment or off study treatment. This population is used for the primary estimand in support of EU filing.

7 Participant Disposition

The number of participants in the ITT, Safety, and mITT Populations will be summarized by treatment group; the number of participants screened will be summarized for overall only. The number of participants in the ITT Population will also be summarized by treatment group for the

following factors: 1) Randomization stratification factor (prior exposure [yes/no] to a migraine prevention medication with proven efficacy) from IWRS; 2) Prior exposure to migraine prevention medication with proven efficacy based on prior medication collected from eCRF, which will be termed as "actual strata" in the SAP. The list of participants with incorrect randomization stratum will be provided.

Screen-failure participants (i.e., participants screened but not randomized) and the associated reasons for failure to randomize will be tabulated overall for the all screened participants. The number and percentage of participants who enter the double-blind treatment period, complete the double-blind treatment period and of participants who prematurely discontinue during the same period will be presented for each treatment group and pooled across treatment groups for all randomized participants. The reasons for premature discontinuation from the double-blind treatment period as recorded on the termination pages of the electronic case report forms will be summarized (number and percentage) by treatment group. The percentage is relevant to the total number of randomized participants. Similar disposition information to the double-blind treatment period will be presented for the follow-up period. All randomized participants who prematurely discontinue during the double-blind treatment period or the follow-up period will be listed by discontinuation reason. The number of participants who signed informed consent for Safety Extension Study 3101-309-002 will be provided.

8 Demographic and Other Baseline Characteristics

Demographic parameters (age; age group [< 20, 20-29, 30-39, 40-49, 50-59, 60-69, and ≥ 70]; race; race group [white, all other races]; ethnicity; sex), baseline characteristics (weight; height; and body mass index, calculated as weight [kg]/(height [m])^2 will be summarized descriptively by treatment group for the Safety and mITT Populations, and Off-treatment Hypothetical Estimand Population. Continuous variables will be summarized by number of participants and mean, SD, median, first quartile (Q1), third quartile (Q3), minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants.

Abnormalities in participants' medical and surgical history will be coded using the Medical Dictionary for Regulatory Activities, version 22.0 or newer. The number and percentage of participants with abnormalities in medical and surgical histories in each system organ class and preferred term will be summarized by treatment group for the Safety Population.

Migraine history, including diagnosis, duration of disorder, use of migraine prevention medication in the past, average number of migraine or headache days per month in the last 3

months, acute medications taken to treat migraine headaches, and advice on lifestyle alterations will be reported in total and by treatment group for the Safety Population.

Prior medication is defined as any medication taken before the first dose of double-blind study treatment. Concomitant medication is defined as any medication taken on or after the date of the first dose of the double-blind study treatment.

Prior medication use will be summarized by the number and proportion of participants in each treatment group receiving each medication within each therapeutic class for the Safety Population. Concomitant medication use will be summarized by the number and percentage of participants in each treatment group receiving each medication within each therapeutic class for the double-blind treatment period and follow-up period for the Safety Population. If a participant took a specific medication multiple times or took multiple medications within a specific therapeutic class, that participant would be counted only once for the coded drug name or therapeutic class. Any prior and concomitant medications will be included in listings.

The World Health Organization (WHO) Drug Dictionary Enhanced, March 2017 or newer, will be used to classify prior and concomitant medications by therapeutic class and drug name.

Protocol deviations will be defined in Protocol Deviation Requirement Specification (PDRS), including significant classification. The number and percentage of participants with significant protocol deviations will be summarized by treatment group for all categories specified in PDRS for all randomized participants.

Baseline efficacy parameters (monthly migraine days, monthly headache days, monthly acute medication use days, Migraine Specific Quality of Life Questionnaire [MSQ] v2.1 Role Function Restrictive domain score, Performance of Daily Activities domain score of the AIM-D, and Physical Impairment domain score of the AIM-D) will be summarized by treatment group for mITT Population and Off-treatment Hypothetical Estimand Population.

9 Extent of Exposure and Treatment Compliance

9.1 Extent of Exposure

Exposure to double-blind study treatment for the Safety Population during the treatment period will be summarized for treatment duration, calculated as the number of days from the date of the first dose of double-blind study treatment taken to the date of the last dose taken, inclusive. The number and percentage of participants with each treatment duration of ≥ 1 day, ≥ 7 days, ≥ 14 days, ≥ 21 days, ≥ 28 days, ≥ 35 days, ≥ 42 days, ≥ 49 days, ≥ 56 days, ≥ 63 days, ≥ 70 days, ≥ 77 days, ≥ 84 days will be summarized by treatment group respectively. Descriptive

statistics (number of participants, mean, SD, median, Q1, Q3, minimum, and maximum) will also be summarized by treatment group.

Participant-years, defined as exposure to the study treatment in years, will be summarized by treatment group for the Safety Population.

9.2 Measurement of Treatment Compliance

Dosing compliance for a specified period is defined as the total number of double-blind study medications actually taken by a participant during that period divided by the number of double-blind study medications that were expected to be taken during the same period multiplied by 100. The total number of tablets actually taken during a specific period will be calculated from the study medication record. The prescribed number of tablets during a specific period will be calculated as following: 3 tablets/day × the number of days during the period. Descriptive statistics for double-blind study medication dosing compliance together with the compliance categories (< 80%, 80% - 120%, > 120%) will be summarized by treatment group for each period between 2 consecutive visits, as well as for the period from the first dose of the double-blind study interventions actually taken to the last dose of double-blind study intervention actually taken for the Safety Population.

10 Efficacy Analyses

10.1 Efficacy and Health Outcome Measures

10.1.1 Efficacy Measures

A migraine day is defined as any calendar day on which a headache occurs which meets criteria A, B, and C **OR** meets criteria D and E, as listed below, as per participant eDiary. Calendar days begin at midnight and last until 11:59 PM (23:59).

A. Headache has at least two of the following four characteristics:
    i. Unilateral location
    ii. Pulsating quality
    iii. Moderate or severe pain intensity
    iv. Aggravated by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
B. At least one of the following:
    i. Nausea and/or vomiting
    ii. Photophobia and phonophobia

iii. Typical aura (i.e., visual, sensory, or speech/language) accompanying or within 60 minutes before headache begins

C. Duration of headache lasting 2 hours or longer on a calendar day unless an acute, migraine-specific medication (i.e., triptan or ergot derivative) was used after the start of the headache, in which case no minimum duration will be specified

OR

D. Any headache which fulfills one criterion from (1) and at least one criterion from (2) **OR** fulfills at least two criteria from (1) and no criteria from (2).

1) Headache characteristics:
   i. Unilateral location
   ii. Pulsating quality
   iii. Moderate or severe pain intensity
   iv. Aggravated by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
2) Symptoms:
   i. Nausea and/or vomiting
   ii. Photophobia and phonophobia
   iii. Typical aura (i.e., visual, sensory, or speech/language) accompanying or within 60 minutes before headache begins

E. Duration of headache lasting 2 hours or longer on a calendar day unless an acute, migraine-specific medication (i.e., triptan or ergot derivative) was used after the start of the headache, in which case no minimum duration will be specified.

A headache day is defined as any calendar day on which headache pain lasting 2 hours or longer occurs unless an acute headache medication (eg, ibuprofen, triptan) was used after the start of the headache, in which case no minimum duration will be specified. Note that antiemetics will not be counted as an acute headache medication for headache day identification. Calendar days begin at midnight and last until 11:59 PM (23:59).

An acute medication use day is defined as any day on which a participant reports, per eDiary, the intake of allowed medication(s) to treat an acute migraine. The allowed medications include the following categories of drugs: triptans, ergots, opioids, analgesics (including acetaminophen), NSAIDs (including aspirin), and antiemetics.

A triptan use day is defined as any day on which a participant reports intake of a triptan to treat a migraine per participant diary.

Headache day pain intensity is defined as the worst pain intensity on any headache day where headache pain intensity will be subjectively rated by the patient on a scale from mild to severe:

- Mild pain (=1)
- Moderate pain (=2)
- Severe pain (=3)

If participants experience no headache in a day, then the corresponding pain intensity of that day will be set as missing.

10.1.2 Health Outcome Measures

The AIM-D is an 11-item daily diary measure that assesses the impact of migraine and is comprised of two domains that evaluate performance of daily activities (7 items) and physical impairment (4 items). Participants are asked to rate the level of difficulty experienced in the past 24 hours with performance of daily activities (i.e., difficulty with household chores, errands, leisure activities at home, leisure or social activities outside the home, strenuous physical activities, concentrating, and thinking clearly) and physical impairment (i.e., difficulty walking, moving body, bending forward, moving head) using a 6-point rating scale ranging from "Not difficult at all," "A little difficult," "Somewhat difficult," "Very difficult," "Extremely difficult," and "I could not do it at all." Three items include a response of "I did not…," for example, "I did not have errands planned." The AIM-D was developed as an electronic daily diary with the same set of questions administered in headache and non-headache versions. The Headache version is administered on days when a participant reports a headache and the Non-Headache version is administered on days when a participant does not report having a headache. The AIM-D instructs participants to answer each question based on the level of difficulty experienced in the past 24 hours for both versions, with "during your headache" indicated for the AIM-D Headache version. In addition to the two domain scores, a total score using all 11 items can also be calculated. Each raw daily domain score, as well as the raw daily total score, are transformed to a 0-100 scale, with higher scores indicating greater impact of migraine (i.e., higher disease burden).

Two items based on a 24-hour recall will be administered daily using Headache and Non-headache versions as additional health outcome measures and for evaluation of the AIM-D. The first item will be used to assess activity level within the past 24 hours with a 5-level response scale ranging from "No activity – Spent all day lying down" to "Exercised – Brisk

walk, running, jogging, biking or other activity for 30 or more minutes." The second item will be used to evaluate activity limitation with a 5-level response scale ranging from "Not at all limited – I could do everything" to "Extremely limited".

Overall satisfaction with the study medication for prevention of migraine will be assessed using a single item and a 7-point rating scale ranging from extremely satisfied (0) to extremely dissatisfied (6).

The MSQ v2.1 is a 14-item questionnaire designed to measure health-related quality-of-life impairments attributed to migraine in the past 4 weeks. It is divided into three domains: Role Function Restrictive assesses how migraines limit one's daily social and work-related activities; Role Function Preventive assesses how migraines prevent these activities; and the Emotional Function domain assesses the emotions associated with migraines. Participants respond to items using a 6-point scale ranging from "none of the time" to "all of the time." Raw dimension scores are computed as a sum of item responses and rescaled to a 0 to 100 scale, where higher scores indicate better quality of life.

The Headache Impact test (HIT-6) is a 6-question assessment used to measure the impact headaches have on a participant's ability to function on the job, at school, at home and in social situations. It assesses the effect that headaches have on normal daily life and the participants' ability to function. Responses are based on frequency using a 5-point scale ranging from never to always. The HIT-6 total score, which ranges from 36 to 78, is the sum of the responses – each of which is assigned a score ranging from 6 points (never) to 13 points (always).

The Migraine Disability Assessment (MIDAS) is a 7-item questionnaire designed to quantify headache-related disability over a 3-month period. The MIDAS score is the sum of missed work or school days, days at work or school plus days of household work where productivity was reduced by half or more, missed household work days, and missed non-work activity days due to headaches and in the last 3 months.

The Patient Global Impression of Change (PGIC) is a single item used to measure the participant's impression of overall change in migraine since the first dose of study intervention. The measure uses a 7-point rating scale with responses ranging from "very much better" to "very much worse."

The Patient Global Impression - Severity (PGI-S) is a single item used to measure the participant's impression of severity in relation to migraine symptoms overall at the time of administration of the measure. The measure uses a 5-point rating scale with responses ranging from "none" to "very severe."

The Work Productivity and Activity Impairment Questionnaire: Migraine v2.0 (WPAI:MIGRAINE) is used to assess work productivity specific to migraine. The measure uses a 1-week recall and contains 6 questions related to work productivity. The WPAI measures both presenteeism and absenteeism. The measure yields four scores expressed as impairment percentages ranging from 0 to 100%: Percent work time missed, percent impairment while working, percent overall work impairment, and percent activity impairment due to migraine.

The detailed algorithms for derivation of the above health outcome measures are presented in Section 17.2.2.

10.2 Primary Efficacy Endpoints

The primary efficacy endpoint is the change from baseline in mean monthly migraine days across the 12-week treatment period. The primary null hypothesis is that atogepant treatment doses (atogepant 10 mg, atogepant 30 mg, and atogepant 60 mg once a day) are each equally effective to placebo in mean change from baseline in mean monthly migraine days across the 12-week treatment period. The alternative hypothesis is that at least 1 of the 3 doses of atogepant has a different effect than placebo. Baseline is defined as the number of migraine days during the last 28 days prior to the randomization date.

10.2.1 Primary Analysis in Support of US Filing

The endpoint will be analyzed using a mixed model for repeated measures (MMRM). The response variable is the change from baseline to each postbaseline month in monthly migraine days. The model will include treatment group, visit (derived as month), prior exposure (yes/no) to a migraine prevention medication with proven efficacy, and treatment group by visit interaction as categorical fixed effects. It will also include the baseline score and baseline-by-visit interaction as covariates. The stratum “prior exposure (Yes/No)” will use the actual stratification factor from prior medication collected by eCRF. The analysis will be performed based on evaluable postbaseline data using only the observed cases without missing data imputation. Only data collected during the double-blind period will be included in the analysis. Participants are always analyzed based on the treatment group assigned by randomization.

Restricted maximum likelihood method will be used. The within-patient correlation will be modeled using the unstructured covariance matrix. If the model does not converge, then the Toeplitz covariance structure will be used. if the model with the Toeplitz covariance structure does not converge, then the compound symmetry covariance structure will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Contrasts will be constructed to obtain the average treatment effects across the 12-week treatment period to compare each atogepant treatment group versus the placebo group. Each

treatment effect and treatment comparisons will be estimated by the LS Means and their differences in LS Means, along with their SE and 95% confidence intervals, and the p-value corresponding to the between-treatment group difference. The sample SAS code is given as follows

```
proc mixed data = efficacy_dataset METHOD=REML;
  class trt visit prior_exposure subjid;
  model chg = base trt visit prior_exposure trt*visit base*visit
              / s ddfm= kr;
  Repeated visit / type = UN subject = subjid;
  lsmestimate trt*visit
  '10QD vs placebo' -1 -1 -1 1 1 1 0 0 0 0 0 0 divisor = 3,
  '30QD vs placebo' -1 -1 -1 0 0 0 1 1 1 0 0 0 divisor = 3,
  '60QD vs placebo' -1 -1 -1 0 0 0 0 0 0 1 1 1 divisor = 3 / CL;
run;
```

The impact of dropouts on the primary efficacy measure will be explored graphically by plotting the response profiles by the dropout reason. Plot of mean change from baseline in the number of migraine days versus visit (month) based on the observed cases will be provided in each treatment group by major reason of early termination, such as, adverse events, lack of efficacy, withdrawal of consent, lost to follow-up, etc. Similar plot for completers in each treatment group will be provided as a reference.

10.2.2 Sensitivity Analysis for Possible Violation of Normality Assumption

This sensitivity analysis uses MI in conjunction with robust regression to assess the robustness of the primary MMRM analysis to the possible violation of normality assumption. This method has been described and referred as ADAP [R] in Mehrotra et al. 2012. The details of the method are as follows.

The normality test is performed on the residuals which are generated by the same MMRM as used for the primary efficacy analysis. The residuals are scaled by the inverse Cholesky root of its estimated variance-covariance matrix. The Kolmogorov-Smirnov test for normality is applied to the de-correlated and scaled residuals and normality test is rejected if p-value from the Kolmogorov-Smirnov test is less than 0.01.

If the normality test is rejected, sensitivity analysis below will be performed:

1. Create complete datasets using MI based on the Markov chain Monte Carlo (MCMC) approach. Imputed data will consist of 20 complete datasets.

2. Each of the 20 complete datasets will be analyzed using robust regression (M-estimation) to protect against either observed outliers in the original incomplete dataset, or imputed outliers in the completed datasets. For a given complete dataset, the average change from baseline in monthly migraine days is calculated across the 3 post-baseline months and is used as the response variable in the robust regression model. The model includes treatment group as a fixed factor, baseline score and prior exposure (yes/no) to a migraine prevention medication with proven efficacy as covariates. The mean difference and corresponding SE are estimated from the model comparing each atogepant treatment group with the placebo group.
3. The robust analysis results from 20 completed datasets are combined for overall estimation and inference using Rubin's rule (Rubin 1987) to produce a pooled estimate of treatment difference, its SE, and corresponding p-value for the test of null hypothesis of no treatment effect.

10.2.3 Sensitivity Analyses in Missing Data Handling

ANCOVA Model Based on 3-month Average of the Monthly Migraine Days

The response variable for the ANCOVA model is the change from baseline in the 3-month average of the monthly migraine days for each participant. The ANCOVA model includes terms for treatment, prior exposure (yes/no) to a migraine prevention medication with proven efficacy, and baseline score. The treatment difference for atogepant doses versus placebo will be estimated and reported along with the corresponding 95% CI and nominal p-value for superiority testing. This analysis was recommended by FDA at the End of Phase 2 meeting and termed as supportive analysis. There are no missing data based on this derivation because patients who discontinued the treatment are assumed to maintain the same mean (observed while on treatment) for 3 months (12 weeks).

Within-group Imputation Based on Observed Data

Sensitivity analysis will be performed based on imputation using participants from the same treatment group with observed data under the MAR assumption. The details of imputation are as follows

1. Create partial imputation dataset using MI based on the MCMC approach in each treatment group. Imputed dataset will consist of 100 copies of original dataset and is assumed to follow monotone missing pattern.
2. Impute missing data in each existing copy by treatment group using observed data in the corresponding treatment group based on monotone regression. Each of the 100 imputed

datasets will then be analyzed using an ANCOVA model with terms for treatment, prior exposure (yes/no) to a migraine prevention medication with proven efficacy, and baseline score.

3. The ANCOVA analysis results from 100 completed datasets are combined for overall estimation and inference using Rubin's rule (Rubin 1987) to produce a pooled estimate of LS mean difference, its SE, and corresponding p-value for the test of null hypothesis of no treatment effect.

Copy-reference Approach

Copy-reference approach is one type of pattern-mixture models (PMM), under which data could be missing-not-at-random (MNAR), with repeated analyses combined via the reference based multiple imputation (MI) procedure (Carpenter et al, 2013). This approach is to assess the robustness of the MMRM analysis to possible violation of the missing-at-random (MAR) assumption in the primary analysis.

Step 1. A few intermittent missing values will be imputed by the Markov Chain Monte Carlo (MCMC) at first. The MCMC imputation assumes missing-at-random (MAR) for intermittent missing data. The MCMC method will be implemented using SAS Proc MI statement "MCMC impute=monotone". This is achieved with the use of option IMPUTE = MONOTONE in the MCMC statement. Then the rest of the missing data will follow monotone missing pattern.

Step 2. Implementation of the copy reference method are as follows:

1. The reference-based approach uses the placebo group as the reference. The missing values in the reference group are imputed using the observed data in that group under the missing-at-random assumption. The missing pattern is defined by the participant's last visit with a non-missing value. The mean vector and the covariance matrix of the multivariate normal distribution are estimated for reference group. The imputation of missing data is not based on each of the reasons of early termination, because there may not be sufficient non-missing efficacy data in each of the reason categories to serve as a stable reference.
2. For atogepant treatment groups, missing values are imputed based on the distribution estimated from the reference group (placebo group).

The first PROC MI will be performed 100 times using MCMC method for partial imputation of the data with a non-monotone missing pattern. The output dataset will then be used as the input dataset for the next PROC MI. Note that the output dataset already contains 100 copies of the original dataset. With the next invocation of MI procedure, the missing data will be filled in (Step 1 and 2) for the existing copies. This is achieved with the use of NIMPUTE=1 and a BY

Imputation statement. Finally, each of the 100 imputed datasets will be analyzed using an analysis of covariance (ANCOVA) model. For a given imputed dataset, the average change from baseline in monthly migraine days is calculated across the 3 post-baseline months and is used as the response variable in the model. The model includes treatment group as a fixed factor, baseline monthly migraine days and prior exposure (yes/no) to a migraine prevention medication with proven efficacy as covariates. The LS mean difference and corresponding SE is estimated from the model comparing each atogepant treatment group with the placebo group.

The ANCOVA analysis results from 100 completed datasets are combined for overall estimation and inference using Rubin's rule (Rubin 1987) to produce a pooled estimate of LS mean difference, its SE, and corresponding p-value for the test of null hypothesis of no treatment effect.

MMRM Based on Primary Measures Collected during the Double-blind and Follow-up Periods

The details for this analysis are provided in Section 10.5. The primary analysis in support of EU filing will serve as one sensitivity analysis in support of US filing.

10.3 Secondary Efficacy Endpoints

The secondary efficacy endpoints for the United States and the EU are as follows:

- Change from baseline in mean monthly headache days across the 12-week treatment period.
- Change from baseline in mean monthly acute medication use days across the 12-week treatment period.
- ≥ 50% reduction in 3-month average of monthly migraine days
- Change from baseline in MSQ v2.1 Role Function Restrictive domain score at Week 12.
- Change from baseline in mean monthly Performance of Daily Activities domain score of the AIM-D across the 12-week treatment period.
- Change from baseline in mean monthly Physical Impairment domain score of the AIM -D across the 12-week treatment period.

The secondary endpoints for headache days, acute medication use days, Performance of Daily Activities domain score of the AIM-D, and Physical Impairment domain score of the AIM-D will be analyzed in the same manner as that used to analyze the primary endpoint. For MSQ v2.1 Role Function Restrictive domain score, the analysis will be performed similarly to the primary MMRM, with focus on the pairwise contrasts of each dose group to placebo at Week 12. Week

16 (follow-up visit) data for MSQ v2.1 Role Function Restrictive domain score will not be included in MMRM analysis, and only summary statistics for Week 16 will be provided. The corresponding sample SAS code is given as follows

```
proc mixed data = e1 METHOD=REML;
  class trt visit prior_exposure subjid;
  model chg = base trt visit prior_exposure trt*visit base*visit
              / s ddfm= kr;
  Repeated visit / type = UN subject = subjid;
  lsmestimate trt*visit
  '10QD vs placebo' 0 0 -1 0 0 1 0 0 0 0 0 0,
  '30QD vs placebo' 0 0 -1 0 0 0 0 0 1 0 0 0,
  '60QD vs placebo' 0 0 -1 0 0 0 0 0 0 0 0 1 / CL;
run;
```

The 50% responder, defined as a participant with at least a 50% reduction from baseline in the 3-month average of monthly migraine days, will be assessed for each individual. A logistic regression model will be used to analyze the 50% responders across the 12-week treatment period. This model assumes a binary distribution for the response and uses a logit link. The analysis model will include treatment group, prior exposure (yes/no) to a migraine prevention medication with proven efficacy, and baseline monthly migraine days. The treatment difference in terms of odds ratio between each atogepant dose group and placebo will be estimated and tested from this model. The sample SAS is given as follows

```
proc logistic data=in_data;
      class TRTP (ref='Placebo') prior_exposure (ref='No')/param=glm;
      model responder(event='1')= TRTP  prior_exposure base ;
      lsmeans TRTP / e diff oddsratio cl;
      ods output diffs=outdata (where= (_TRTP ='Placebo'));
run;
```

Multiplicity Adjustment

The overall familywise error rate (FWER) will be controlled at $\alpha = 0.05$ for the set of primary and secondary endpoint comparisons between each dose level of atogepant vs placebo. Specifically, the overall type I error rate for multiple comparisons across three atogepant doses and the primary and secondary efficacy endpoints will be controlled at the 0.05 level using a graphical approach with weighted-Bonferroni test procedure (Bretz 2009). The overall graphic approach procedure is defined in Table 10–1 and Figure 10-1. In the graph, each of the nodes is corresponding to one null hypothesis, for example, 30mg/P1 represents the null hypothesis that there is no statistically significant difference comparing 30 mg QD versus placebo on the primary endpoint. The number inside each node is the proportion of overall alpha initially allocated to that hypothesis. The number on the edge between two nodes represents the proportion of local alpha propagated from one hypothesis to the other given the rejection of preceding null hypothesis.

The initial allocation of the overall significant level to 3 primary hypotheses will be 1/3 of the overall significance level for each dose, and no initial α is allocated to the hypotheses for secondary endpoints.

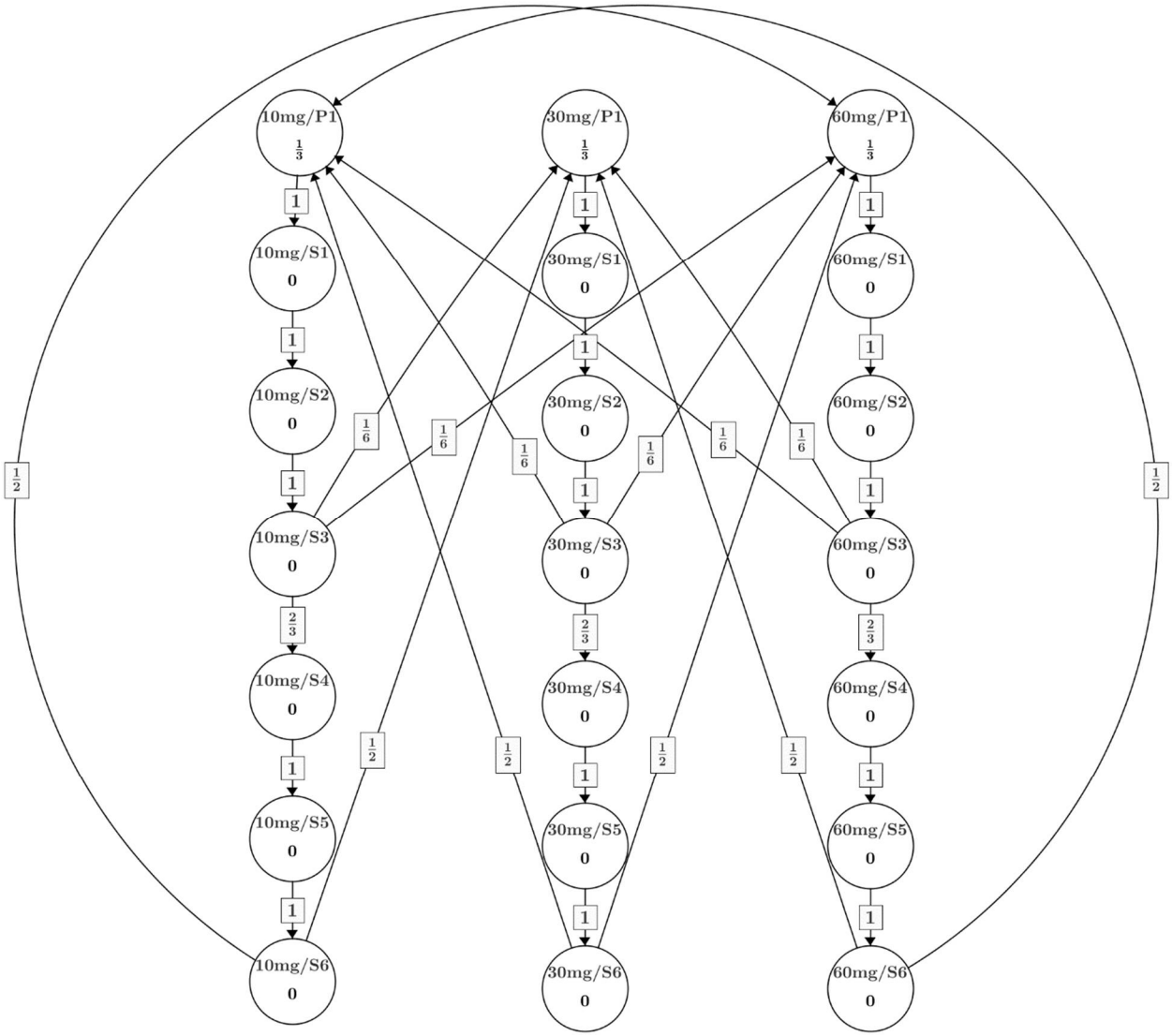
Within each individual dose, testing will start from the primary endpoint, and then test the secondary endpoints in a prespecified order. The order of testing for the first three secondary endpoints is determined by the power of individual endpoints based on the results from Phase 2/3 study CGP-MD-01. Endpoints related to AIM-D and MSQ are placed in the last three positions in the testing hierarchy because there is no prior information about the treatment effect for the three health outcome (HO) endpoints associated with MSQ 2.1 RR and AIM-D, and AIM-D related endpoints are still under validation. If the null hypotheses for both the primary and the first three secondary endpoints are rejected for one of the doses, 1/3 of the associated alpha is passed to the other doses (1/6 fraction for each dose) to increase the chances of success for the other doses in testing endpoints in the primary positions of the hierarchy, and the remaining 2/3 of the associated alpha is reserved for testing HO endpoints within the same dose. If hypotheses for three HO endpoints are rejected within a dose based on remaining alpha, the alpha for this dose will be propagated to the other two doses to make full use of the alpha.

Table 10–1 Multiple Comparisons Procedure Definitions

Nodes	Alternate Hypothesis	Weight	*Initial* Local Significance Level
10mg/P1	Atogepant 10 mg is significantly different from placebo in change from baseline in mean monthly migraine days across the 12-week treatment period (P1)	1/3	$\alpha\times(1/3) = \alpha/3$
30mg/P1	Atogepant 30 mg is significantly different from placebo in change from baseline in mean monthly migraine days across the 12-week treatment period (P1)	1/3	$\alpha\times(1/3) = \alpha/3$
60mg/P1	Atogepant 60 mg is significantly different from placebo in change from baseline in mean monthly migraine days across the 12-week treatment period (P1)	1/3	$\alpha\times(1/3) = \alpha/3$
10mg/S1	Atogepant 10 mg is significantly different from placebo in change from baseline in mean monthly headache days across the 12-week treatment period (S1)	0	$\alpha\times0=0$
30mg/S1	Atogepant 30 mg is significantly different from placebo in change from baseline in mean monthly headache days across the 12-week treatment period (S1)	0	$\alpha\times0=0$
60mg/S1	Atogepant 60 mg is significantly different from placebo in change from baseline in mean monthly headache days across the 12-week treatment period (S1)	0	$\alpha\times0 = 0$
10mg/S2	Atogepant 10 mg is significantly different from placebo in change from baseline in mean monthly acute medication use days across the 12-week treatment period	0	$\alpha\times0=0$
30mg/S2	Atogepant 30 mg is significantly different from placebo in change from baseline in mean monthly acute medication use days across the 12-week treatment period	0	$\alpha\times0=0$
60mg/S2	Atogepant 60 mg is significantly different from placebo in change from baseline in mean monthly acute medication use days across the 12-week treatment period	0	$\alpha\times0=0$
10mg/S3	Atogepant 10 mg is significantly different from placebo in ≥ 50% reduction in 3-month average of monthly migraine days	0	$\alpha\times0 = 0$
30mg/S3	Atogepant 30 mg is significantly different from placebo in ≥ 50% reduction in 3-month average of monthly migraine days	0	$\alpha\times0 = 0$
60mg/S3	Atogepant 60 mg is significantly different from placebo in ≥ 50% reduction in 3-month average of monthly migraine days	0	$\alpha\times0=0$
10mg/S4	Atogepant 10 mg is significantly different from placebo in change from baseline in MSQ v2.1 Role Function Restrictive domain score at Week 12	0	$\alpha\times0=0$
30mg/S4	Atogepant 30 mg is significantly different from placebo in change from baseline in MSQ v2.1 Role Function Restrictive domain score at Week 12	0	$\alpha\times0=0$
60mg/S4	Atogepant 60 mg is significantly different from placebo in change from baseline in MSQ v2.1 Role Function Restrictive domain score at Week 12	0	$\alpha\times0=0$
10mg/S5	Atogepant 10 mg is significantly different from placebo in change from baseline in mean monthly Performance of Daily Activities domain score of the AIM-D across the 12-week treatment period	0	$\alpha\times0 = 0$

30mg/S5	Atogepant 30 mg is significantly different from placebo in change from baseline in mean monthly Performance of Daily Activities domain score of the AIM-D across the 12-week treatment period	0	α×0 = 0
60mg/S5	Atogepant 60 mg is significantly different from placebo in change from baseline in mean monthly Performance of Daily Activities domain score of the AIM-D across the 12-week treatment period	0	α×0=0
10mg/S6	Atogepant 10 mg is significantly different from placebo in change from baseline in mean monthly Physical Impairment domain score of the AIM-D across the 12-week treatment period	0	α×0 = 0
30mg/S6	Atogepant 30 mg is significantly different from placebo in change from baseline in mean monthly Physical Impairment domain score of the AIM-D across the 12-week treatment period	0	α×0 = 0
60mg/S6	Atogepant 60 mg is significantly different from placebo in change from baseline in mean monthly Physical Impairment domain score of the AIM-D across the 12-week treatment period	0	α×0=0

Figure 10-1 Multiple Comparisons Procedure



10.4 Additional Endpoints

Additional Efficacy Endpoints

Additional efficacy endpoints for the United States and the EU are listed below:

- ≥ 25%, ≥ 50%, ≥ 75%, and 100% improvement (reduction) in monthly migraine days at Weeks 1-4, 5-8, and 9-12.
- ≥ 25%, ≥ 75%, and 100% improvement (reduction) in 3-month average of monthly migraine days.
- Change from baseline in monthly migraine days at Weeks 1-4, 5-8, and 9-12.
- Change from baseline in monthly headache days at Weeks 1-4, 5-8, and 9-12.
- Change from baseline in monthly cumulative headache hours at Weeks 1-4, 5-8, 9-12, and average across the 12-week treatment period.
- Change from baseline in monthly acute medication use days at Weeks 1-4, 5-8, and 9-12.
- Change from baseline in monthly triptan use days at Weeks 1-4, 5-8, 9-12, and average across the 12-week treatment period.
- Change from baseline in monthly moderate/severe headache days at Weeks 1-4, 5-8, 9-12, and average across the 12-week treatment period.
- Change from baseline in monthly severe headache days at Weeks 1-4, 5-8, 9-12, and average across the 12-week treatment period.
- Change from baseline in weekly migraine days at Weeks 1, 2, 3, and 4.
- Participant reporting a migraine day on the day of initial dose and on each day of the 6 days post the initial dose.

Additional Health Outcomes Endpoints

The following health outcomes endpoints for the United States and the EU are planned to be reported in CSR main body:

- Change from baseline in the HIT-6 total score at Weeks 4, 8, and 12.
- ≥ 5-point improvement (decrease) from baseline in HIT-6 total score at Weeks 4, 8, and 12.

- Participant assessed by the PGIC as "much better" or "very much better" at Week 12.
- Participant "Satisfied" or "extremely satisfied" with study medication for migraine prevention at Weeks 4, 8, and 12.
- Change from baseline in percent work time missed, percent impairment while working, percent overall impairment, and percent activity impairment due to migraine at Weeks 4, 8, and 12 as assessed by the WPAI:MIGRAINE.
- Change from baseline in the MIDAS total score at Week 12.
- Change from baseline in MIDAS absenteeism score (Questions 1, 3, and 5) at Week 12.
- Change from baseline in MIDAS presenteeism score (Questions 2 and 4) at Week 12.
- Change from baseline in PGI-S score at Weeks 4, 8, and 12.
- Change from baseline in the MSQ v2.1 Role Function Preventive domain score at Weeks 4, 8, 12, and 16.
- Change from baseline in the MSQ v2.1 Role Function Restrictive domain score at Weeks 4, 8, and 16.
- Change from baseline in the MSQ v2.1 Emotional Function domain score at Weeks 4, 8, 12, and 16.
- Change from baseline in monthly Performance of Daily Activities domain score of the AIM-D at Weeks 1-4, 5-8, and 9-12.
- Change from baseline in monthly Physical Impairment domain score of the AIM-D at Weeks 1-4, 5-8, and 9-12.
- Change from baseline in monthly AIM-D total score at Weeks 1-4, 5-8, and 9-12, and average across the 12-week treatment period
- Change from baseline in monthly activity level at Weeks 1-4, 5-8, 9-12, and average across the 12-week treatment period.
- Change from baseline in monthly activity limitation at Weeks 1-4, 5-8, 9-12, and average across the 12-week treatment period.

For variables with a continuous response range, analyses will be performed similarly to that used for the primary analysis, with focus again on the pairwise contrasts of each dose group to placebo. Baseline in the primary MMRM model will be replaced with corresponding endpoint baseline. There is only one post-baseline assessment for MIDAS, and thus ANCOVA model will

be used to analyze MIDAS related endpoints with model terms including treatment group, prior exposure (yes/no) to a migraine prevention medication with proven efficacy, and corresponding baseline score. For the endpoint change from baseline in each MSQ v2.1 domain score, Week 16 (follow up visit) will not be included in MMRM model fitting.

For variables where the data are essentially binary, comparisons between treatment groups will be done using a generalized linear mixed model for variables with multiple postbaseline assessments. A generalized linear mixed model will assume a binary distribution for the response and uses a logit link. The analysis model will include treatment group, visit, prior exposure (yes/no) to a migraine prevention medication with proven efficacy, and treatment group-by-visit interaction as categorical fixed effects; baseline value and baseline-by-visit interaction will be included as covariates. Participants will be included as random effects with unstructured covariance matrix in the model to account for the correlation among repeated measurements. The analysis will be performed based on all postbaseline values using only the observed cases without imputation of missing values. As there is no baseline assessment for the endpoint patient's satisfaction with study medication, baseline monthly migraine days will be included in the model.

For binary endpoints with only one postbaseline assessment (for example, PGIC responder) or responders across 12-week double-blind treatment period, a logistic regression model will be used to model the probability of a response or event with model terms including treatment group, prior exposure (yes/no) to a migraine prevention medication with proven efficacy, and corresponding baseline. As there is no baseline assessment for PGIC, baseline monthly migraine days will be used in the logistic regression model as a covariate for PGIC responder analyses.

For daily efficacy variables, the number and percentage of participants with a migraine day will be summarized by each day under consideration. A generalized linear mixed model as described above will be used to analyze the proportion of participants with a migraine day as repeated measures from the initial dose day to 6 days after. Here baseline value is the daily rate for participants with a migraine day during the baseline period.

In addition, percent reduction in the proportion of participants with a migraine day will be provided by each day under consideration. It is defined as

$$100 \times \left(1 - \frac{\text{proportion of participants with a migraine day on a specific day}}{\text{baseline daily rate of participants with a migraine day}}\right).$$

The proportion of participants with a migraine day will be calculated relative to the number of participants in mITT Population with available eDiary record on the day of consideration. The

numerator will be the number of participants with a migraine day on that day. The baseline daily rate of participants with a migraine day will be calculated as the average of monthly migraine days (prorated if less than 28 days of baseline data are reported) at baseline period for participants in mITT Population divided by 28.

Plots of fitted (least squares) mean changes and their standard errors for monthly migraine days, monthly headache days and monthly acute medication use days from the MMRM will be presented by treatment group and 4-week interval.

Plots of ≥ 25%, ≥ 50%, ≥ 75%, and 100% improvement (reduction) in monthly migraine days will be presented by treatment group and 4-week interval, respectively.

In addition, cumulative distribution graph of percent improvement (decrease) in mean monthly migraine days across 12-week treatment period will be provided by treatment group, and by prior exposure (yes/no) to a migraine prevention medication with proven efficacy and treatment group.

10.5 Off-treatment Hypothetical Estimand

This section defines an estimand, termed as off-treatment hypothetical estimand, which will be the primary estimand in support of EU filing and serve as one sensitivity analysis in support of US filing.

Per study design (Protocol Sections 8.4.3.1 and 8.8), eDiary data will be collected for participants who early terminated from the double-blind treatment period during the 4 weeks between V7 (Early termination visit) and V8 (Follow-up Visit), i.e., participants who prematurely discontinued (before Week 12) will continue to complete eDiary efficacy assessments while off-treatment.

10.5.1 Treatment Condition of Interest

Participants take assigned treatment by randomization during the double-blind treatment period. In addition, permissible and prohibited mediations are described below:

- Participants are allowed to take acute migraine medications (Protocol Section 4.4.1) to keep the participants in the study.
- The protocol prohibits patients from starting any new migraine preventive treatments (Protocol Section 4.4.2) during the study (including the double-blind treatment period and the follow-up period).

10.5.2 Population

The target population is patients suffering from migraine with aura or migraine without aura satisfying the inclusion and exclusion criteria as specified in Section 4 of protocol.

The analysis population for off-treatment hypothetical estimand is defined to be all randomized participants who received at least 1 dose of study treatment, had an evaluable baseline period of eDiary data and had at least 1 evaluable post-baseline 4-week period (Weeks 1 to 4, 5 to 8, 9 to 12) of eDiary data, regardless of whether on study treatment or off study treatment.

This population will be the primary efficacy analysis population in support of EU filing. On study treatment is from the first dose till the last dose of study intervention. As the analysis-visit mapping window (Table 17–2) is defined for the entire postbaseline period (not limited to the double-blind treatment period for participants who prematurely discontinued), the number of participants in the analysis population for off-treatment hypothetical estimand is expected to be greater than or equal to the number of participants in the mITT Population.

10.5.3 Variable

The variable is the same as the primary efficacy endpoint defined in Section 10.2, which is the change from baseline in the participant's mean monthly (4-weeks) migraine days across the 12-week treatment period as derived from the eDiary data.

10.5.4 Accounting of Intercurrent Events

Intercurrent events and their handling rules are as follows:

- Participants who started a new migraine prophylaxis treatment during the double-blind or safety follow-up period will have their data during the follow-up period after starting the new migraine prophylaxis treatment excluded from the analysis.
- Participants who discontinue study treatment due to all reasons other than starting a new migraine prophylaxis treatment will have their data collected after discontinuation of study treatment, and those off-treatment data will be included in the analysis.

If a participant provides less than 14 days of efficacy data during a monthly period regardless in the double-blind treatment period or the follow-up period, then he/she is considered to have missing data during that monthly period. When a participant provides at least 14 days of efficacy

data during a monthly period, he/she is considered to have efficacy data during that monthly period.

As the protocol prohibits participants from starting any new prophylaxis treatment until the study is completed. Only a limited number of participants as protocol deviators might take new prophylaxis treatment during the study. The criteria for identifying the participants who started a new migraine prophylaxis treatment are described in Section 17.11.

10.5.5 Population-level Summary

The population-level summary for the primary endpoint is the difference in primary variable means between each atogepant group and placebo.

Participants are always analyzed based on their treatment assignment by randomization. To obtain the estimate of treatment effect defined in the off-treatment hypothetical estimand, an MMRM similar to the primary analysis specified in Section 10.2.1 will be performed on observed data collected from both double-blind treatment period and follow-up period. The model terms include treatment group, visit (derived as month), prior exposure (yes/no) to a migraine prevention medication with proven efficacy, treatment- by-visit interaction, the baseline score and baseline-by-visit interaction.

10.5.6 Off-treatment Hypothetical Estimand Approach for the Secondary Endpoints

Continuous secondary endpoints based on eDiary data will be handled using the same estimand approach defined above for the primary endpoint.

The secondary endpoint of 50% responders are derived at least a 50% reduction from baseline in the 3-month average of monthly migraine days using data collected from the double-blind period and follow-up period. Data after participants started a new prophylaxis treatment during the follow-up period will be excluded. The population-level summary for this endpoint is the odds ratio from a logistic regression for each atogepant group relative to placebo with baseline monthly migraine days as a covariate, prior exposure (yes/no) to a migraine prevention medication with proven efficacy and treatment group as fixed factors.

The graphical approach to control the overall Type I error rate described in Section 10.3 will be provided for primary and key secondary endpoints in the analysis population for off-treatment hypothetical estimand.

11 Safety Analyses

The safety analysis will be performed using the Safety Population. The safety parameters will include adverse events (AEs), clinical laboratory, vital sign, electrocardiographic (ECG), and C-SSRS. For clinical laboratory, vital sign, and ECG, the last non-missing safety assessment before the first dose of treatment will be used as the baseline for all analyses of that safety parameter. Continuous variables will be summarized by number of participants and mean, SD, median, Q1, Q3, minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants.

11.1 Adverse Events

Adverse events will be coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), version 22.0 or newer.

An AE will be considered as a treatment-emergent adverse event (TEAE) if the AE began or worsened (increased in severity or became serious) on or after the date of the first dose of double-blind study treatment. An AE that occurs more than 30 days after the last dose of double-blind study treatment or Visit 8 whichever comes later will not be counted as a TEAE. Per case report form instructions, a new AE record will be created for any AE that worsens; therefore, TEAEs can be identified as those AEs captured in Study 3101-301-002 with recorded onset date on or after the date of the first dose of double-blind study treatment and within 30 days after the last dose of double-blind study treatment or Visit 8 whichever comes later. An AE will be considered as a treatment-emergent SAE (TESAE) if it is a TEAE that also meets SAE criteria. TEAEs that started after the date of last dose of study treatment will be considered as newly emergent.

Only AEs captured in Study 3101-301-002 will be considered for TEAEs in this study. For participants rolling over into Study 3101-309-002 (extension study) who start the first dose on Visit 1 or beyond, AEs captured in Study 3101-309-002 will be summarized in that study although some AEs might occur within 30 days after the last dose from Study 3101-301-002.

Overall summary of AEs will be provided on a per-participant basis for categories of TEAEs, treatment-related TEAEs, deaths, TESAEs, and TEAEs leading to treatment discontinuation.

The number and percentage of participants reporting TEAEs in each treatment group will be tabulated by system organ class and preferred term, and further categorized by severity to the study treatment.

The number and percentage of participants reporting treatment-related TEAEs in each treatment group will be tabulated by system organ class and preferred term.

The number and percentage of participants reporting newly emergent TEAEs in each treatment group will be tabulated by system organ class and preferred term.

The number and percentage of participants who have TEAEs leading to treatment discontinuation will be summarized by system organ class, preferred term and treatment group.

The incidence of common (≥ 2% of participants in any treatment group) TEAEs will be summarized by preferred term, and treatment group. A similar 5% table will be provided as well.

The number and percentage of participants who have TESAE in each treatment group will be tabulated by system organ class and preferred term.

In addition, separate tabular displays will be presented for patients who died, participants with SAEs, and participants with TEAEs leading to treatment discontinuation.

11.2 Clinical Laboratory Assessments

Descriptive statistics for clinical laboratory values (in SI units) at baseline, postbaseline, and changes from baseline values at each postbaseline timepoint will be presented by treatment group for the following laboratory parameters:

Hematology:	Hemoglobin, hematocrit, red blood cell count, red blood cell indices (mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration), white blood cell count, including differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), platelet count
Chemistry:	Sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine kinase, total protein, albumin, calcium, phosphorus, uric acid, total cholesterol, eGFR
Urinalysis:	Specific gravity, pH

In addition, descriptive statistics for values and changes from the baseline values in conventional units at each assessment time point will be presented for selected clinical laboratory parameters

listed in Appendix I. A description of reporting the lab values in conventional units in patient narratives (along with the standard reporting in SI units) is presented at the end of Appendix I.

Clinical laboratory test values will be considered potentially clinically significant (PCS) if they meet either the lower-limit or higher-limit PCS criteria listed in Table 11–1. The normal range for eGFR was not collected in the lab. Therefore, eGFR<60 mL/min/1.73m^2 is defined in Table 11–2 to classify renal function as the category of "Moderate eGFR Decrease or Worse" based on FDA guidance on PK studies in Patients with impaired renal function. The number and percentage of participants who have PCS postbaseline clinical laboratory values will be tabulated by treatment group. The percentages will be calculated relative to the number of participants with available non-PCS baseline values and at least 1 postbaseline assessment for the double-blind treatment period. The numerator will be the total number of participants with available non-PCS baseline values and at least 1 PCS postbaseline value during the study. A supportive tabular display of participants with PCS postbaseline values will be provided, including the PID number, baseline and all postbaseline (including non-PCS) values.

In addition, a tabular display showing all AEs that occurred in participants who had PCS postbaseline clinical laboratory values will be provided.

Shift tables from baseline to end of the double-blind treatment period for clinical laboratory parameters will be presented by treatment group for the following categories: low, normal, and high, which are provided by the laboratory vendor.

Potential Hy's Law criteria within a 24-hour window is defined by a post baseline elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 x ULN, along with total bilirubin (TBL) ≥ 2 x ULN and a non-elevated alkaline phosphatase (ALP) < 2 x ULN, all based on blood draws collected within a 24-hour period. Potential Hy's Law criteria without time window is defined by maximum of post baseline elevation of ALT or AST ≥ 3 x ULN, along with maximum of post baseline elevation of TBL ≥ 2 x ULN. Patients who meet the potential Hy's Law criteria from the first dose of study drug to the end of study will be summarized. Supportive tabular displays will also be provided.

Table 11–1 Criteria for Potentially Clinically Significant Laboratory Values

Category	Parameter	SI Unit	PCS Criteria	
			PCS Low	PCS High
Chemistry	Albumin	g/L	< 0.8 × LLN	> 1.2 × ULN
	Alanine aminotransferase	U/L	—	≥ 3.0 × ULN
	Alkaline phosphatase	U/L	—	≥ 3.0 × ULN
	Aspartate aminotransferase	U/L	—	≥ 3.0 × ULN
	Bicarbonate	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Bilirubin, total	µmol/L	—	≥ 1.5 × ULN
	Blood urea nitrogen	mmol/L	—	> 1.5 × ULN
	Calcium	mmol/L	< 0.9 × LLN	> 1.1 × ULN

Table 11–1 Criteria for Potentially Clinically Significant Laboratory Values

Category	Parameter	SI Unit	PCS Criteria	
			PCS Low	PCS High
	Chloride	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Cholesterol, total	mmol/L	—	> 1.6 × ULN
	Creatinine	µmol/L	—	> 1.5 × ULN
	Creatine kinase	U/L	—	> 2.0 × ULN
	Estimated glomerular filtration rate	mL/min/1.73m^2	< 60	—
	Glucose, nonfasting	mmol/L	< 0.8 × LLN	> 2.0 × ULN
	Lactate dehydrogenase (LDH)	U/L	—	> 3.0 × ULN
	Phosphorus	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Potassium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Protein, total	g/L	< 0.9 × LLN	> 1.1 × ULN
	Sodium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Triglycerides	mmol/L	—	> 2.0 × ULN
	Uric acid	µmol/L	—	> 1.2 × ULN
Hematology	Basophils, absolute cell count	10^9/L	—	> 2.0 × ULN
	Eosinophils, absolute cell count	10^9/L	—	> 2.0 × ULN
	Hematocrit	Ratio	< 0.9 × LLN	> 1.1 × ULN
	Hemoglobin	g/L	< 0.9 × LLN	> 1.1 × ULN
	Lymphocytes, absolute cell count	10^9/L	< 0.7 × LLN	> 1.3 × ULN
	Monocytes, absolute cell count	10^9/L	< 0.5 × LLN	> 2.0 × ULN
	Neutrophils, absolute cell count	10^9/L	< 0.7 × LLN	> 1.3 × ULN
	Platelet count	10^9/L	< 0.5 × LLN	> 1.5 × ULN
	Red blood cell count	10^{12}/L	< 0.9 × LLN	> 1.1 × ULN
	White blood cell count	10^9/L	< 0.9 × LLN	> 1.5 × ULN
Urinalysis	pH	pH	< 0.9 × LLN	> 1.1 × ULN
	Glucose	—	—	At least 1+
	Protein	—	—	At least 1+
	Specific gravity	—	—	> 1.1 × ULN

LLN = lower limit of normal value; ULN = upper limit of normal value; normal value provided by laboratory.
SI = Le Système International d'Unités (International System of Units).
eGFR<60 mL/min/1.73m^2 indicates moderate eGFR decrease or worse.

The number and percentage of participants meeting each of the following criteria for postbaseline hepatic laboratory abnormalities listed in Table 11–2 will be summarized by treatment group. The percentages will be calculated relative to the number of participants with at least 1 available postbaseline assessment. The numerator will be the total number of participants having at least 1 postbaseline value that meets the specific category during the study. A supportive listing will also be provided.

Table 11–2 Criteria for Hepatic Laboratory Abnormalities

Laboratory Parameter	Categories
ALT	≥ 1 × ULN
	≥ 1.5 × ULN
	≥ 2 × ULN
	≥ 3 × ULN
	≥ 5 × ULN
	≥ 10 × ULN
	≥ 20 × ULN
AST	≥ 1 × ULN
	≥ 1.5 × ULN
	≥ 2 × ULN
	≥ 3 × ULN
	≥ 5 × ULN
	≥ 10 × ULN
	≥ 20 × ULN
ALT or AST	≥ 1 × ULN
	≥ 1.5 × ULN
	≥ 2 × ULN
	≥ 3 × ULN
	≥ 5 × ULN
	≥ 10 × ULN
	≥ 20 × ULN
Bilirubin Total	≥ 1 × ULN
	≥ 1.5 × ULN
	≥ 2 × ULN
	≥ 3 × ULN
	≥ 5 × ULN
	≥ 10 × ULN
	≥ 20 × ULN
Alkaline Phosphatase	≥ 1 × ULN
	≥ 1.5 × ULN
	≥ 2 × ULN
	≥ 3 × ULN
	≥ 5 × ULN
	≥ 10 × ULN
	≥ 20 × ULN
Concurrent Elevations[1]	ALT or AST >= 3 × ULN and Bilirubin Total ≥ 1.5 × ULN
	ALT or AST >= 3 × ULN and Bilirubin Total ≥ 2 × ULN
Potential Hy's Law[1]	ALT or AST ≥ 3 × ULN and Bilirubin Total ≥ 2 × ULN and ALP < 2 × ULN

ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ALP = alkaline phosphatase; ULN = upper limit of normal (value provided by the laboratory).

[1] Elevations are from the same day

The number and percentage of participants with an adjudicated case (i.e., ALT ≥ 3 x ULN and/or AST ≥ 3 x ULN) will be summarized by treatment group and by relationship of ALT or AST elevation to study medication. The percentages will be calculated relative to the number of participants with at least 1 adjudicated case. The numerator will be the number of participants with at least 1 adjudicated case in the specific category of relationship. If a participant has more than 1 adjudicated case, he or she will be counted in the most relevant category of relationship.

Participants with an adjudicated case (i.e. ALT ≥ 3 x ULN or AST ≥ 3 x ULN) will be listed with their ALT and AST assessments, adjudication dates, relationship of ALT or AST elevation to study medication, and confounding factor(s). Additional listings will be provided for participants who meet ALT ≥ 3 x ULN or AST ≥ 3 x ULN and/or potential Hy's law and have one of the following categories: at least 1 abnormal liver biochemistry risk factor, at least 1 liver disease sign and symptom, at least 1 liver diagnostic test performed, consultation with a specialist for liver evaluation, liver lab tests performed, and drug screen performed, respectively. A listing of urine pregnancy test results will be provided for female participants of child-bearing potential with at least one positive result.

11.3 Vital Signs

Descriptive statistics for vital signs (systolic and diastolic blood pressures [sitting and standing], pulse rate [sitting and standing], respiratory rate, temperature, weight, orthostatic systolic blood pressure, orthostatic diastolic blood pressure, and orthostatic pulse rate) values at baseline, postbaseline, and changes from baseline values at each postbaseline timepoint will be presented by treatment group. Orthostatic vital sign values (orthostatic systolic and diastolic blood pressures, and orthostatic pulse rate) are defined as the corresponding standing measurement minus sitting measurement of systolic and diastolic blood pressures and pulse rate respectively.

Vital sign values will be considered PCS if they meet both the observed value criterion and the change from baseline value criterion, if both criteria are available, or meet either the observed value criterion or the change from baseline value criterion that will be detailed in Table 11–3. The number and percentage of participants who have PCS postbaseline vital sign values will be tabulated by treatment group. For criteria related with systolic blood pressure, diastolic blood pressure, pulse rate and weight, the denominator will be the number of participants who have available baseline and at least 1 postbaseline assessment. For criteria related with orthostatic measures, the denominator will be the number of participants who have available non-PCS baseline and at least 1 postbaseline assessment. The numerator will be the total number of participants with at least 1 PCS postbaseline value during the study. A supportive listing of participants with PCS postbaseline values will be provided. In addition, a tabular display

showing all AEs that occurred in participants who had PCS postbaseline vital sign values will be provided.

Table 11–3 Criteria for Potentially Clinically Significant Vital Signs

Parameter	Flag	Criteria	
		Observed Value	Change from Baseline
Systolic blood pressure, mm Hg	High	≥ 180	Increase of ≥ 20
	Low	≤ 90	Decrease of ≥ 20
Diastolic blood pressure, mm Hg	High	≥ 105	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Pulse rate, bpm	High	≥ 120	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Weight, kg	High	—	Increase of ≥ 7%
	Low	—	Decrease of ≥ 7%
Orthostatic SBP change, mm Hg	Low	≤ -20	—
Orthostatic DBP change, mm Hg	Low	≤ -15	—
Orthostatic Pulse rate change, bpm	High	≥ 25	—

SBP = Systolic blood pressure, DBP = Diastolic blood pressure, bpm = beats per minute.

11.4 Electrocardiograms

Descriptive statistics for ECG parameters (i.e., heart rate, PR interval, QRS interval, RR interval, QT interval, and QTc interval) at baseline, postbaseline, and changes from baseline values at each postbaseline timepoint will be presented by treatment group.

ECG parameter values are considered PCS if ECG values meet either the actual value or change from baseline PCS high criteria listed in Table 11-4. The number and percentage of participants with PCS postbaseline values will be tabulated by study treatment. The percentages will be calculated relative to the number of participants with an available non-PCS baseline value and at least 1 postbaseline assessment. The numerator will be the total number of participants with an available non-PCS baseline value and at least 1 PCS postbaseline ECG value during the study. A supportive listing of participants with PCS postbaseline values will be provided. A listing of all AEs for participants with PCS ECG values will also be provided.

AddTableTitle

Table 11-4 Criteria for Potentially Clinically Significant Electrocardiograms

Parameter	Unit	Criterion
QRS interval	msec	≥ 150
PR interval	msec	≥ 250
QTc (QTcB or QTcF) interval	msec	> 500
QTc (QTcB or QTcF) interval	msec	Increase from baseline > 60

QTc = QT interval corrected for heart rate.
QTcB = QT interval corrected for heart rate using the Bazett formula.
QTcF = QT interval corrected for heart rate using the Fridericia formula.

To evaluate ECG postbaseline values of clinical interest, the number and percentage of participants with post-treatment QTcF > 450 msec, > 480 msec, and > 500 msec will be tabulated by treatment group.

The number and percentage of participants with an increase > 30 msec but ≤ 60 msec, and with an increase > 60 msec in QTcF will be tabulated. Participants will be counted only once for the most severe category. A supportive listing of participants with postbaseline QTcF increases > 30 msec will be provided, including the PID number, study center, and all QTc values (including changes from baseline). A listing of all AEs for participants with postbaseline QTcF increases > 30 msec will also be provided.

A shift table from baseline to the end of double-blind treatment period in the investigator's overall interpretation of the ECG will be presented by treatment group for the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant. A tabular display of participants with postbaseline clinically significant ECG abnormalities according to the investigator's overall interpretation will be provided.

11.5 Columbia-Suicide Severity Rating Scale

For C-SSRS, the number and percentage of participants with suicidal ideation or suicidal behavior as recorded on the C-SSRS will be summarized by treatment group for the Safety Population. The distribution of responses for most severe suicidal ideation and most severe suicidal behavior in the participant's lifetime history, in the past 6 months, in the double-blind treatment period, and in the follow-up period will also be presented by treatment group. Supportive listings will be provided and will include the PID number, study center number, treatment group, lifetime history, and postbaseline values. Intensity of suicidal ideation and suicidal behavior type will also be included in these listings.

12 Health Outcome Analyses

Health outcomes which are planned to be reported in CSR main body are provided in Section 10.4. Other health outcome analyses are documented in health economics and outcomes research SAP.

13 Subgroup Analyses

Subgroup analysis based on prior exposure (yes/no) to a migraine prevention medication with proven efficacy will be performed for the following efficacy endpoints

- Change from baseline in mean monthly migraine days across the 12-week treatment period
- Change from baseline in mean monthly headache days across the 12-week treatment period
- Change from baseline in mean monthly acute medication use days across the 12-week treatment period
- ≥ 50% reduction in 3-month average of monthly migraine days
- ≥ 75% reduction in 3-month average of monthly migraine days
- 100% reduction in 3-month average of monthly migraine days

Subgroup analyses for primary efficacy endpoint based on demographic factors (age, sex, race) will be provided in the integrated summary of efficacy to facilitate the comparison across pivotal studies.

14 Interim Analysis

No interim analysis is planned.

15 Determination of Sample Size

A total sample size of 218 participants will be randomized per treatment group and that will provide at least 98% power to detect the treatment difference between each of the 3 atogepant doses (assumed equally effective) and placebo for the primary efficacy endpoint. The sample size of this study was selected to provide sufficient power for the primary efficacy endpoint and first 3 secondary endpoints as shown in Table 15–1. The power calculations are performed by using nQuery Advisor 7.0 and based on the following assumptions:

1) The treatment difference from placebo will be similar to the average value across the migraine prevention studies for atogepant (Phase 2/3 Study CGP-MD-01), telcagepant (Ho 2014) and monoclonal antibodies (Dodick 2014a; Dodick 2014b; Bigal 2015). The standard deviation of each endpoint was estimated from an internal study that randomized approximately 800 participants. In particular, the assumed treatment difference from placebo in change from baseline in mean monthly migraine days across the 12-week treatment period is assumed -1.5 days, and the standard deviation is 3.5 days. Detailed treatment difference and standard deviation assumptions are listed in Table 15–1.

2) The study statistical testing plan controls the overall type 1 error at 5%. The power calculations of the primary and secondary endpoints have taken the multiple comparisons into consideration by testing each dose versus placebo at a 0.0167 significance level, 2-sided. Once the primary endpoint for each dose is significant at 0.0167 (2-sided), the secondary endpoints will be tested sequentially.

Table 15–1 Statistical Power for Primary and the First Three Secondary Endpoints

Hypothesis Testing	Endpoint	Treatment Difference from Placebo	Standard Deviation	Statistical Power
Primary	Change from baseline in mean monthly migraine days across the 12-week treatment period	–1.5	3.5[a]	98%
Secondary 1	Change from baseline in mean monthly headache days across the 12-week treatment period	–1.5	3.8[a]	95%[b]
Secondary 2	Change from baseline in mean monthly acute medication use days across the 12-week treatment period	–1.2	3.2[a]	93%[b]
Secondary 3	Proportion of participants with at least a 50% reduction in mean monthly migraine days across the 12-week treatment period	33% Placebo rate	50% Atogepant rate	89%[b]

[a] Standard deviations observed in an internal study that randomized approximately 800 participants

[b] Statistical power for secondary endpoints are conditional on success of prior endpoints (assuming independence among the endpoints) in the sequence for the comparisons of each dose versus placebo.

16 Statistical Software

Statistical analyses will be performed using version 9.4 (or newer) of SAS.

17 Data Handling Convention

17.1 Visit Time windows

For analysis purposes, Day 1 is defined on the date of the first dose of double-blind study intervention. On-treatment Period is defined to from the first dose till the last dose.

The analysis visit windows for monthly efficacy endpoints based on daily eDiary data are defined as follows.

Table 17–1 Efficacy Analysis Visit Definitions for eDiary Data

Analysis Phase	Analysis Visit (Derived)	eDiary Window
Pretreatment	Baseline	The last 28 days prior to randomization
Double-blind treatment period	Weeks 1 – 4	Days [1, 28]
	Weeks 5 – 8	Days [29, 56]
	Weeks 9 – 12	Days [57, minimum (End of the double-blind treatment period, 84)]

Day 1 = the date of the first dose of double-blind study intervention.

The analysis visit windows for monthly efficacy endpoints in the estimand approach based on daily eDiary data are defined as follows.

Table 17–2 Efficacy Analysis Visit Definitions in the Estimand Approach for eDiary Data

Analysis Phase	Analysis Visit (Derived)	eDiary Window
Pretreatment	Baseline	The last 28 days prior to randomization
On or after the first dose of study intervention	Weeks 1 – 4 (on/off study treatment)	Days [1, 28]
	Weeks 5 – 8 (on/off study treatment)	Days [29, 56]
	Weeks 9 – 12 (on/off study treatment)	Days [57, 84]

Day 1 = the date of the first dose of double-blind study intervention.
See Section 10.5.3 for determining whether the efficacy data are on study treatment or off study treatment.

The analysis visit windows for weekly efficacy endpoints in the first monthly period based on daily eDiary data are defined as follows:

Table 17–3 Efficacy Analysis Visit Definitions for eDiary Data in the First Monthly Period

Analysis Phase	Analysis Visit (Derived)	eDiary Window
Pretreatment	Baseline	The last 28 days prior to randomization
Double-blind treatment period	Week 1	Treatment Day [1, 7]
	Week 2	Treatment Day [8, 14]
	Week 3	Treatment Day [15, 21]
	Week 4	Treatment Day [22, 28]

The analysis visit windows for daily efficacy endpoints in the first weekly period based on daily eDiary data are defined as follows:

Table 17–4 Efficacy Analysis Visit Definitions for eDiary Data

Analysis Phase	Analysis Visit (Derived)	eDiary Window
Pretreatment	Baseline	The last 28 days prior to randomization
Double-blind treatment period	Initial Dose Day	Treatment Day 1
	1 Day after Initial Dose	Treatment Day 2
	2 Days after Initial Dose	Treatment Day 3
	3 Days after Initial Dose	Treatment Day 4
	4 Days after Initial Dose	Treatment Day 5
	5 Days after Initial Dose	Treatment Day 6
	6 Days after Initial Dose	Treatment Day 7

The analysis visit windows for MSQ v2.1 are defined as follows:

Table 17–5 Efficacy Analysis Visit Definitions for MSQ v2.1

Analysis Phase	Analysis Visit (Derived)	Scheduled Study Visit (eCRF)	Window
Pretreatment	Baseline	Visit 2 (Randomization)	Treatment Day ≤ 1
Double-blind Treatment Period	Week 4	Visit 4	Treatment Day [2, 41]
	Week 8	Visit 6	Treatment Day [42, 69]
	Week 12	Visit 7/ET	Treatment Day [70, End of the double-blind treatment period]
Follow-up	Week 16 (Follow-up)	Visit 8	Treatment Day [End of the double-blind treatment period +1, the last study visit]

ET = early termination. Follow-up visit will not be included in the MMRM analysis and will only be used in summary statistics.

Table 17–6 Efficacy Analysis Visit Definitions in the Off-treatment Estimand for MSQ v2.1

Analysis Phase	Analysis Visit (Derived)	Window
Pretreatment	Baseline	Treatment Day ≤ 1
On or after the first dose of study intervention	Week 4	Treatment Day [2, 41]
	Week 8	Treatment Day [42, 69]
	Week 12	Treatment Day [70, the last study visit]

If there are two assessments in an analysis window with one from the double-blind period and the other from follow-up visit, then the one from double-blind period will be used in order to align with the mapping in Table 17–5.

The analysis visit windows for HIT-6, PGI-S, and WPAI:MIGRAINE are defined as follows:

Table 17–7 Efficacy Analysis Visit Definitions for HIT-6, PGI-S, and WPAI:MIGRAINE

Analysis Phase	Analysis Visit (Derived)	Scheduled Study Visit (eCRF)	Window
Pretreatment	Baseline	Visit 2 (Randomization)	Treatment Day ≤ 1
Double-blind Treatment Period	Week 4	Visit 4	Treatment Day [2, 41]
	Week 8	Visit 6	Treatment Day [42, 69]
	Week 12	Visit 7/ET	Treatment Day [70, End of the double-blind treatment period]

ET = early termination.

The analysis visit windows for PGIC are defined as follows:

Table 17–8 Efficacy Analysis Visit Definitions for PGIC

Analysis Phase	Analysis Visit (Derived)	Scheduled Study Visit (eCRF)	Window
Double-blind Treatment Period	Week 12	Visit 7/ET	Treatment Day [2, End of the double-blind treatment period]

ET = early termination.

The analysis visit windows for Patient Satisfaction with Study are defined as follows:

Table 17–9 Efficacy Analysis Visit Definitions for Patient Satisfaction with Study

Analysis Phase	Analysis Visit (Derived)	Scheduled Study Visit (eCRF)	Window
Double-blind Treatment Period	Week 4	Visit 4	Treatment Day [2, 41]
	Week 8	Visit 6	Treatment Day [42, 69]
	Week 12	Visit 7/ET	Treatment Day [70, End of the double-blind treatment period]

ET = early termination.

The analysis visit windows for MIDAS are defined as follows:

Table 17–10 Efficacy Analysis Visit Definitions for MIDAS

Analysis Phase	Analysis Visit (Derived)	Scheduled Study Visit (eCRF)	Window
Pretreatment	Baseline	Visit 2 (Randomization)	Treatment Day ≤ 1
Double-blind Treatment Period	Week 12	Visit 7/ET	Treatment Day [2, End of the double-blind treatment period]

ET = early termination.

The analysis visit windows for safety endpoints are defined as follows:

Table 17–11 Safety Analysis Visit Definitions

Analysis Phase	Analysis Visit (Derived)	Scheduled Study Visit (eCRF)	Window
Pretreatment	Baseline	Visit 2 (Randomization)	Treatment Day ≤ 1
Double-blind Treatment Period	Week 2	Visit 3	Treatment Day [2, 20]
	Week 4	Visit 4	Treatment Day [21, 34]
	Week 6	Visit 5	Treatment Day [35, 48]
	Week 8	Visit 6	Treatment Day [49, 69]
	Week 12	Visit 7/ET	Treatment Day [70, End of the double-blind treatment period]
	End of the Double-blind Treatment Period		Last available assessment during double-blind treatment period
	Week 16 (Follow-up)	Visit 8	Treatment Day [End of the double-blind treatment period +1, the last study visit]
	End of study		Last available assessment after treatment start date, i.e. occurs at final visit (expected Day 112) or ET

Follow-up visit will be presented in analysis tables for clinical laboratory values and vital signs.

End of the Double-blind Treatment Period is defined as the last available assessment during double-blind treatment period. End of the Double-blind Treatment Period results will be presented in analysis tables for clinical laboratory values, vital signs and ECG.

End of Study is defined as the last available assessment during the study, including double-blind and follow-up period. End of Study results will be presented in analysis tables for safety parameters, including but not limited to clinical laboratory values, and vital signs.

ET = early termination.

For endpoints collected by visit (not for eDiary data), if a participant has 2 or more visits within the same window, the last visit with a non-missing value will be used for analysis, unless specified otherwise.

The following algorithm is used to define the Double-blind Treatment Period and the Follow-up Period unless specified otherwise. The double-blind treatment period starts with the date of the first dose of double-blind study treatment and ends with the latest date of the last study medication date, and the last scheduled assessment date of V2 to V7 for participants who entered the follow-up period; or ends with the latest date of the last study medication date, and last assessment date for participants who did not entered the follow-up period. The follow-up period starts with the 1 day after the end of the double-blind period and ends with the last assessment date for participants who entered the follow-up period.

17.2 Derived Efficacy and Health Outcome endpoints

17.2.1 Derivation of Efficacy Endpoints Based on eDiary Data

For analysis purposes, four weeks (28 days) will be considered as one month. On a daily basis during the 4-week baseline period and throughout the double-blind treatment period, participants are to record eDiary information on the duration of headache, headache specific characteristics and symptoms, the pain severity, and use of any acute headache pain medication. Daily headache diary data consists of data from "today's dairy" completed on that day and "yesterday's diary" completed on the following day. Participants are to report headache data in "today's diary" in the evening at any time from 19:00 to 23:59 and to complete "yesterday's diary" on the following day to add the remaining headache data of previous evening until midnight. In case participants miss "today's diary", they can report the whole-day headache data in "yesterday's diary" on the following day. In case participants miss "yesterday's diary", headache data from "today's diary" alone will be used as daily headache diary data. If both "today's diary" and "yesterday's dairy" are missing on one day, the daily headache diary data will be treated as missing.

Daily headache diary data will be merged from "today's diary" and "yesterday's diary" as following and will be used to derive migraine day and headache day.

- Daily headache total duration: summation of headache durations from "today's diary" and "yesterday's diary"
- Daily headache pain severity: the worst pain severity from "today's diary" and "yesterday's diary"
- Daily headache characteristics and symptoms: present if present in one of "today's diary" and "yesterday's diary"
- Daily acute headache medication usage: combination of acute headache medications usage from "today's diary" and "yesterday's diary".
- For the derivation of headache day, the participant is considered to have taken a non-antiemetic acute headache medication if the participant has taken such a medication in either "today's diary" or "yesterday's diary".

Moderate/severe headache day is defined as a headache day during which the maximum pain severity is either moderate or severe

Severe headache day is defined as a headache day during which the maximum pain severity is severe

If a participant confirmed no headache for the Question 1 in eDiary, then the participant will not answer subsequent questions related to headache symptoms, duration, and acute headache mediation use by design. Thus, the acute medication use for that diary ('today' or 'yesterday') will be treated as 'No' when deriving acute medication use day.

If a participant reported multiple records on the same day for one specific category (‘Today’ or ‘Yesterday’) and records are inconsistent, then the records for that eDiary category on the date with discrepancy will be excluded from endpoint derivation and thus excluded from the analyses. The corresponding records will be flagged in the analysis datasets. If there are duplicated records of daily diary data for the same participant on the same day with the same type, the set of records with the last form access datetime will be used in the analysis because records are duplicated.

The monthly migraine days is defined the total number of recorded migraine days in the eDiary divided by the total number of days with eDiary records during each monthly period and multiplied by 28. For baseline, a minimum of 20 days’ eDiary data during the 4-week baseline period is required for the migraine days to be evaluable. For each postbaseline 4-week treatment period, a minimum of 14 days’ eDiary data during that period is required for the migraine days to be evaluable. If a participant does not have at least 14 days of diary data for a monthly treatment period, the migraine days for that period will be considered as missing. Migraine days will be derived for each participant at baseline and for each postbaseline monthly treatment period (Weeks 1-4, 5-8, 9-12). The same method to derive monthly migraine days will be used to derive monthly headache days, monthly acute medication use days, monthly triptan use days, monthly cumulative headache hours, , monthly moderate/severe headache days, and monthly severe headache days.

If a participant confirmed that acute medications were taken and entered medications in the eDiary, then the acute medication use day will be set to ‘Yes’. If a subject reports ‘Yes’ to the intake of allowed medication(s) to treat an acute migraine but does not list any of them in the diary, then the acute medication use days will not be counted in this situation and vice versa.

For weekly data analysis purposes, baseline is defined to be the baseline derived in monthly basis divided by 4, and change from baseline in the weekly migraine days will be calculated for consecutive 7-day periods beginning with Day 1. Subsequent to treatment start, the number of headache days will be counted in successive and non-overlapping 1-week (i.e., 7-day) windows. Headaches that continue into a subsequent 1-week period will be counted (with recorded severity and duration) as occurring in each period. If any postbaseline eDiary window for a participant has at least 4 but less than 7 days of reported data, the prorated approach will be used. If a participant reports less than 4 days of headache data, the participant’s observed counts in that particular 7-day eDiary window will be set to missing for that window.

17.2.2 Derivation of Health Outcome Endpoints

If a participant reported multiple records on the same day and records are inconsistent, then the records on the date with discrepancy will be excluded from endpoint derivation and thus excluded from the analyses. The corresponding records will be flagged in the analysis datasets.

AIM-D Related Endpoints Derivation

As described in SAP Section 10.1.2 (copied from protocol Section 6.2.1), the AIM-D was developed as a daily eDiary with a recall period 24 hours. By design, it is collected in the today diary only. The scoring of the following endpoints is completed in 2 steps.

- Monthly Performance of Daily Activities domain score of the AIM-D
- Monthly Physical Impairment domain score of the AIM -D
- Monthly AIM -D total score

Step 1: Calculate AIM-D daily domain score and total score

Daily performance of daily activities score will be calculated based on the summation of items 1-5 and 10 and 11, ranging from 0-35. A daily performance of daily activities domain score will be calculated if 4 or more item scores have non-missing responses. When the response category "I did not have <errands, leisure or social, strenuous activities> planned" (items 2, 4, and 5), is selected, the response will be considered missing. The corresponding performance of daily activities domain score will be calculated by summing the non-missing item scores and dividing by the number of non-missing items and then multiplying by 7, provided that 4 or more item scores are available; otherwise it will be set to missing. The raw daily score will be transformed to a 0-100 scale by multiplying by 100 and dividing by the highest raw score (35).

Daily physical impairment scores will be calculated based on the summation of items 6-9, ranging from 0-20. A daily physical Impairment score will be calculated if 2 or more item scores have non-missing responses. The corresponding physical Impairment score will be calculated by summing the non-missing item scores and dividing by the number of non-missing items and then multiplying by 4, provided that 2 or more item scores are available; otherwise it will be set to missing. The raw daily score will be transformed to a 0-100 scale by multiplying by 100 and dividing by the highest raw score (20).

A daily total score will be calculated based on the summation of items 1-11, ranging from 0-55. A Total Score will be calculated if 6 or more items scores have non-missing responses. When the response category "I did not have <errands, leisure or social, strenuous activities> planned" (items 2, 4, and 5), is selected, the response will be considered missing. The corresponding Total

Score will be calculated by summing the non-missing item scores and dividing by the number of non-missing items and then multiplying by 11, provided that 6 or more item scores are available; otherwise it will be set to missing. The raw score will be transformed to a 0-100 scale by multiplying by 100 and dividing by the highest raw score (55).

Step 2: Calculate Monthly Scores and Baseline Score

Monthly scores will be calculated using the average daily scores only if there are at least 14 non-missing daily scores in the corresponding monthly (28-day) period. The corresponding monthly scores will be calculated by summing the non-missing daily domain scores and dividing by the number of non-missing daily domain, provided that 14 or more daily scores are available; otherwise it will be set to missing.

Monthly activity level score will be calculated by summing the non-missing daily scores and dividing by the number of these scores, provided that 14 or more daily scores are available in the corresponding monthly (28-day) period; otherwise it will be set to missing. Same rule will be applied to the calculation of monthly activity limitation score.

MSQ Related Endpoints Derivation

MSQ v2.1 consists of 14 items with a 4-week recall period. The scoring of the MSQ is completed in following 3 steps.

Step 1: Final item value assignment.

Precoded item values and final item values for each MSQ item response are shown in Table 17–12.

Table 17–12 Item Values for MSQ Item Responses

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

Step 2: Computation of raw domain(dimension) scores

Once a final item value has been assigned to each item, a raw score can be computed for each MSQ domain. Role Function Restrictive domain includes Items 1 - 7, Role Function Preventive domain includes Items 8 - 11, and Emotional Function domain includes Items 12 - 14. The raw score for each domain is the algebraic sum of the final item values for all items in that domain.

Missing data handling: if a respondent answered at least half of the items in a domain (or half plus one in the case of scales with an odd number of items), a missing item value can be estimated using the average of the other completed items within the same dimension.

In detail, for MSQ v2.1 Role Function Restrictive domain, the 7 individual item responses using final item value will be summed, resulting in the raw domain score ranging from 7 to 42 with higher scores indicating better quality of life. If there are missing item responses, the raw domain score will be calculated by summing the non-missing item responses using final item value and dividing by the number of non-missing items and then multiplying by 7 provided that 4 or more items in the domain are completed; otherwise it will be set to missing. For MSQ v2.1 Role Function Preventive and Emotional domains, the raw domain scores will be calculated similarly using final item value respectively. If there are missing item responses, the corresponding raw domain score will be calculated by summing the non-missing item responses using final item value and dividing by the number of non-missing items and then multiplying by the number of questions in that domain provided that 2 or more domain items are completed; otherwise it will be set to missing.

Step 3: Linear transformation to a 0 to 100 scale.

The transformation formula for each MSQ 2.1 domain are listed below

- Role Function -Restrictive: $\frac{(raw\ score-7)*100}{35}$
- Role Function-Preventive: $\frac{(raw\ score-4)*100}{20}$
- Emotional Function: $\frac{(raw\ score-3)*100}{15}$

HIT-6 Total Score Derivation

For HIT-6 total score, pre-coded item values and final item values for each item response are shown in Table 17–13. Total score is calculated by summing 6 sub-item responses, resulting in

the total score ranging from 36 to 78 with higher scores indicating greater impact. If any sub item is missing, then total score will be missing.

Table 17–13 Item Values for HIT-6 Item Responses

Response Categories	Precoded Item Value	Final Item Value
Never	0	6
Rarely	1	8
Sometimes	2	10
Very Often	3	11
Always	4	13

The HIT-6 instrument has a recall period of 4 weeks for 3 of the 6 items.

MIDAS Related Endpoints Derivation

MIDAS total score is derived as the sum of first 5 of questions (i.e., the sum of days missing work or school, Productivity at work or school reduced, Not do household work, Productivity in household work reduced, Miss family social or leisure activities). If any sub item is missing, the MIDAS total score will be missing.

The MIDAS absenteeism score is derived as the sum of Questions 1, 3 and 5. If any sub item is missing, then the MIDAS absenteeism score will be missing. The MIDAS presenteeism score is derived as the sum of Questions 2 and 4. If any sub item is missing, then the MIDAS presenteeism score will be missing.

WPAI:MIGRAINE Related Endpoints Derivation

WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes, as follows:

Questions:

- Q1 = currently employed (working for pay).

- Q2 = missed work hours because of problems associated with your migraine
- Q3 = missed work hours due to other reason.
- Q4 = hours actually worked.
- Q5 = migraine affected productivity while working.
- Q6 = migraine affected regular daily activity.

Scores:

Multiply scores by 100 to express in percentages.

- Percent work time missed due to migraine (absenteeism): Q2/(Q2 + Q4)
- Percent impairment while working due to migraine (presenteeism): Q5/10
- Percent overall work impairment due to migraine (overall work productivity loss): Q2/(Q2 + Q4) + [(1- (Q2/(Q2 + Q4)))x(Q5/10)]
- Percent activity impairment due to migraine (regular activity impairment): Q6/10

If the response to Q1 ("Currently employed?") is *No* or missing, absenteeism, presenteeism, and overall work productivity loss will all be set to missing.

17.3 Repeated or Unscheduled Assessments of Safety Parameters

Baseline is defined as the last assessment made before the first dose of double-blind study treatment. If a participant has 2 or more visits within the same window, the last visit with a non-missing value will be used for summary over time unless specified otherwise. If end-of-study assessments are repeated or if unscheduled visits occur, the last non-missing postbaseline assessment will be used as the end-of-study assessment for generating summary statistics. However, all postbaseline assessments will be used for PCS value determinations, and all assessments will be presented in the data listings.

17.4 Missing Date of the Last Dose of Study treatment

When the date of the last dose of the double-blind study treatment is missing, all efforts should be made to obtain the date from the Investigator. If it is still missing after all efforts have been made, the last available study medication date will be used in the calculation of treatment duration.

17.5 Missing Severity Assessment for Adverse Events

If severity is missing for an AE that started before the date of the first dose of double-blind study treatment, an intensity of mild will be assigned. If severity is missing for an AE that started on or after the date of the first dose of double-blind study treatment, an intensity of severe will be assigned. The imputed values for severity assessment will be used for the incidence summary; the values will be shown as missing in the data listings.

17.6 Missing Causal Relationship to Study treatment for Adverse Events

If the causal relationship to the double-blind study treatment is missing for an AE that started on or after the date of the first dose of double-blind study treatment, a causality of yes will be assigned. The imputed values for causal relationship to double-blind treatment will be used for the incidence summary; the values will be shown as missing in the data listings.

17.7 Missing Date Information for Adverse Events

The following imputation rules only apply to cases in which the start date for AEs is incomplete (i.e., partly missing).

17.7.1 Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of double-blind study treatment, the month and day of the first dose of double-blind study treatment will be assigned to the missing fields

- If the year of the incomplete start date is before the year of the first dose of double-blind study treatment, *December 31* will be assigned to the missing fields

- If the year of the incomplete start date is after the year of the first dose of double-blind study treatment, *January 1* will be assigned to the missing fields

17.7.2 Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

17.7.3 Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of double-blind study treatment, the day of the first dose of double-blind study treatment will be assigned to the missing day

- If either the year of the incomplete start date is before the year of the date of the first dose of double-blind study treatment or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of double-blind study treatment, the last day of the month will be assigned to the missing day

- If either the year of the incomplete start date is after the year of the date of the first dose of double-blind study treatment or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of double-blind study treatment, the first day of the month will be assigned to the missing day

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

If the start date is completely missing and the stop date is complete, the following algorithm will be used to impute the start date:

- If the stop date is after the date of the first dose of double-blind study treatment, the date of the first dose of double-blind study treatment will be assigned to the missing start date

- If the stop date is before the date of the first dose of double-blind study treatment, the stop date will be assigned to the missing start date

17.8 Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, including rescue medications, incomplete (i.e., partly missing) start dates and/or stop dates will be imputed. When the start date and the stop date are both incomplete for a participant, the start date will be imputed first.

17.8.1 Incomplete Start Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication start date. If the stop date is complete (or imputed) and the imputed start date is after the stop date, the start date will be imputed using the stop date.

17.8.2 Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of double-blind study treatment, the month and day of the first dose of double-blind study treatment will be assigned to the missing fields

- If the year of the incomplete start date is before the year of the first dose of double-blind study treatment, *December 31* will be assigned to the missing fields

- If the year of the incomplete start date is after the year of the first dose of double-blind study treatment, *January 1* will be assigned to the missing fields

17.8.3 Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

17.8.4 Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of double-blind study treatment, the day of the first dose of double-blind study treatment will be assigned to the missing day

- If either the year of the incomplete start date is before the year of the date of the first dose of double-blind study treatment or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of double-blind study treatment, the last day of the month will be assigned to the missing day.

- If either the year of the incomplete start date is after the year of the date of the first dose of double-blind study treatment or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of double-blind study treatment, the first day of the month will be assigned to the missing day

17.8.5 Incomplete Stop Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication stop date. If the date of the last dose of study treatment is missing, replace it with the last visit date in the imputations described below. If the imputed stop date is before the start date (imputed or nonimputed start date), the imputed stop date will be equal to the start date.

17.8.6 Missing month and day

- If the year of the incomplete stop date is the same as the year of the last dose of study treatment, the month and day of the last dose of study treatment will be assigned to the missing fields

- If the year of the incomplete stop date is before the year of the last dose of study treatment, *December 31* will be assigned to the missing fields

- If the year of the incomplete stop date is after the year of the last dose of study treatment, *January 1* will be assigned to the missing fields

17.8.7 Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

17.8.8 Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the last dose of study treatment, the day of the last dose of study treatment will be assigned to the missing day

- If either the year of the incomplete stop date is before the year of the date of the last dose of study treatment or if both years are the same but the month of the incomplete stop date is before the month of the date of the last dose of study treatment, the last day of the month will be assigned to the missing day

- If either the year of the incomplete stop date is after the year of the date of the last dose of study treatment or if both years are the same but the month of the incomplete stop date is after the month of the date of the last dose of study treatment, the first day of the month will be assigned to the missing day

17.9 Character Values of Clinical Laboratory Parameters

If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table because, for example, a character string is reported for a parameter of the numeric type, a coded value must be appropriately determined for use in the statistical analyses. The actual values, however, as reported in the database will be presented in the data listings.

17.10 Identifying Prior Exposure (yes/no) to a Migraine Prevention Medications with Proven Efficacy Based on Prior Medications Reported in eCRF

According to Appendix 12.3.1 in the protocol, a list of migraine-preventive medications with proven efficacy was identified by clinical team and coding team as shown in Table 17–14.

If a participant has taken medications before the screening visit with preferred names in Table 17–14, and the prior medications are classified as “Migraine Prevention Medication” in the prior and concomitant medications eCRF, then the prior exposure to migraine prevention medications with proven efficacy will be “Yes” for this participant, otherwise, it is set as “No.”

Table 17–14 List of Migraine-preventive Medications with Proven Efficacy

Protocol Pharmacologic Category	Drug Class	Preferred Name
Tricyclic Antidepressant	Amitriptyline	ABMIRAZIN
Tricyclic Antidepressant	Amitriptyline	ADEPSIQUE
Tricyclic Antidepressant	Amitriptyline	AMICODEX
Tricyclic Antidepressant	Amitriptyline	AMITRIPTYLINE
Tricyclic Antidepressant	Amitriptyline	AMITRIPTYLINE AND PSYCHOLEPTICS
Tricyclic Antidepressant	Amitriptyline	AMITRIPTYLINE HYDROCHLORIDE
Tricyclic Antidepressant	Amitriptyline	AMITRIPTYLINE HYDROCHLORIDE W/GABAPENTIN
Tricyclic Antidepressant	Amitriptyline	AMITRIPTYLINE PAMOATE
Tricyclic Antidepressant	Amitriptyline	AMITRIPTYLINE W/DIAZEPAM
Tricyclic Antidepressant	Amitriptyline	AMITRIPTYLINE W/DIAZEPAM/PERPHENAZINE
Tricyclic Antidepressant	Amitriptyline	AMITRIPTYLINE W/GABAPENTIN
Tricyclic Antidepressant	Amitriptyline	AMITRIPTYLINE W/KETAMINE
Tricyclic Antidepressant	Amitriptyline	AMITRIPTYLINE W/MECOBALAMIN
Tricyclic Antidepressant	Amitriptyline	AMITRIPTYLINE W/PERPHENAZINE
Tricyclic Antidepressant	Amitriptyline	AMITRIPTYLINE;CODEINE;DEXTROPROPOXYPHENE;META
Tricyclic Antidepressant	Amitriptyline	AMITRIPTYLINE;MEDAZEPAM
Tricyclic Antidepressant	Amitriptyline	AMITRIPTYLINE;PRIDINOL
Tricyclic Antidepressant	Amitriptyline	CHLORDIAZEPOXIDE W/AMITRIPTYLINE
Tricyclic Antidepressant	Amitriptyline	CUAIT D /06340901/
Tricyclic Antidepressant	Amitriptyline	ETRAFON-D

Protocol Pharmacologic Category	Drug Class	Preferred Name
Tricyclic Antidrepressant	Amitriptyline	KALTRYPTIN
Tricyclic Antidrepressant	Amitriptyline	LIMBATRIL /00033501/
Tricyclic Antidrepressant	Amitriptyline	LIMBITROL /00164901/
Tricyclic Antidrepressant	Amitriptyline	NOBRITOL-F
Tricyclic Antidrepressant	Amitriptyline	PARKS-PLUS
Tricyclic Antidrepressant	Amitriptyline	TRIPTAFEN /01846901/
Beta-Blockers	Atenolol	AMILORIDE;ATENOLOL;HYDROCHLOROTHIAZIDE
Beta-Blockers	Atenolol	AMLODIPINE;ATENOLOL;CHLORTALIDONE
Beta-Blockers	Atenolol	AMLONG-A
Beta-Blockers	Atenolol	ATENOLOL
Beta-Blockers	Atenolol	ATENOLOL HYDROCHLORIDE
Beta-Blockers	Atenolol	ATENOLOL W/HYDROCHLOROTHIAZIDE
Beta-Blockers	Atenolol	ATENOLOL;BENDROFLUMETHIAZIDE;HYDRALAZINE
Beta-Blockers	Atenolol	ATENOLOL;CHLORTALIDONE;HYDRALAZINE
Beta-Blockers	Atenolol	ATENOLOL;HYDROCHLOROTHIAZIDE;LOSARTAN
Beta-Blockers	Atenolol	ATENOLOL;LERCANIDIPINE
Beta-Blockers	Atenolol	ATENOLOL;LOSARTAN
Beta-Blockers	Atenolol	CARDIF BETA
Beta-Blockers	Atenolol	CARDIORETIC A
Beta-Blockers	Atenolol	FIXOCARD
Beta-Blockers	Atenolol	ISOBETA
Beta-Blockers	Atenolol	KALTEN
Beta-Blockers	Atenolol	LOSAR BETA-H
Beta-Blockers	Atenolol	LOTENSYL AT
Beta-Blockers	Atenolol	NEATENOL DIU
Beta-Blockers	Atenolol	NEATENOL DIUVAS
Beta-Blockers	Atenolol	NIF-TEN
Beta-Blockers	Atenolol	NITRENOL
Beta-Blockers	Atenolol	NOR-PA
Beta-Blockers	Atenolol	NUSAR-ATN

Protocol Pharmacologic Category	Drug Class	Preferred Name
Beta-Blockers	Atenolol	POLYCAP
Beta-Blockers	Atenolol	TEKLO
Beta-Blockers	Atenolol	TENORETIC
Beta-Blockers	Atenolol	TONORMA
Beta-Blockers	Atenolol	TRI-NORMIN
Beta-Blockers	Atenolol	ZOLAT /03453901/
Beta-Blockers	Bisoprolol	ACETYLSALICYLIC ACID;BISOPROLOL
Beta-Blockers	Bisoprolol	AMLODIPINE;BISOPROLOL
Beta-Blockers	Bisoprolol	BISELECT /01166101/
Beta-Blockers	Bisoprolol	BISOBLOCK PLUS
Beta-Blockers	Bisoprolol	BISOPROLOL
Beta-Blockers	Bisoprolol	BISOPROLOL FUMARATE
Beta-Blockers	Bisoprolol	BISOPROLOL FUMARATE W/PERINDOPRIL ARGININE
Beta-Blockers	Bisoprolol	BISOPROLOL W/HYDROCHLOROTHIAZIDE /06833601/
Beta-Blockers	Bisoprolol	BISOPROLOL W/PERINDOPRIL
Beta-Blockers	Bisoprolol	CONCOR AM
Beta-Blockers	Bisoprolol	CONCORAM
Angiotensin Receptor Blocker (ARB)	Candesartan	AMLODIPINE BESILATE W/CANDESARTAN CILEXETIL/H
Angiotensin Receptor Blocker (ARB)	Candesartan	AMLODIPINE W/CANDESARTAN CILEXETIL
Angiotensin Receptor Blocker (ARB)	Candesartan	AMLODIPINE;CANDESARTAN
Angiotensin Receptor Blocker (ARB)	Candesartan	AMLODIPINE;CANDESARTAN;HYDROCHLOROTHIAZIDE
Angiotensin Receptor Blocker (ARB)	Candesartan	ATACAND DUO
Angiotensin Receptor Blocker (ARB)	Candesartan	BLOPRESS PLUS
Angiotensin Receptor Blocker (ARB)	Candesartan	CANDESAR A
Angiotensin Receptor Blocker (ARB)	Candesartan	CANDESARTAN
Angiotensin Receptor Blocker (ARB)	Candesartan	CANDESARTAN CILEXETIL
Angiotensin Receptor Blocker (ARB)	Candesartan	CANDESARTAN W/HYDROCHLOROTHIAZIDE

Protocol Pharmacologic Category	Drug Class	Preferred Name
Angiotensin Receptor Blocker (ARB)	Candesartan	CANDESARTAN;FELODIPINE
SNRI	Desvenlafaxine	CLONAZEPAM W/DESVENLAFAXINE SUCCINATE
SNRI	Desvenlafaxine	CLONAZEPAM;DESVENLAFAXINE
SNRI	Desvenlafaxine	DESVENLAFAXINE
SNRI	Desvenlafaxine	DESVENLAFAXINE FUMARATE
SNRI	Desvenlafaxine	DESVENLAFAXINE SUCCINATE
Calcium Channel Blocker	Flunarizine	ANGIOLIT
Calcium Channel Blocker	Flunarizine	BETACAP PLUS
Calcium Channel Blocker	Flunarizine	DIHYDROERGOCRISTINE;FLUNARIZINE
Calcium Channel Blocker	Flunarizine	DOMPERIDONE;FLUNARIZINE;PARACETAMOL
Calcium Channel Blocker	Flunarizine	FLUNARIZINE
Calcium Channel Blocker	Flunarizine	FLUNARIZINE BETADEX
Calcium Channel Blocker	Flunarizine	FLUNARIZINE DIHYDROCHLORIDE
Calcium Channel Blocker	Flunarizine	FLUNARIZINE;NICERGOLINE
Calcium Channel Blocker	Flunarizine	FLUNARIZINE;PROPRANOLOL
Calcium Channel Blocker	Flunarizine	MIGREST
Calcium Channel Blocker	Flunarizine	VERTIZINE D
ACE inhibitor	Lisinopril	ACEDIP
ACE inhibitor	Lisinopril	AMLODIPINE BESILATE W/LISINOPRIL DIHYDRATE/RO
ACE inhibitor	Lisinopril	AMLODIPINE BESILATE W/LISINOPRIL/ROSUVASTATIN
ACE inhibitor	Lisinopril	AMLODIPINE W/LISINOPRIL/ROSUVASTATIN
ACE inhibitor	Lisinopril	AMLOPRES L
ACE inhibitor	Lisinopril	CARACE PLUS /01613901/
ACE inhibitor	Lisinopril	CARSIPRIL D
ACE inhibitor	Lisinopril	DIRONORM

Protocol Pharmacologic Category	Drug Class	Preferred Name
ACE inhibitor	Lisinopril	LISINOPRIL
ACE inhibitor	Lisinopril	LISINOPRIL DIHYDRATE
ACE inhibitor	Lisinopril	ZESTORETIC
Beta-Blockers	Metoprolol	ACETYLSALICYLIC ACID;ATORVASTATIN;METOPROLOL;
Beta-Blockers	Metoprolol	ACETYLSALICYLIC ACID;METOPROLOL
Beta-Blockers	Metoprolol	AMLODIPINE W/METOPROLOL
Beta-Blockers	Metoprolol	ARBITEL MT
Beta-Blockers	Metoprolol	ATORVASTATIN;METOPROLOL
Beta-Blockers	Metoprolol	ATORVASTATIN;METOPROLOL;RAMIPRIL
Beta-Blockers	Metoprolol	BELNIF
Beta-Blockers	Metoprolol	BELOC /01739801/
Beta-Blockers	Metoprolol	BELOC-ZOC COMP
Beta-Blockers	Metoprolol	BETAFIT AM
Beta-Blockers	Metoprolol	BETAONE AM
Beta-Blockers	Metoprolol	CHLORTALIDONE W/METOPROLOL
Beta-Blockers	Metoprolol	CILNIDIPINE W/METOPROLOL SUCCINATE
Beta-Blockers	Metoprolol	CILNIDIPINE W/METOPROLOL TARTRATE
Beta-Blockers	Metoprolol	CILNIPAR M
Beta-Blockers	Metoprolol	CO-BETALOC
Beta-Blockers	Metoprolol	CVPILL
Beta-Blockers	Metoprolol	FELODIPINE W/METOPROLOL
Beta-Blockers	Metoprolol	HYDRALAZINE;HYDROCHLOROTHIAZIDE; METOPROLOL
Beta-Blockers	Metoprolol	ISOSORBIDE MONONITRATE;METOPROLOL
Beta-Blockers	Metoprolol	IVABRADINE HYDROCHLORIDE W/METOPROLOL TARTRAT
Beta-Blockers	Metoprolol	IVABRADINE W/METOPROLOL
Beta-Blockers	Metoprolol	LOPRESORETIC
Beta-Blockers	Metoprolol	MET XL AM
Beta-Blockers	Metoprolol	MET XL R
Beta-Blockers	Metoprolol	METONCE AM
Beta-Blockers	Metoprolol	METOPROLOL
Beta-Blockers	Metoprolol	METOPROLOL FUMARATE
Beta-Blockers	Metoprolol	METOPROLOL SUCCINATE
Beta-Blockers	Metoprolol	METOPROLOL TARTRATE
Beta-Blockers	Metoprolol	METOPROLOL W/MORPHINE
Beta-Blockers	Metoprolol	METOPROLOL W/RAMIPRIL
Beta-Blockers	Metoprolol	METOPROLOL W/TELMISARTAN

Protocol Pharmacologic Category	Drug Class	Preferred Name
Beta-Blockers	Metoprolol	METOPROLOL;NIFEDIPINE
Beta-Blockers	Metoprolol	METOPROLOL;OLMESARTAN
Beta-Blockers	Metoprolol	METPURE AR
Beta-Blockers	Metoprolol	METPURE ST
Beta-Blockers	Metoprolol	MODILOC
Beta-Blockers	Metoprolol	OLSAR M
Beta-Blockers	Metoprolol	RASOTAN BETA
Beta-Blockers	Metoprolol	SELOKEN COMP.
Beta-Blockers	Metoprolol	SELOKEN ZOC/ASA
Beta-Blockers	Metoprolol	STARPRESS MN XL
Beta-Blockers	Metoprolol	STARPRESS R
Beta-Blockers	Metoprolol	TELISTA MT
Beta-Blockers	Metoprolol	TRELOC
Beta-Blockers	Metoprolol	VINICOR D
Beta-Blockers	Nadolol	CORGARETIC
Beta-Blockers	Nadolol	NADOLOL
Tricyclic Antidrepressant	Nortriptyline	AMIVAL /03167601/
Tricyclic Antidrepressant	Nortriptyline	BENPON
Tricyclic Antidrepressant	Nortriptyline	DIAZEPAM;NORTRIPTYLINE
Tricyclic Antidrepressant	Nortriptyline	FLUPENTIXOL;NORTRIPTYLINE
Tricyclic Antidrepressant	Nortriptyline	FLUPHENAZINE;NORTRIPTYLINE
Tricyclic Antidrepressant	Nortriptyline	GABAPENTIN W/NORTRIPTYLINE HYDROCHLORIDE
Tricyclic Antidrepressant	Nortriptyline	GABAPENTIN;NORTRIPTYLINE
Tricyclic Antidrepressant	Nortriptyline	MECOBALAMIN W/NORTRIPTYLINE HYDROCHLORIDE/PRE
Tricyclic Antidrepressant	Nortriptyline	MECOBALAMIN;NORTRIPTYLINE;PREGABALIN
Tricyclic Antidrepressant	Nortriptyline	MOTIVAL /00226501/
Tricyclic Antidrepressant	Nortriptyline	NORFENAZIN
Tricyclic Antidrepressant	Nortriptyline	NORTRIPTYLINE

Protocol Pharmacologic Category	Drug Class	Preferred Name
Tricyclic Antidrepressant	Nortriptyline	NORTRIPTYLINE HYDROCHLORIDE
Tricyclic Antidrepressant	Nortriptyline	NORTRIPTYLINE HYDROCHLORIDE W/PREGABALIN
Tricyclic Antidrepressant	Nortriptyline	NORTRIPTYLINE;PERPHENAZINE
Tricyclic Antidrepressant	Nortriptyline	NORTRIPTYLINE;PREGABALIN
Tricyclic Antidrepressant	Nortriptyline	TROPARGAL
Beta-Blockers	Propranolol	AMBULAX HD
Beta-Blockers	Propranolol	AMOBARBITAL;ATROPA BELLADONNA;CLAVICEPS PURPU
Beta-Blockers	Propranolol	BENDROFLUMETHIAZIDE;HYDRALAZINE; PROPRANOLOL
Beta-Blockers	Propranolol	BENDROFLUMETHIAZIDE;PROPRANOLOL
Beta-Blockers	Propranolol	BENZALKONIUM;PROPRANOLOL
Beta-Blockers	Propranolol	BETACAP PLUS
Beta-Blockers	Propranolol	BETADIPRESAN
Beta-Blockers	Propranolol	CHLORTALIDONE;NIFEDIPINE;PROPRANOLOL
Beta-Blockers	Propranolol	CLONAZEPAM;PROPRANOLOL
Beta-Blockers	Propranolol	CLOTAS PLUS
Beta-Blockers	Propranolol	DECOSEPT PLUS
Beta-Blockers	Propranolol	DI ER KANG XIN
Beta-Blockers	Propranolol	DIAZEPAM;PROPRANOLOL
Beta-Blockers	Propranolol	DIHYDRALAZINE;PROPRANOLOL
Beta-Blockers	Propranolol	DISTONOCALM
Beta-Blockers	Propranolol	DOCIDRAZIN
Beta-Blockers	Propranolol	DOCITEREN
Beta-Blockers	Propranolol	DOCITON 80 DYTIDE H
Beta-Blockers	Propranolol	ETIZOLAM;PROPRANOLOL
Beta-Blockers	Propranolol	FLUNARIZINE;PROPRANOLOL
Beta-Blockers	Propranolol	HYDRALAZINE;PROPRANOLOL
Beta-Blockers	Propranolol	HYDROCHLOROTHIAZIDE;PROPRANOLOL
Beta-Blockers	Propranolol	INDERETIC
Beta-Blockers	Propranolol	INDERIDE
Beta-Blockers	Propranolol	INDUCOR
Beta-Blockers	Propranolol	INDUCOR D
Beta-Blockers	Propranolol	NIFEDIPINE;PROPRANOLOL

Protocol Pharmacologic Category	Drug Class	Preferred Name
Beta-Blockers	Propranolol	NITRO-OBSIDAN
Beta-Blockers	Propranolol	OBSILAZIN
Beta-Blockers	Propranolol	PENTAERITHRITYL TETRANITRATE;PROPRANOLOL
Beta-Blockers	Propranolol	PROPRANOLOL
Beta-Blockers	Propranolol	PROPRANOLOL HYDROCHLORIDE
Beta-Blockers	Propranolol	PROPRANOLOL PHENOBARBITAL
Beta-Blockers	Propranolol	PROPRANOLOL;SPIRONOLACTONE
Beta-Blockers	Propranolol	SOLOPOSE BETA
Beta-Blockers	Propranolol	SPIROPROP
Beta-Blockers	Propranolol	TENSYN PLUS
Beta-Blockers	Propranolol	ZEPRO /02777801/
Beta-Blockers	Timolol	ACECLIDINE;TIMOLOL
Beta-Blockers	Timolol	AMILORIDE;HYDROCHLOROTHIAZIDE;TIMOLOL
Beta-Blockers	Timolol	AZARGA
Beta-Blockers	Timolol	BENZALKONIUM;SODIUM HYDROXIDE;SODIUM PHOSPHAT
Beta-Blockers	Timolol	BENZALKONIUM;TIMOLOL
Beta-Blockers	Timolol	BETACENTYL
Beta-Blockers	Timolol	BETALOL /03186001/
Beta-Blockers	Timolol	BIMATOPROST;TIMOLOL
Beta-Blockers	Timolol	BLOCANOL /01100601/
Beta-Blockers	Timolol	BRIMONIDINE TARTRATE W/TIMOLOL
Beta-Blockers	Timolol	BRIMONIDINE W/TIMOLOL
Beta-Blockers	Timolol	BRIMONIDINE;DORZOLAMIDE;TIMOLOL
Beta-Blockers	Timolol	COMBIGAN
Beta-Blockers	Timolol	COSOPT
Beta-Blockers	Timolol	DORZOLAMIDE W/TIMOLOL
Beta-Blockers	Timolol	DORZOPT /06421101/
Beta-Blockers	Timolol	DUOTRAV
Beta-Blockers	Timolol	ELAZOP
Beta-Blockers	Timolol	GANFORT
Beta-Blockers	Timolol	GLAUTIMOL /06108601/
Beta-Blockers	Timolol	HYALURONIC ACID;TIMOLOL
Beta-Blockers	Timolol	HYDROCHLOROTHIAZIDE;TIMOLOL
Beta-Blockers	Timolol	HYPROMELLOSE;TIMOLOL
Beta-Blockers	Timolol	KRITANTEK OFTENO
Beta-Blockers	Timolol	KRYTANTEK OFTENO
Beta-Blockers	Timolol	MODUCREN

Protocol Pharmacologic Category	Drug Class	Preferred Name
Beta-Blockers	Timolol	PILOBLOQ
Beta-Blockers	Timolol	PILOCARPINE;TIMOLOL
Beta-Blockers	Timolol	PILOFLAX
Beta-Blockers	Timolol	PRESTYL
Beta-Blockers	Timolol	TAFLUPROST W/TIMOLOL MALEATE
Beta-Blockers	Timolol	TAFLUPROST;TIMOLOL
Beta-Blockers	Timolol	TIMED
Beta-Blockers	Timolol	TIMOLIDE
Beta-Blockers	Timolol	TIMOLO
Beta-Blockers	Timolol	TIMOLOL
Beta-Blockers	Timolol	TIMOLOL HEMIHYDRATE
Beta-Blockers	Timolol	TIMOLOL MALEATE
Beta-Blockers	Timolol	TIMOLOL MALEATE, R-ENANTIOMER
Beta-Blockers	Timolol	TIMOLOL MALEATE, S-ENANTIOMER
Beta-Blockers	Timolol	TIMOLOL;TRAVOPROST
Beta-Blockers	Timolol	TIMPILO
Beta-Blockers	Timolol	XALACAR-T
Beta-Blockers	Timolol	XALACOM
Antiepileptic Category 2	Topiramate	QNEXA
Antiepileptic Category 2	Topiramate	QSYMIA
Antiepileptic Category 2	Topiramate	TOPIRAMATE
Antiepileptic Category 1	Valproate Semisodium	CLONAZEPAM W/VALPROATE SEMISODIUM
Antiepileptic Category 1	Valproate Semisodium	VALPROATE SEMISODIUM
Antiepileptic Category 1	Valproate Sodium	ERGENYL CHRONO
Antiepileptic Category 1	Valproate Sodium	VALPROATE SODIUM
Antiepileptic Category 1	Valproic Acid	CLONAZEPAM;VALPROIC ACID
Antiepileptic Category 1	Valproic Acid	ERGENYL CHRONO
Antiepileptic Category 1	Valproic Acid	VALPROIC ACID
SNRI	Venlafaxine	VENLAFAXINE
SNRI	Venlafaxine	VENLAFAXINE HYDROCHLORIDE

17.11 Identifying Participants Who Took a New Migraine Prophylaxis Treatment with Proven Efficacy Based on Concomitant Medications Reported in eCRF for the Intercurrent Events Specified in the Off-Treatment Hypothetical Estimand

To identify the participants who started a new migraine prophylaxis treatment as specified in Section 10.5.4 (Accounting of Intercurrent Events), the following criteria are used:
A participant has taken prophylaxis medications during the double-blind or follow-up period with preferred names in the Table 17–14, and the concomitant medications are classified as "Migraine Prevention Medication" in concomitant medications eCRF.

18 COVID-19 Related Analyses

To eliminate immediate potential hazards to participants and study staff due to the COVID-19 pandemic while ensuring participant safety and maintaining data integrity, the protocol clarification letter and corresponding protocol amendment were sent to sites during the pandemic to allow remote visits (as described in the protocol Table 2 Schedule of Visits and Procedures for Visits Conducted Remotely Due to the COVID-19 Pandemic).

This section specifies analyses for evaluating the impact of COVID-19.

18.1 Efficacy Evaluation

Efficacy Endpoints

Table 18–1 describes the collection devices for primary and key secondary endpoints. The primary endpoint and 5 key secondary endpoints are collected via eDiary according to protocol design. Minimal disruption is expected for these endpoints because participants are expected to complete eDiary at home and submit the responses every day.

The endpoint, MSQ v2.1 Role Function Restrictive domain score at Week 12, will be collected using eTablet as one electronic patient reported outcome (ePRO) at site. The remote collection for this endpoint was in production starting from April 20,2020. Participants are required to complete the ePRO measures remotely at Visit 7 (Week 12) according to remote-visit procedure (Table 4–2).

To evaluate the missing rate for this endpoint at Week 12, the number of participants who missed at least one ePRO assessment due to COVID-19 will be summarized at each visit in the mITT Population (efficacy analyses population).

Table 18–1 Summary of Collection Devices for Primary and Key secondary endpoints

Hypothesis Testing	Node	Endpoint	Collection device
Primary	P1	Change from baseline in mean monthly migraine days across the 12-week treatment period	eDiary
Secondary 1	S1	Change from baseline in mean monthly headache days across the 12-week treatment period	eDiary
Secondary 2	S2	Change from baseline in mean monthly acute medication use days across the 12-week treatment period	eDiary
Secondary 3	S3	≥ 50% reduction in 3-month average of monthly migraine days	eDiary
Secondary 4	S4	Change from baseline in MSQ v2.1 Role Function Restrictive domain score at Week 12	eTablet
Secondary 5	S5	Change from baseline in mean monthly Performance of Daily Activities domain score of the AIM-D across the 12-week treatment period.	eDiary
Secondary 6	S6	Change from baseline in mean monthly Physical Impairment domain score of the AIM -D across the 12-week treatment period.	eDiary

Power and Sample Size Evaluation

The study achieved the last participants first visit on January 31, 2020. A total of 910 patients were randomized, and the number of randomized participants exceeded the planned sample size 872. It is expected the missing rate during the pandemic might be slightly higher than the missing rate before the pandemic. No big impact for the power and sample size calculation is anticipated.

18.2 Safety and other evaluations

This section specifies analyses related to COVID-19 pandemic from the following aspects:

- Disposition
- Study visit (missing entire visit due to COVID-19 or missing assessments due to COVID-19)
- Protocol deviation
- Study drug disruption due to COVID-19
- TEAEs related with COVID-19

Safety Population will be used for the planned analyses described above. The number of participants impacted by COVID-19 during the study will be summarized by treatment group and overall. In addition, the number of participants impacted by COVID-19 and their corresponding disposition status in the double-blind treatment period and the follow-up period will be summarized respectively.

The number of participants who missed at least one entire visit due to COVID-19 will be summarized by treatment group and overall. Furthermore, the number of participants who missed

at least one assessment due to COVID-19 will be summarized by assessment category (laboratory, C-SSRS, urine pregnancy test, vital signs, ECG, and ePRO) and overall. Similar summaries will be provided by visit.

The number of participants with significant protocol deviation due to COVID-19 will be provided. The number of participants with study drug disruption due to COVID-19 will be provided as well. The number of participants with TEAEs related to corona virus infection or coronavirus test positive will be provided.

Supporting listings for the described analyses above will be provided.

19 Changes to Analyses Specified in Protocol

None.

20 References

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Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics 1997; 53:983-97.

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APPENDIX I. REPORTING SELECTED LABORATORY PARAMETERS IN CONVENTIONAL UNIT

All clinical laboratory parameters will be reported in the International System (SI) units as standard practice. In addition, descriptive statistics for values and changes from baseline in conventional units at all assessed visits will be reported for selected laboratory parameters as listed in Table 20–1 below.

Table 20–1 List of Selected Parameters to be Reported in Conventional Units

Number	*Laboratory Parameter*	*Conventional Unit*	*Decimal Places*
1	Alanine Aminotransferase (SGPT)	U/L	0
2	Albumin	g/dL	1
3	Alkaline Phosphatase	U/L	0
4	Aspartate Aminotransferase (SGOT)	U/L	0
5	Bilirubin, Direct (Conjugated)	mg/dL	1
6	Bilirubin, Indirect (Unconjugated)	mg/dL	1
7	Bilirubin, Total	mg/dL	1
8	Blood Urea Nitrogen	mg/dL	0
9	Calcium	mg/dL	1
10	Cholesterol, HDL	mg/dL	0
11	Cholesterol, LDL	mg/dL	0
12	Cholesterol, LDL direct and calculated (combined) *(This lab parameter could be the same as #11)*	mg/dL	0
13	Cholesterol, Total	mg/dL	0
14	Creatine Kinase	U/L	0
15	Creatinine	mg/dL	1
16	Glucose	mg/dL	0
17	Insulin	uIU/mL	1
18	Triglycerides	mg/dL	0
19	Uric Acid	mg/dL	1
20	Hemoglobin	g/dL	1

Patient narratives will also include the values in conventional units for the selected lab parameters (Table 20–1). That will be accomplished by presenting the values in conventional

units within the parentheses next to the values in SI units. As shown in Table 20–2 below for 'Bilirubin, Total' parameter, for which 'umol/L' is the SI unit and 'mg/dL' is the conventional unit.

Table 20–2 Presenting Laboratory Data Using SI and Conventional Units in Narratives

LABORATORY DATA						
Lab Test	**Test Name**	**Normal Range**		**VISIT01**	**VISIT05**	**VISIT07**
		Low	**High**	**2012-07-03**	**2012-08-07**	**2012-09-04**
CHEMISTRY	Bilirubin, Total (umol/L(mg/dL))	0 (0)	18.81 (1.1)	6.84 (0.4)	5.13 (0.3)	5.13 (0.3)

APPENDIX II. SUMMARY OF CHANGES FOR AMENDMENT 1

Amendment #1 specifies the following changes to the Statistical Analysis Plan for Study 3101-301-002 dated 13 Mar 2019. The major changes are summarized below:

1. Clarify that eDiary data will be collected up to follow-up visit for those who terminated early.
2. For safety analyses, participants will be summarized according to the study treatment period received for majority of treatment period.
3. Clarify that mITT population is defined during double-blind treatment period.
4. Added analysis population for off-treatment hypothetical estimand in Section 6.
5. Clarify that randomization stratification from IWRS and based on prior medication collected from eCRF will be summarized.
6. Clarify that rollover participants will be summarized.
7. Clarify that demographic parameters and baseline characteristics will also be summarized for Off-treatment Hypothetical Estimand Population.
8. Concomitant medication use will be summarized for both double-blind treatment period and follow-up period.
9. Added the algorithm for calculation of the prescribed number of tablets during a specific period.
10. Updated the language and derivation for AIM-D related endpoints.
11. Added the language and derivation for HIT-6, MIDAS, PGIC, WPAI:MIGRAINE, PGI-S related endpoints.
12. Section 10.2 was further split into Section 10.2.1 (primary analysis in support of US filing), Section 10.2.2 (sensitivity analysis for possible violation of normality assumption), Section 10.2.3 (sensitivity analyses in missing data handling).
13. Clarify that actual strata (based on prior medication collected from eCRF) will be used.
14. Added ANCOVA model based on 3-month average of the monthly migraine days.
15. Added within-group imputation based on observed data.
16. Clarify that for copy-reference approach, intermittent missing values will be imputed by MCMC at first.
17. Add prior exposure in the SAS sample codes.
18. Revised the names for endpoints related with ≥ 25%, ≥ 50%, ≥ 75% and 100% responders.
19. Clarify that endpoint of 50% responder will be analyzed using a logistic regression.
20. Switched the hierarchical order for secondary endpoints between AIM-D and MSQ 2.1 in the multiplicity control procedure and updated multiplicity procedure in Figure 10-1.
21. Added HO endpoints and the corresponding statistical analyses.

22. Added daily efficacy variables for the first week of double-blind treatment period and the corresponding analyses.
23. Updated the statistical analyses of population-level summary for primary and secondary endpoints.
24. Revised TEAE definition.
25. Clarify that newly emergent AEs is for TEAEs occurred after the date of last dose of study treatment.
26. Clarify that common TEAEs will be not summarized by system organ class. Furthermore, a table with ≥ 5% incidence of common TEAEs in any treatment group will be provided.
27. Added a list of selected parameters in conventional units in Appendix I.
28. Updated the calculation for the summary of PCS vital signs.
29. Updated ECG PCS criteria and add analyses for ECG values of clinical interest.
30. Added subgroup analyses for ≥ 50% reduction, ≥ 50% reduction, and 100% reduction in 3-month average of monthly migraine days.
31. Updated the analysis windows.
32. Clarify that inconsistent multiple eDiary records on the same day for one specific category will be excluded from the analyses.
33. Added Section 17.10 in identifying the actual stratification.
34. Added Section 18 to specify analyses related to COVID-19.

The table below provides details related to content changes that were made in the SAP, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
Section 4, Introduction	Added protocol amendment 3 date	To follow protocol amendment 3
Section 4, Introduction	Added: Per study design (Protocol Sections 8.4.3.1 and 8.8), eDiary data will be collected for participants who early terminated from the double-blind treatment period during the 4 weeks between V7 (Early termination visit) and V8 (Follow-up Visit)	For clarity
Section 6, Analysis Population	Added: All safety analyses will be performed using the Safety Population and based on the treatment actually received, regardless of assigned treatment according to the planned randomization. **Participants will be summarized according to the study treatment received for the majority of treatment period.**	For clarity
Section 6, Analysis Population	Updated: The Modified Intent-to-Treat (mITT) Population includes all randomized participants who received at least 1 dose of study intervention, had an evaluable baseline period of eDiary data and had at least 1 evaluable post-baseline 4-week period (Weeks 1 to 4, 5 to 8, and 9 to 12) of eDiary data ~~while on study treatment~~ **during the double-blind treatment period**.	For clarity
Section 6, Analysis Population	Added: The analysis population for Off-treatment Hypothetical Estimand includes all randomized participants who received at least 1 dose of study treatment, had an evaluable baseline period of eDiary data and had at least 1 evaluable post-baseline 4-week period (Weeks 1 to 4, 5 to 8, 9 to 12) of eDiary data during the DB treatment period and follow-up period, regardless of whether on study treatment or off study treatment. This population is used for the primary esimand in support of EU filing.	For clarity
Section 7, Participant Disposition	Updated: The number of participants in the ITT, Safety, and mITT Populations will be summarized by treatment group and study center; the number of participants screened will be summarized overall only by study center. The number of participants in the ITT Population will also be summarized by treatment group for ~~each randomization stratification factor (prior exposure [yes/no] to a migraine prevention medication with proven efficacy)~~ **the following factors: 1) Randomization stratification factor (prior exposure [yes/no] to a migraine prevention medication with proven efficacy) from IWRS; 2) Prior exposure to migraine prevention medication with proven efficacy based on prior medication collected from eCRF, which will be termed as "actual strata" in the SAP. The list of participants with incorrect randomization stratum will be provided.**	For clarity, since efficacy analyses and related subgroup analyses will use the actual strata
Section 7, Participant Disposition	Added: All randomized participants who prematurely discontinue during the double-blind treatment period or the follow-up period will be listed by discontinuation reason. **The number of participants who signed informed consent for 3101-309-002 will provided; of these participants, number (%) of participants who entered the follow-up period of this study or not will be summarized.**	To clarify that participants will rollover into Study 3101-309-002

Section	Revision	Rationale
Section 8, Demographic and Other Baseline Characteristics	Added: Demographic parameters (age; age group [< 20, 20-29, 30-39, 40-49, 50-59, 60-69, and ≥ 70]; race; race group [white, all other races]; ethnicity; sex), baseline characteristics (weight; height; and body mass index, calculated as weight [kg]/(height [m])^2 will be summarized descriptively by treatment group for the Safety and mITT Populations, **and Off-treatment Hypothetical Estimand Population**.	For clarity, since Off-treatment Hypothetical Estimand Population is used in the support of EU filings.
Section 8, Demographic and Other Baseline Characteristics	Deleted: ~~Prior migraine prevention medication use with the corresponding failure information in mechanism of action or medication will be summarized by treatment group for the Safety Population. In addition, the number and percentage of participants with prior migraine prevention medication use will be tabulated by mechanism of action and medication, further tabulated for the participants who met the medication failure definition and by the reason for stopping the medication.~~	For clarity
Section 8, Demographic and Other Baseline Characteristics	Deleted: Prior medication is defined as any medication taken before the first dose of double-blind study treatment. Concomitant medication is defined as any medication taken on or after the date of the first dose of the double-blind study treatment. ~~Any medications started 1 day after the double-blind study treatment end date will not be summarized but will be included in listings.~~	For clarity
Section 8, Demographic and Other Baseline Characteristics	Updated: ~~Both prior and concomitant medication use will be summarized by the number and proportion of participants in each treatment group receiving each medication within each therapeutic class for the double-blind treatment period for the Safety Population.~~ Prior medication use will be summarized by the number and proportion of participants in each treatment group receiving each medication within each therapeutic class for the Safety Population. Concomitant medication use will be summarized by the number and percentage of participants in each treatment group receiving each medication within each therapeutic class for the double-blind treatment period and follow-up period for the Safety Population	For clarity
Section 8, Demographic and Other Baseline Characteristics	Updated: Protocol deviations will be defined in Protocol Deviation Requirement Specification **(PDRS)**, including ~~importance~~ **significant** classification. The number and percentage of participants with ~~important~~ **significant** protocol deviations will be summarized by treatment group **for all categories specified in PDRS** for randomized participants	For clarity

Section	Revision	Rationale
Section 8, Demographic and Other Baseline Characteristics	Updated: Baseline efficacy parameters (monthly migraine days, monthly headache days, monthly acute medication use days, Migraine Specific Quality of Life Questionnaire [MSQ] v2.1 Role Function Restrictive domain score, Performance of Daily Activities domain score of the AIM-D, and Physical Impairment domain score of the AIM-D) will be summarized by treatment group for mITT Population **and Off-treatment Hypothetical Estimand Population**.	For clarity
Section 9.2, Measurement of Treatment Compliance	Added: The total number of tablets actually taken during a specific period will be calculated from the study medication record. **The prescribed number of tablets during a specific period will be calculated as following: 3 tablets/day × the number of days during the period**.	For clarity
Section 10.1.1, Efficacy Measures	Added: A headache day is defined as any calendar day on which headache pain lasting 2 hours or longer occurs unless an acute headache medication (eg, ibuprofen, triptan) was used after the start of the headache, in which case no minimum duration will be specified. **Please note, antiemetics will not be counted as an acute headache medication for headache day identification**.	For clarity

Section 10.1.2, Health Outcome Measures	Updated: ~~The Activity Impairment in Migraine – Diary (AIM-D) is a 9-item PRO measure that assesses the impact of migraine on the performance of daily activities and physical impairment. Participants are asked to rate the level of difficulty experienced in the past 24 hours with performance of daily activities (ie, difficulty with household chores, errands, leisure activities at home, leisure or social activities outside the home, strenuous physical activities) and physical impairment (ie, difficulty walking, moving body, bending forward, moving head) using the following 6 point rating scale: "Not difficult at all," "A little difficult," "Somewhat difficult," "Very difficult," "Extremely difficult," and "I could not do it at all." Some items included a response of "I did not…," for example, "I did not have errands planned." The AIM-D was developed as an electronic daily diary with Headache and Non-headache versions. The Headache version is administered on days when a participant reports a headache and the Non-headache version is administered on days when a participant does not report having a headache. The AIM-D instructs participants to answer each question based on the level of difficulty experienced in the past 24 hours for both versions, with "during your headache" indicated for the AIM-D Headache version.~~ The AIM-D is an 11-item daily diary measure that assesses the impact of migraine and is comprised of two domains that evaluate performance of daily activities (7 items) and physical impairment (4 items). Participants are asked to rate the level of difficulty experienced in the past 24 hours with performance of daily activities (ie, difficulty with household chores, errands, leisure activities at home, leisure or social activities outside the home, strenuous physical activities, concentrating, and thinking clearly) and physical impairment (ie, difficulty walking, moving body, bending forward, moving head) using a 6-point rating scale ranging from "Not difficult at all," "A little difficult," "Somewhat difficult," "Very difficult," "Extremely difficult," and "I could not do it at all." Three items include a response of "I did not…," for example, "I did not have errands planned." The AIM-D was developed as an electronic daily diary with the same set of questions administered in headache and non-headache versions. The Headache version is administered on days when a participant reports a headache and the Non-Headache version is administered on days when a participant does not report having a headache. The AIM-D instructs participants to answer each question based on the level of difficulty experienced in the past 24 hours for both versions, with "during your headache" indicated for the AIM-D Headache version. In addition to the two domain scores, a total score using all 11 items can also be calculated. Each raw daily domain score, as well as the raw daily total score, are transformed to a 0-100 scale, with higher scores indicating greater impact of migraine (i.e., higher disease burden). Two items based on a 24-hour recall will be administered daily using Headache and Non-headache versions as additional health outcome measures and for evaluation of the AIM-D. The first item will be used to assess activity level within the past 24 hours with a 5-level response scale ranging from "No activity – Spent all day lying down" to "Exercised – Brisk walk, running, jogging, biking or other activity for 30 or more minutes." The second item will be used to evaluate activity limitation with a 5-level response scale ranging from "Not at all limited – I could do everything" to "Extremely limited".	For clarity, since AIM-D scoring algorithm is updated

Section	Revision	Rationale
	Overall satisfaction with the study medication for prevention of migraine will be assessed using a single item and a 7-point rating scale ranging from extremely satisfied (0) to extremely dissatisfied (6).	
Section 10.1.2, Health Outcome Measures	Added: The Headache Impact test (HIT-6) is a 6-question assessment used to measure the impact headaches have on a participant's ability to function on the job, at school, at home and in social situations. It assesses the effect that headaches have on normal daily life and the participants' ability to function. Responses are based on frequency using a 5-point scale ranging from never to always. The HIT-6 total score, which ranges from 36 to 78, is the sum of the responses – each of which is assigned a score ranging from 6 points (never) to 13 points (always). The Migraine Disability Assessment (MIDAS) is a 7-item questionnaire designed to quantify headache-related disability over a 3-month period. The MIDAS score is the sum of missed work or school days, days at work or school plus days of household work where productivity was reduced by half or more, missed household work days, and missed non-work activity days due to headaches and in the last 3 months. The Patient Global Impression of Change (PGIC) is a single item used to measure the participant's impression of overall change in migraine since the first dose of study intervention. The measure uses a 7-point rating scale with responses ranging from "very much better" to "very much worse." The Patient Global Impression - Severity (PGI-S) is a single item used to measure the participant's impression of severity in relation to migraine symptoms overall at the time of administration of the measure. The measure uses a 5-point rating scale with responses ranging from "none" to "very severe." The Work Productivity and Activity Impairment Questionnaire: Migraine v2.0 (WPAI:MIGRAINE) is used to assess work productivity specific to migraine. The measure uses a 1-week recall and contains 6 questions related to work productivity. The WPAI measures both presenteeism and absenteeism. The measure yields four scores expressed as impairment percentages ranging from 0 to 100%: Percent work time missed, percent impairment while working, percent overall work impairment, and percent activity impairment due to migraine.	These endpoints previously were included in HEOR SAP and now in clinical SAP
Section 10.2 Primary Efficacy Endpoints	Updated: Baseline is defined as the number of migraine days during the last 28 days ~~of the baseline phase, i.e., Day 28 to -1~~ **prior to the randomization date**.	For clarity

Section	Revision	Rationale
Section 10.2.1, Primary Analysis in Support of US Filing	Added: **The endpoint will be analyzed using a mixed model for repeated measures (MMRM).** The response variable is the change from baseline to each postbaseline month in monthly migraine days. The model will include treatment group, visit (derived as month), prior exposure (yes/no) to a migraine prevention medication with proven efficacy, and treatment group by visit interaction as categorical fixed effects. It will also include the baseline score and baseline-by-visit interaction as covariates. **The stratum "prior exposure (Yes/No)" will use the actual stratification factor from prior medication collected by eCRF. The analysis will be performed based on evaluable postbaseline data using only the observed cases without missing data imputation. Only data collected during the double-blind period will be included in the analysis. Participants are always analyzed based on the treatment group assigned by randomization**.	For clarity
Section 10.2.1, Primary Analysis in Support of US Filing	Added: The impact of dropouts on the primary efficacy measure will be explored graphically by plotting the response profiles by the dropout reason. Plot of mean change from baseline in the number of migraine days versus visit (month) based on the observed cases will be provided in each treatment group by major reason of early termination, such as, adverse events, lack of efficacy, withdrawal of consent, lost to follow-up, etc. Similar plot for completers in each treatment group will be provided as a reference.	For clarity

Section	Revision	Rationale
Section 10.2.3, Sensitivity Analyses in Missing Data Handling	Added: **ANCOVA Model Based on 3-month Average of the Monthly Migraine Days** The response variable for the ANCOVA model is the change from baseline in the 3-month average of the monthly migraine days for each participant. The ANCOVA model includes terms for treatment, prior exposure (yes/no) to a migraine prevention medication with proven efficacy, and baseline score. The treatment difference for atogepant doses versus placebo will be estimated and reported along with the corresponding 95% CI and nominal p-value for superiority testing. This analysis was recommended by FDA at the End of Phase 2 meeting and termed as supportive analysis. There are no missing data based on this derivation because patients who discontinued the treatment are assumed to maintain the same mean (observed while on treatment) for 3 months (12 weeks). **Within-group Imputation Based on Observed Data** Sensitivity analysis will be performed based on imputation using participants from the same treatment group with observed data under the MAR assumption. The details of imputation are as follows 1. Create partial imputation dataset using MI based on the MCMC approach in each treatment group. Imputed dataset will consist of 100 copies of original dataset and is assumed to follow monotone missing pattern. 2. Impute missing data in each existing copy by treatment group using observed data in the corresponding treatment group based on monotone regression. Each of the 100 imputed datasets will then be analyzed using an ANCOVA model with terms for treatment, prior exposure (yes/no) to a migraine prevention medication with proven efficacy, and baseline score. The ANCOVA analysis results from 100 completed datasets are combined for overall estimation and inference using Rubin's rule (Rubin 1987) to produce a pooled estimate of LS mean difference, its SE, and corresponding p-value for the test of null hypothesis of no treatment effect.	For clarity

Section 10.2.3, Sensitivity Analyses in Missing Data Handling	Updated: ~~The sensitivity analysis will be done using a pattern-mixture model (PMM), under which data could be missing-not-at-random (MNAR), with repeated analyses combined via the reference based multiple imputation (MI) procedure (Carpenter et al, 2013). This approach is to assess the robustness of the MMRM analysis to possible violation of the missing-at-random (MAR) assumption in the primary analysis.~~ ~~Note that the missingness is assumed monotonic. Any intermediate missing values, if any, will be imputed at first. If the intermediate missing value exists at the first postbaseline month, it is imputed using the average of baseline and next available postbaseline values; otherwise, intermediate missing values are imputed using last observation carried forward (LOCF) approach.~~ Copy-reference approach is one type of pattern-mixture models (PMM), under which data could be missing-not-at-random (MNAR), with repeated analyses combined via the reference based multiple imputation (MI) procedure (Carpenter et al, 2013). This approach is to assess the robustness of the MMRM analysis to possible violation of the missing-at-random (MAR) assumption in the primary analysis. Step 1. **A few intermittent missing values will be imputed by the Markov Chain Monte Carlo (MCMC) at first. The MCMC imputation assumes missing-at-random (MAR) for intermittent missing data. The MCMC method will be implemented using SAS Proc MI statement "MCMC impute=monotone". This is achieved with the use of option IMPUTE = MONOTONE in the MCMC statement. Then the rest of the missing data will follow monotone missing pattern**. Step 2. Implementation of the copy reference method are as follows: 1. The reference-based approach uses the placebo group as the reference. The missing values in the reference group are imputed using the observed data in that group under the missing-at-random assumption. The missing pattern is defined by the participant's last visit with a non-missing value. The mean vector and the covariance matrix of the multivariate normal distribution are estimated for reference group. The imputation of missing data is not based on each of the reasons of early termination, because there may not be sufficient non-missing efficacy data in each of the reason categories to serve as a stable reference. ~~Plot of mean change from baseline in the number of migraine days versus visit (month) based on the observed cases will be provided in each treatment group by major reason of early termination, such as, adverse events, lack of efficacy, withdrawal of consent, lost to follow-up, etc. Similar plot for completers in each treatment group will be provided as a reference~~ 2. For atogepant treatment groups, missing values are imputed based on the distribution estimated from the reference group (placebo group). **The first PROC MI will be performed 100 times using MCMC method for partial imputation of the data with a non-monotone missing pattern. The output dataset will then be used as the input dataset for the next PROC MI. Note that the output dataset already contains 100 copies of the original dataset. With the next invocation of MI procedure, the missing data will be filled in (Step 1 and 2) for the existing copies. This is achieved with the use of NIMPUTE=1 and a BY _Imputation_**	For clarity

Section	Revision	Rationale
	statement. Finally, each of the 100 imputed datasets will be analyzed using an analysis of covariance (ANCOVA) model.	
Section 10.2.3, Sensitivity Analyses in Missing Data Handling	Added: **MMRM Based on Primary Measures Collected during the Double-blind and Follow-up Periods** The details for this analysis are provided in Section 10.5. The primary analysis in support of EU filing will serve as one sensitivity analysis in support of US filing.	For clarity
Section 10.3, Secondary Efficacy Endpoints	Updated: The secondary efficacy endpoints for the United States and the EU are as follows: • Change from baseline in mean monthly headache days across the 12-week treatment period. • Change from baseline in mean monthly acute medication use days across the 12-week treatment period. • ≥ 50% reduction **in 3-month average of** monthly migraine days • Change from baseline in MSQ v2.1 Role Function Restrictive domain score at Week 12. • **Change from baseline in mean monthly Performance of Daily Activities domain score of the AIM-D across the 12-week treatment period.** • **Change from baseline in mean monthly Physical Impairment domain score of the AIM -D across the 12-week treatment period**. The secondary endpoints for headache days, acute medication use days, **Performance of Daily Activities domain score of the AIM-D, and Physical Impairment domain score of the AIM-D** will be analyzed in the same manner as that used to analyze the primary endpoint.	To reflect that hierarchical order in multiplicity procedure between MSQ RR and AIM-D domains was changed.
Section 10.3, Secondary Efficacy Endpoints	Updated: For MSQ v2.1 Role Function Restrictive domain score, the analysis will be performed similarly to the primary MMRM, with focus on the pairwise contrasts of each dose group to placebo at Week 12. ~~For the estimand approach described in Section 10.5, some participants may have their MSQ v2.1 assessed at Visit 8, which~~ **Week 16 (follow-up visit) data for MSQ v2.1 Role Function Restrictive domain score** will not be included in MMRM **analysis**, and ~~instead the~~ **only** summary statistics **for Week 16** will be provided.	For clarity

Section	Revision	Rationale

Section 10.3, Secondary Efficacy Endpoints	Updated:
	~~The proportion of 50% responders, defined as participants with at least a 50% reduction from baseline in monthly migraine days, will be summarized for each study month during the 12-week treatment period. A generalized linear mixed model will be used to analyze the proportion of 50% responders as repeated measures across the 12-week treatment period. This model assumes a binary distribution for the response and uses a logit link. The analysis model will include treatment group, visit, prior exposure (yes/no) to a migraine prevention medication with proven efficacy, and treatment group-by-visit interaction as categorical fixed effects; baseline value and baseline-by-visit interaction will be included as covariates. Participants will be included as random effects with unstructured covariance matrix in the model to account for the correlation among repeated measurements. The analysis will be performed based on all postbaseline values using only the observed cases without imputation of missing values. The treatment difference in terms of odds ratio between each atogepant dose group and placebo will be estimated and tested from this model. The sample SAS is given as follows~~
	~~**proc glimmix** data = in_data1;~~
	~~class trt visit subjid;~~
	~~model responder (event = "1")= trt visit base trt*visit base*visit / link = logit dist = binary;~~
	~~random visit / type = UN subject = subjid residual;~~
	~~lsmestimate trt*visit~~
	~~'10QD vs placebo' **1 1 1 1 1 1 0 0 0 0 0 0** divisor = **3**;~~
	~~'30QD vs placebo' **1 1 1 0 0 0 1 1 1 0 0 0** divisor = **3**;~~
	~~'60QD vs placebo' **1 1 1 0 0 0 0 0 0 1 1 1** divisor = **3** /exp cl;~~
	~~ods output LSMEstimates = oddsratio;~~
	~~**run**;~~
	The 50% responder, defined as a participant with at least a 50% reduction from baseline in the 3-month average of monthly migraine days, will be assessed for each individual. A logistic regression model will be used to analyze the 50% responders across the 12-week treatment period. This model assumes a binary distribution for the response and uses a logit link. The analysis model will include treatment group, prior exposure (yes/no) to a migraine prevention medication with proven efficacy, and baseline monthly migraine days. The treatment difference in terms of odds ratio between each atogepant dose group and placebo will be estimated and tested from this model. The sample SAS is given as follows
	
	proc logistic data=in_data;
	class TRTP (ref='Placebo') prior_exposure (ref='No')/param=glm;
	model responder(event='1')= TRTP prior_exposure base ;
	lsmeans TRTP / e diff oddsratio cl;
	ods output diffs=outdata (where= (_TRTP ='Placebo'));
	run;
		For clarity

Section	Revision	Rationale
Section 10.3, Secondary Efficacy Endpoints	Added: **Multiplicity Adjustment** The overall familywise error rate (FWER) will be controlled at $\alpha = 0.05$ for the set of primary and secondary endpoint comparisons between each dose level of atogepant vs placebo. Specifically, the overall type I error rate for multiple comparisons across three atogepant doses and the primary and secondary efficacy endpoints will be controlled at the 0.05 level using a graphical approach with **weighted-Bonferroni test procedure** (Bretz 2011). The overall graphic approach procedure is defined in Table 10-1 and Figure 10-1. In the graph, each of the nodes is corresponding to one null hypothesis, for example, 30mg/P1 represents the null hypothesis that there is no statistically significant difference comparing 30 mg QD versus placebo on the primary endpoint. The number inside each node is the proportion of overall alpha initially allocated to that hypothesis. The number on the edge between two nodes represents the proportion of local alpha propagated from one hypothesis to the other given the rejection of preceding null hypothesis. **The initial allocation of the overall significant level to 3 primary hypotheses will be 1/3 of the overall significance level for each dose, and no initial α is allocated to the hypotheses for secondary endpoints.** **Within each individual dose, testing will start from the primary endpoint, and then test the secondary endpoints in a prespecified order. The order of testing for the first three secondary endpoints is determined by the power of individual endpoints based on the results from Phase 2/3 study CGP-MD-01. Endpoints related to AIM-D and MSQ are placed in the last three positions in the testing hierarchy because there is no prior information about the treatment effect for the three health outcome (HO) endpoints associated with MSQ 2.1 RR and AIM-D, and AIM-D related endpoints are still under validation. If the null hypotheses for both the primary and the first three secondary endpoints are rejected for one of the doses, 1/3 of the associated alpha is passed to the other doses (1/6 fraction for each dose) to increase the chances of success for the other doses in testing endpoints in the primary positions of the hierarchy, and the remaining 2/3 of the associated alpha is reserved for testing HO endpoints within the same dose. If hypotheses for three HO endpoints are rejected within a dose based on remaining alpha, the alpha for this dose will be propagated to the other two doses to make full use of the alpha.**	For clarity
Section 10.4, Additional Endpoints	Updated: • ≥ 25%, ≥ 50%, ≥ 75%, and 100% improvement (~~decrease~~ redcution) in monthly migraine days at Weeks 1-4, 5-8, and 9-12. • ≥ 25%, ≥ 75%, and 100% improvement (~~decrease~~ reduction) in 3-month average of monthly migraine days.	For clarity

Section	Revision	Rationale
Section 10.4, Additional Endpoints	Added: **<u>Additional Health Outcomes Endpoints</u>** The following health outcomes endpoints for the United States and the EU are planned to be reported in CSR main body: • Change from baseline in the HIT-6 total score at Weeks 4, 8, and 12. • ≥ 5-point improvement (decrease) from baseline in HIT-6 total score at Weeks 4, 8, and 12. • Participants assessed by the PGIC as "much better" or "very much better" at Week 12. • P "Satisfied" or "extremely satisfied" with study medication for migraine prevention at Weeks 4, 8, and 12. • Change from baseline in percent work time missed, percent impairment while working, percent overall impairment, and percent activity impairment due to migraine at Weeks 4, 8, and 12 as assessed by the WPAI:MIGRAINE. • Change from baseline in the MIDAS total score at Week 12. • Change from baseline in MIDAS absenteeism score (Questions 1, 3, and 5) at Week 12. • Change from baseline in MIDAS presenteeism score (Questions 2 and 4) at Week 12. • Change from baseline in PGI-S score at Weeks 4, 8, and 12. • Change from baseline in the MSQ v2.1 Role Function Preventive domain score at Weeks 4, 8, 12, and 16. • Change from baseline in the MSQ v2.1 Role Function Restrictive domain score at Weeks 4, 8, and 16. • Change from baseline in the MSQ v2.1 Emotional Function domain score at Weeks 4, 8, 12, and 16. • Change from baseline in monthly Performance of Daily Activities domain score of the AIM-D at Weeks 1-4, 5-8, and 9-12. • Change from baseline in monthly Physical Impairment domain score of the AIM-D at Weeks 1-4, 5-8, and 9-12. • Change from baseline in monthly AIM-D total score at Weeks 1-4, 5-8, and 9-12, and average across the 12-week treatment period • Change from baseline in monthly activity level at Weeks 1-4, 5-8, 9-12, and average across the 12-week treatment period. Change from baseline in monthly activity limitation at Weeks 1-4, 5-8, 9-12, and average across the 12-week treatment period.	For clarity

Section	Revision	Rationale
Section 10.4, Additional Endpoints	Added For variables with a continuous response range, analyses will be performed similarly to that used for the primary analysis, with focus again on the pairwise contrasts of each dose group to placebo. **Baseline in the primary MMRM model will be replaced with corresponding endpoint baseline. There is only one post-baseline assessment for MIDAS, and thus ANCOVA model will be used to analyze MIDAS related endpoints with model terms including treatment group, prior exposure (yes/no) to a migraine prevention medication with proven efficacy, and corresponding baselinescore.** For the endpoint change from baseline in each MSQ v2.1 domain score, Week 16 (follow up visit) will not be included in MMRM model fitting. For variables where the data are essentially binary, comparisons between treatment groups will be done using a generalized linear mixed model for variables with multiple postbaseline assessments. **A generalized linear mixed model will assume a binary distribution for the response and uses a logit link. The analysis model will include treatment group, visit, prior exposure (yes/no) to a migraine prevention medication with proven efficacy, and treatment group-by-visit interaction as categorical fixed effects; baseline value and baseline-by-visit interaction will be included as covariates. Participants will be included as random effects with unstructured covariance matrix in the model to account for the correlation among repeated measurements. The analysis will be performed based on all postbaseline values using only the observed cases without imputation of missing values. As there is no baseline assessment for the endpoint patients satisfaction with study medication, baseline monthly migraine days will be included in the model.** **For binary endpoints with only one postbaseline assessment (for example, PGIC responder) or responders across 12-week double-blind treatment period, a logistic regression model will be used to model the probability of a response or event with model terms including treatment group, prior exposure (yes/no) to a migraine prevention medication with proven efficacy, and corresponding baseline. As there is no baseline assessment for PGIC, baseline monthly migraine days will be used in the logistic regression model as a covariate for PGIC responder analyses.**	For clarity

Section	Revision	Rationale
Section 10.4, Additional Endpoints	Added: For daily efficacy variables, the number and percentage of participants with a migraine day will be summarized by each day under consideration. A generalized linear mixed model as described above will be used to analyze the proportion of participants with a migraine day as repeated measures from the initial dose day to 6 days after. Here baseline value is the daily rate for participants with a migraine day during the baseline period. In addition, percent reduction in the proportion of participants with a migraine day will be provided by each day under consideration. It is defined as 100×(1-(proportion of participants with a migraine day on a specific day)/(baseline daily rate of participants with a migraine day)). The proportion of participants with a migraine day will be calculated relative to the number of participants in mITT Population with available eDiary record on the day of consideration. The numerator will be the number of participants with a migraine day on that day. The baseline daily rate of participants with a migraine day will be calculated as the average of monthly migraine days (prorated if less than 28 days of baseline data are reported) at baseline period for participants in mITT Population divided by 28.	For clarity
Section 10.4, Additional Endpoints	Added: In addition, cumulative distribution graph of percent improvement (decrease) in mean monthly migraine days across 12-week treatment period will be provided by treatment group, **and by prior exposure (yes/no) to a migraine prevention medication with proven efficacy and treatment group.**	For clarity
Section 10.5, Off-Treatment Hypothetical Estimand	Added: This section defines an estimand, termed as off-treatment hypothetical estimand, which will be the primary estimand in support of EU filing and serve as one sensitivity analysis in support of US filing. Per study design (Protocol Sections 8.4.3.1 and 8.8), eDiary data will be collected for participants who early terminated from the double-blind treatment period during the 4 weeks between V7 (Early termination visit) and V8 (Follow-up Visit), i.e., participants who prematurely discontinued (before Week 12) will continue to complete eDiary efficacy assessments while off-treatment.	For clarity
Section 10.5.1, Treatment Condition of Interest	Added: Participants take assigned treatment by randomization during the double-blind treatment period. In addition, permissible and prohibited mediations are described below: • Participants are allowed to take acute migraine medications (Protocol Section 4.4.1) to keep the participants in the study. The protocol prohibits patients from starting any new migraine preventive treatments (Protocol Section 4.4.2) during the study (including the double-blind treatment period and the follow-up period).	For clarity

Section	Revision	Rationale
Section 10.5.2, Population	Added: This population will be the primary efficacy analysis population in support of EU filing. On study treatment is from the first dose till the last dose of study intervention. As the analysis-visit mapping window (Table 17–2) is defined for the entire postbaseline period (not limited to the double-blind treatment period for participants who prematurely discontinued), the number of participants in the analysis population for off-treatment hypothetical estimand is expected to be greater than or equal to the number of participants in the mITT Population.	For clarity
Section 10.5.4, Accounting of Intercurrent Events	Updated: Intercurrent events and their handling rules are as follows: • Participants who ~~discontinue study treatment and switch to other prophylaxis~~ **started a new migraine prophylaxis treatment during the double-blind or follow-up period** will have their data ~~after switching treatment~~ **during the follow-up period after starting the new migraine prophylaxis treatment** excluded from the analysis. • Participants who discontinue study treatment due to all reasons other than **starting a new migraine prophylaxis treatment** will have their data collected after discontinuation of study treatment, and **those off-treatment data** will be included in the analysis.	For clarity
Section 10.5.4, Accounting of Intercurrent Events	Added: As the protocol prohibits participants from starting any new prophylaxis treatment until the study is completed. Only a limited number of participants as protocol deviators might take new prophylaxis treatment during the study. The criteria for identifying the participants who started a new migraine prophylaxis treatment are described in Section 17.11.	For clarity

Section 10.5.4, Accounting of Intercurrent Events	Deleted: ~~Missing data are assumed to follow monotone pattern. Any intermediate missing values will be imputed first by the same method discussed in Section 10.2. Possible monotone missing data patterns are discussed below, and a summary is provided in Table 20 .~~ ~~Participants may provide three-month efficacy data in the following patterns:~~ ~~• three months on study treatment (pattern group 1)~~ ~~• two months on study treatment and one month off study treatment (pattern group 2)~~ ~~• one months on study treatment and two months off study treatment (pattern group 3)~~ ~~• three months off study treatment (pattern group 4)~~ ~~Participants may provide two months efficacy data in the following patterns:~~ ~~• two months on study treatment (pattern group 5)~~ ~~• one months on study treatment and the other month off study treatment (pattern group 6)~~ ~~• two months off study treatment (pattern group 7)~~ ~~Participants may provide only one month efficacy data while on or off study treatment (pattern groups 8 and 9, respectively).~~ ~~The number and percentage of participants in each pattern group will be summarized by treatment group for the estimand analysis population defined in Section 10.5.1.~~ ~~**Table 20-3 Monotone Missing Data Patterns**~~ ~~Pattern Group / Month 1 (Weeks 1-4) / Month 2 (Weeks 5-8) / Month 3 (Weeks 9-12)~~ ~~1: x / x / x~~ ~~2: x / x / o~~ ~~3: x / o / o~~ ~~4: o / o / o~~ ~~5: x / x / .~~ ~~6: x / o / .~~ ~~7: o / o / .~~ ~~8: x / . / .~~ ~~9: o / . / .~~ ~~x = available efficacy data on study treatment;~~ ~~o = available efficacy data off study treatment;~~ ~~. = missing data~~ ~~Participants with missing data up to the 12-week treatment period will have their data imputed using participants in the same treatment group who provide data while off study treatment. Same as before (Section 10.2), the imputation of missing data is not based on each of the reasons of early~~	For clarity, since some patterns do not have enough number of participants to sever as a reference for multiple imputation

Section	Revision	Rationale
	~~termination, because there may not be sufficient non-missing efficacy data in each of the reason categories to serve as a stable reference.~~ ~~The details of imputation are as follows:~~ ~~Step 1. Impute month 2 missing data in pattern groups 8 and 9 by treatment group using data from pattern groups 3, 4, 6, and 7 in the corresponding treatment group based on monotone regression.~~ ~~Step 2. Impute month 3 missing data in pattern groups 5 – 9 respectively by treatment group using data from pattern groups 2, 3, and 4 in the corresponding treatment group based on monotone regression.~~ ~~Repeat the above procedures 100 times, then we have 100 complete datasets. The ANCOVA analysis results from these completed datasets are combined for overall estimation and inference using Rubin's rule (Rubin 1987) to produce a pooled estimate of LS mean difference, its SE, and corresponding p-value for the test of null hypothesis of no treatment effect.~~	
Section 10.5.5, Population-level Summary	Added: Participants are always analyzed based on their treatment assignment by randomization. To obtain the estimate of treatment effect defined in the off-treatment hypothetical estimand, an MMRM similar to the primary analysis specified in Section 10.2.1 will be performed on observed data collected from both double-blind treatment period and follow-up period. The model terms include treatment group, visit (derived as month), prior exposure (yes/no) to a migraine prevention medication with proven efficacy, treatment- by-visit interaction, the baseline score and baseline-by-visit interaction.	For clarity
Section 10.5.6, Off-treatment Hypothetical Estimand Approach for the Secondary Endpoints	Updated: Continuous secondary endpoints based on eDiary data will be handled using the same estimand approach defined above for the primary endpoint. The secondary endpoint of 50% responders are derived **at least a 50% reduction from baseline in the 3-month average of monthly migraine days using data collected from the double-blind period and follow-up period**. **Data after participants started a new prophylaxis treatment during the follow-up period will be excluded.** The population-level summary for this endpoint is the odds ratio from a logistic regression for each atogepant group relative to placebo with baseline monthly migraine days as a covariate, prior exposure (yes/no) to a migraine prevention medication with proven efficacy and treatment group as fixed factors. ~~Rubin's rule will be applied to the log odds ratio before transforming back to odds ratio for reporting purposes.~~ **The graphical approach to control the overall Type I error rate described in Section 10.3 will be provided for primary and key secondary endpoints in the analysis population for off-treatment hypothetical estimand.**	For clarity

Section	Revision	Rationale
Section 11.1, Adverse Events	Updated: An AE that occurs more than 30 days after the last dose of double-blind study treatment or Visit 8 whichever comes later will not be counted as a TEAE~~, except for participants rolling over into Study 3101-309-002 (longterm safety extension study). For these participants, if Visit 7 in this study is conducted on the same day as Visit 1 in Study 3101-309-002, then an AE that occurs after Visit 7 will not be counted as a TEAE; if Visit 8 in this study is conducted on the same day as Visit 1 in Study 3101-309-002, then an AE that occurs after Visit 8 will not be counted as a TEAE; if there is a gap between Visit 8 in this study and Visit 1 in Study 3101-309-002, then an AE occurs more than 30 days after the last dose of double-blind study treatment or Visit 8 whichever comes later will not be counted as a TEAE, except that Visit 1 in Study 3101-309-002 occurs within 30 days after the last dose of double-blind study treatment, in which case an AE that occurs after Visit 1 in Study 3101-309-002 will not be counted as a TEAE.~~ Per case report form instructions, a new AE record will be created for any AE that worsens; therefore, TEAEs can be identified as those AEs **captured in Study 3101-301-002** with recorded onset date on or after the date of the first dose of double-blind study treatment and within 30 days after the last dose of double-blind study treatment or Visit 8 whichever comes later. ~~For rollover participants, an AE that occurs after Visit 1 dosing in Study 3101-309-002 will be captured in that study.~~	For clarity
Section 11.1, Adverse Events	Added: Only AEs captured in Study 3101-301-002 will be considered for TEAEs in this study. For participants rolling over into Study 3101-309-002 (extension study) who start the first dose on Visit 1 or beyond, AEs captured in Study 3101-309-002 will be summarized in that study although some AEs might occur within 30 days after the last dose from Study 3101-301-002.	For clarity
Section 11.1, Adverse Events	Added: The incidence of common (≥ 2% of participants in any treatment group) TEAEs will be summarized by preferred term, and treatment group. **A similar 5% table will be provided as well.**	For clarity
Section 11.2, Clinical Laboratory Assessments	Added: Clinical laboratory test values will be considered potentially clinically significant (PCS) if they meet either the lower-limit or higher-limit PCS criteria listed in Table 11-1. **The normal range for eGFR was not collected in the lab. Therefore, eGFR<60 mL/min/1.73m^2 is defined in Table 11-1 to classify renal function as the category of "Moderate eGFR Decrease or Worse" based on FDA guidance on PK studies in Patients with impaired renal function.**	For clarity
Section 11.2, Clinical Laboratory Assessments	Updated: Shift tables from baseline to end of ~~study~~ **the double-blind treatment period** for clinical laboratory parameters will be presented by treatment group for the following categories	For clarity
Section 11.2, Clinical Laboratory Assessments	Added: A listing of urine pregnancy test results will be provided for female participants of child-bearing potential with at least one positive result.	For clarity

<table>
<tr><th>Section</th><th>Revision</th><th>Rationale</th></tr>
<tr><td>Section 11.3, Vital Signs</td><td>Updated:
The number and percentage of participants who have PCS postbaseline vital sign values will be tabulated by treatment group. ~~The percentages will be calculated relative to the number of participants who have available baseline or non-PCS baseline (for parameters with only the observed value criterion) values and at least 1 postbaseline assessment.~~ For criteria related with systolic blood pressure, diastolic blood pressure, pulse rate and weight, the denominator will be the number of participants who have available baseline and at least 1 postbaseline assessment. For criteria related with orthostatic measures, the denominator will be the number of participants who have available non-PCS baseline and at least 1 postbaseline assessment.</td><td>For clarity</td></tr>
<tr><td>Section 11.4, Electrocardiograms</td><td>Updated: Table 11-4
<table><tr><th>Parameter</th><th>Unit</th><th>~~Actual Value~~ Criterion</th><th>~~Change from Baseline~~</th></tr><tr><td>QRS interval</td><td>msec</td><td>≥ 150</td><td>—</td></tr><tr><td>PR interval</td><td>msec</td><td>≥ 250</td><td>—</td></tr><tr><td>QTc~~B~~ (QTcB or QTcF) interval</td><td>msec</td><td>> 500</td><td>~~Increase > 60~~</td></tr><tr><td>QTc~~B~~ (QTcB or QTcF) interval</td><td>msec</td><td>Increase from baseline > 60</td><td>~~Increase > 60~~</td></tr></table>QTc = QT interval corrected for heart rate.
QTcB = QT interval corrected for heart rate using the Bazett formula.
QTcF = QT interval corrected for heart rate using the Fridericia formula.</td><td>For clarity</td></tr>
<tr><td>Section 11.4, Electrocardiograms</td><td>Added:
To evaluate ECG postbaseline values of clinical interest, the number and percentage of participants with post-treatment QTcF >450 msec, >480 msec, and >500 msec will be tabulated by treatment group.
The number and percentage of participants with an increase > 30 msec but ≤ 60 msec, and with an increase > 60 msec in QTcF will be tabulated. Participants will be counted only once for the most severe category. A supportive listing of participants with postbaseline QTcF increases > 30 msec will be provided, including the PID number, study center, and all QTc values (including changes from baseline). A listing of all AEs for participants with postbaseline QTcF increases > 30 msec will also be provided.</td><td>For clarity</td></tr>
<tr><td>Section 12, Health Outcome Analyses</td><td>Added:
Health outcomes which are planned to be reported in CSR main body are provided in Section 10.4. Other health outcome analyses are documented in health economics and outcomes research SAP.</td><td>For clarity</td></tr>
</table>

Section	Revision	Rationale
Section 13, Subgroup Analyses	Updated: • ~~Proportion of participants with at least a 50% reduction in mean monthly migraine days across the 12-week treatment period~~ ≥ 50% reduction in 3-month average of monthly migraine days • ~~Proportion of participants with at least a 75% reduction in mean monthly migraine days across the 12-week treatment period~~ ≥ 75% reduction in 3-month average of monthly migraine days • ~~Proportion of participants with 100% reduction in mean monthly migraine days across the 12-week treatment~~ period 100% reduction in 3-month average of monthly migraine days	For clarity
Section 13, Subgroup Analyses	Updated: ~~Additional subgroup analyses for primary efficacy endpoint (i.e., change from baseline in mean monthly migraine days across the 12-week treatment period) will be performed by the presence of allodynia based on the ASC-12 sum score (absence: 0 to 2, presence: >2) and by the number of failed prior migraine prevention medication of proven efficacy (failed 1 or more medications, failed no medications, no prior exposure).~~ Subgroup analyses for primary efficacy endpoint based on demographic factors (age, sex, race) will be provided in the integrated summary of efficacy to facilitate the comparison across pivotal studies.	For clarity
Section 17.1, Visit Time Windows	Updated: Tables 17-1, 17-3 **Analysis Phase** Pretreatment ~~Treatment~~ Double-blind treatment period	For clarity

<table>
<tr><th>Section</th><th>Revision</th><th>Rationale</th></tr>
<tr><td>Section 17.1, Visit Time Windows</td><td>Updated: Table 17-5
<table>
<tr><th>Analysis Phase</th><th>Analysis Visit (Derived)</th><th>Scheduled Study Visit (eCRF)</th><th>Window</th></tr>
<tr><td>Pretreatment</td><td>Baseline</td><td>Visit 2 (Randomization)</td><td>Treatment Day ≤ 1</td></tr>
<tr><td rowspan="3">~~Treatment~~ Double-blind Treatment Period</td><td>Week 4</td><td>Visit 4</td><td>Treatment Day [2, 41]</td></tr>
<tr><td>Week 8</td><td>Visit 6</td><td>Treatment Day [42, 69]</td></tr>
<tr><td>Week 12</td><td>Visit 7/ET</td><td>Treatment Day [70, End of the ~~last~~ double-blind ~~visit~~ treatment period]</td></tr>
<tr><td>Follow-up</td><td>Week 16 (Follow-up)</td><td>Visit 8</td><td>Treatment Day [End of the ~~last~~ double-blind ~~visit~~ treatment period +1, the last study visit]</td></tr>
</table>
ET = early termination. Follow-up visit will not be included in the MMRM analysis and will only be used in summary statistics.</td><td>For clarity</td></tr>
<tr><td>Section 17.1, Visit Time Windows</td><td>Added Tables 17-2, 17-4, 17-6, 17-7, 17-8, 17-9,17-10</td><td>For clarity</td></tr>
<tr><td>Section 17.1, Visit Time Windows</td><td>Updated Table 17-11:
<table>
<tr><th>Window</th></tr>
<tr><td>Treatment Day ≤ 1</td></tr>
<tr><td>Treatment Day [2, 20]</td></tr>
<tr><td>Treatment Day [21, 34]</td></tr>
<tr><td>Treatment Day [35, 48]</td></tr>
<tr><td>Treatment Day [49, 69]</td></tr>
<tr><td>Treatment Day [70, End of the ~~last~~ double-blind ~~visit~~ treatment period]</td></tr>
<tr><td>Last available assessment during double-blind treatment period</td></tr>
<tr><td>Treatment Day [End of the ~~last~~ double-blind ~~visit~~ treatment period +1, the last study visit]</td></tr>
<tr><td>Last available assessment after treatment start date, i.e. occurs at final visit (expected Day 112) or ET</td></tr>
</table></td><td>For clarity</td></tr>
</table>

Section	Revision	Rationale
Section 17.1, Visit Time Windows	Added: For endpoints collected by visit (not for eDiary data), if a participant has 2 or more visits within the same window, the last visit with a non-missing value will be used for analysis. **The following algorithm is used to define the Double-blind Treatment Period and the Follow-up Period unless specified otherwise.** The double-blind treatment period starts with the date of the first dose of double-blind study treatment and ends with the latest date of the last study medication date, and the last scheduled assessment date of V2 to V7 for participants who entered the follow-up period; or ends with the latest date of the last study medication date, and last assessment date for participants who did not entered the follow-up period. The follow-up period starts with the 1 day after the end of the double-blind period and ends with the last assessment date for participants who entered the follow-up period.	For clarity
Section 17.2.1, Derivation of Efficacy Endpoints Based on eDiary Data	Added: • **For the derivation of headache day, the participant is considered to have taken a non-antiemetic acute headache medication if the participant has taken such a medication in either "today's diary" or "yesterday's diary".** **Moderate/severe headache day is defined as a headache day during which the maximum pain severity is either moderate or severe** **Severe headache day is defined as a headache day during which the maximum pain severity is severe** **If a participant confirmed no headache for the Question 1 in eDiary, then the participant will not answer subsequent questions related with headache sysmptoms, duration, and acute headache mediation use by design. Thus, the acute medication use for that diary ('today' or 'yesterday') will be treated as 'No' when deriving acute medication use day.** **If a participant reported multiple records on the same day for one specific category ('Today' or 'Yesterday') and records are inconsistent, then the records for that eDiary category on the date with discrepancy will be excluded from endpoint derivation and thus excluded from the analyses. A list will be provided to show inconsistent records within one specific category on the same day for the same participant.** If there are duplicated records of daily diary data for the same participant on the same day with the same type, the set of records with the last form access datetime will be used in the analysis **because records are duplicated**.	For clarity
Section 17.2.1, Derivation of Efficacy Endpoints Based on eDiary Data	**If a participant confirmed that acute medications were taken and entered medications in the eDiary, then the acute medication use day will be set to 'Yes'.** If a subject reports 'Yes' to the intake of allowed medication(s) to treat an acute migraine but does not list any of them in the diary, then the acute medication use days will not be counted in this situation **and vice versa**.	For clarity

Section 17.2.2, Derivation of Health Outcome Endpoints	Updated AIM-D related endpoints derivation: ~~For performance of daily activities domain, the five individual item scores will be summed and divided by five, resulting in the domain score ranging from 0 to 5 with higher scores indicating greater impairment. If there are missing item level data for a study day, the domain score can be calculated by summing the non-missing item scores and dividing by the number of non-missing items provided that 3 or more items in the domain are completed. If 4 or more daily domain scores are available for a week, a weekly average performance of daily activities domain score will be computed by summing the non-missing daily domain scores and dividing by the number of non-missing domain scores; otherwise it will be set to missing. If 3 or more weekly average domain scores are available and daily domain scores are available for at least 14 days in a month (4 weeks), a monthly average performance of daily activities domain score will be computed by summing the non-missing weekly average domain scores and dividing by the number of non-missing weekly domain scores; otherwise it will be set to missing.~~ ~~For the physical impairment domain, the four individual item scores will be summed and divided by four, resulting in the domain score ranging from 0 to 5 with higher scores indicating greater impairment. For some items, if the response of "I did not…," is selected, then the corresponding item score will be set to missing. If there are missing item level data for a study day, the domain score can be calculated by summing the non-missing item scores and dividing by the number of non-missing items provided that 2 or more items in the domain are completed. If 4 or more daily domain scores are available for a week, a weekly average physical impairment domain score will be computed by summing the non-missing daily domain scores and dividing by the number of non-missing domain scores; otherwise it will be set to missing. If 3 or more weekly average domain scores are available and daily domain scores are available for at least 14 days in a month (4 weeks), a monthly average physical impairment domain score will be computed by summing the non-missing weekly average domain scores and dividing by the number of non-missing weekly domain scores; otherwise it will be set to missing.~~ <u>AIM-D Related Endpoints Derivation</u> As described in SAP Section 10.1.2 (copied from protocol Section 6.2.1), the AIM-D was developed as a daily eDiary with a recall period 24 hours. By design, it is collected in the today diary only. The scoring of the following endpoints is completed in 2 steps. • Monthly Performance of Daily Activities domain score of the AIM-D • Monthly Physical Impairment domain score of the AIM -D • Monthly AIM -D total score Step 1: Calculate AIM-D daily domain score and total score Daily performance of daily activities score will be calculated based on the summation of items 1-5 and 10 and 11, ranging from 0-35. A daily performance of daily activities domain score will be calculated if 4 or more item scores have non-missing responses. When the response category "I did not have <errands, leisure or social, strenuous activities> planned" (items 2, 4, and 5), is selected, the response will be considered missing. The corresponding performance of daily activities domain score will be calculated by summing the non-missing item scores and dividing by the number of non-missing items and then multiplying by 7, provided that 4 or	For clarity

Section	Revision	Rationale
	more item scores are available; otherwise it will be set to missing. The raw daily score will be transformed to a 0-100 scale by multiplying by 100 and dividing by the highest raw score (35). Daily physical impairment scores will be calculated based on the summation of items 6-9, ranging from 0-20. A daily physical Impairment score will be calculated if 2 or more item scores have non-missing responses. The corresponding physical Impairment score will be calculated by summing the non-missing item scores and dividing by the number of non-missing items and then multiplying by 4, provided that 2 or more item scores are available; otherwise it will be set to missing. The raw daily score will be transformed to a 0-100 scale by multiplying by 100 and dividing by the highest raw score (20). A daily total score will be calculated based on the summation of items 1-11, ranging from 0-55. A Total Score will be calculated if 6 or more items scores have non-missing responses. When the response category "I did not have <errands, leisure or social, strenuous activities> planned" (items 2, 4, and 5), is selected, the response will be considered missing. The corresponding Total Score will be calculated by summing the non-missing item scores and dividing by the number of non-missing items and then multiplying by 11, provided that 6 or more item scores are available; otherwise it will be set to missing. The raw score will be transformed to a 0-100 scale by multiplying by 100 and dividing by the highest raw score (55). Step 2: Calculate Monthly Scores and Baseline Score Monthly scores will be calculated using the average daily scores only if there are at least 14 non-missing daily scores in the corresponding monthly (28-day) period. The corresponding monthly scores will be calculated by summing the non-missing daily domain scores and dividing by the number of non-missing daily domain, provided that 14 or more daily scores are available; otherwise it will be set to missing.	

Section 17.2.2, Derivation of Health Outcome Endpoints	Updated: ~~For the MSQ v2.1 Role Function Restrictive domain, precoded item values and final item values for each MSQ item response are shown in Table 20 . The seven individual item responses using final item value will be summed, resulting in the raw domain score ranging from 7 to 42 with higher scores indicating better quality of life.~~ MSQ Related Endpoints Derivation MSQ v2.1 consists of 14 items with a 4-week recall period. The scoring of the MSQ is completed in following 3 steps. Step 1: Final item value assignment. Precoded item values and final item values for each MSQ item response are shown in Table 17–12. ~~If there are missing item responses, the raw domain score can be calculated by summing the non-missing item responses using final item value and dividing by the number of non-missing items and then multiplying by 7 provided that 4 or more items in the domain are completed; otherwise it will be set to missing. The Role Function Restrictive domain score will be transformed to a 0 – 100 scale by subtracting 7 from the raw domain score and multiplying the result by 100/35.~~ **Table 20-~~5~~12 Item Values for MSQ Item Responses** Step 2: Computation of raw domain(dimension) scores Once a final item value has been assigned to each item, a raw score can be computed for each MSQ domain. Role Function Restrictive domain includes Items 1 - 7, Role Function Preventive domain includes Items 8 - 11, and Emotional Function domain includes Items 12 - 14. The raw score for each domain is the algebraic sum of the final item values for all items in that domain. Missing data handling: if a respondent answered at least half of the items in a domain (or half plus one in the case of scales with an odd number of items), a missing item value can be estimated using the average of the other completed items within the same dimension. In detail, for MSQ v2.1 Role Function Restrictive domain, the 7 individual item responses using final item value will be summed, resulting in the raw domain score ranging from 7 to 42 with higher scores indicating better	To reflect that the endpoints related to MSQ 2.1 Role Function Preventive and Emotional Function domain scores are included in this SAP

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

Section	Revision	Rationale
	quality of life. If there are missing item responses, the raw domain score will be calculated by summing the non-missing item responses using final item value and dividing by the number of non-missing items and then multiplying by 7 provided that 4 or more items in the domain are completed; otherwise it will be set to missing. For MSQ v2.1 Role Function Preventive and Emotional domains, the raw domain scores will be calculated similarly using final item value respectively. If there are missing item responses, the corresponding raw domain score will be calculated by summing the non-missing item responses using final item value and dividing by the number of non-missing items and then multiplying by the number of questions in that domain provided that 2 or more domain items are completed; otherwise it will be set to missing. Step 3: Linear transformation to a 0 to 100 scale. The transformation formula for each MSQ 2.1 domain are listed below • Role Function -Restrictive: $\frac{(raw\ score-7)*100}{35}$ • Role Function-Preventive: $\frac{(raw\ score-4)*100}{20}$ • Emotional Function: $\frac{(raw\ score-3)*100}{15}$	

<table>
<tr>
<td>Section 17.2.2, Derivation of Health Outcome Endpoints</td>
<td>
Added:
<u>HIT-6 Total Score Derivation</u>
For HIT-6 total score, pre-coded item values and final item values for each item response are shown in Table 20-3. Total score is calculated by summing 6 sub-item responses, resulting in the total score ranging from 36 to 78 with higher scores indicating greater impact. If any sub item is missing, then total score will be missing.

Table 20-3 Item Values for HIT-6 Item Responses
<table>
<tr><td>Response Categories</td><td>Precoded Item Value</td><td>Final Item Value</td></tr>
<tr><td>Never</td><td>0</td><td>6</td></tr>
<tr><td>Rarely</td><td>1</td><td>8</td></tr>
<tr><td>Sometimes</td><td>2</td><td>10</td></tr>
<tr><td>Very Often</td><td>3</td><td>11</td></tr>
<tr><td>Always</td><td>4</td><td>13</td></tr>
</table>
The HIT-6 instrument has a recall period of 4 weeks for 3 of the 6 items.

<u>MIDAS Related Endpoints Derivation</u>
MIDAS total score is derived as the sum of first 5 of questions (i.e., the sum of days missing work or school, Productivity at work or school reduced, Not do household work, Productivity in household work reduced, Miss family social or leisure activities). If any sub item is missing, the MIDAS total score will be missing.
The MIDAS absenteeism score is derived as the sum of Questions 1, 3 and 5. If any sub item is missing, then the MIDAS absenteeism score will be missing. The MIDAS presenteeism score is derived as the sum of Questions 2 and 4. If any sub item is missing, then the MIDAS presenteeism score will be missing.
<u>WPAI:MIGRAINE Related Endpoints Derivation</u>
WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes, as follows:
Questions:
• Q1 = currently employed (working for pay).
• Q2 = missed work hours because of problems associated with your migraine
• Q3 = missed work hours due to other reason.
• Q4 = hours actually worked.
• Q5 = migraine affected productivity while working.
• Q6 = migraine affected regular daily activity.

Scores:
Multiply scores by 100 to express in percentages.
</td>
<td>To reflect that these endpoints are included in this SAP</td>
</tr>
</table>

Section	Revision	Rationale
	• Percent work time missed due to migraine (absenteeism): Q2/(Q2 + Q4) • Percent impairment while working due to migraine (presenteeism): Q5/10 • Percent overall work impairment due to migraine (overall work productivity loss): Q2/(Q2 + Q4) + [(1- (Q2/(Q2 + Q4)))x(Q5/10)] • Percent activity impairment due to migraine(regular activity impairment): Q6/10 If the response to Q1 ("Currently employed?") is *No* or missing, absenteeism, presenteeism, and overall work productivity loss will all be set to missing.	
Section 17.3, Repeated or Unscheduled Assessments of Safety Parameters	Added: Baseline is defined as the last assessment made before the first dose of double-blind study treatment. **If a participant has 2 or more visits within the same window, the last visit with a non-missing value will be used for summary over time.**	For clarity
Section 17.10, Identifying Prior Exposure (yes/no) to a Migraine Prevention medication with Proven Efficacy Based on Prior Medications Reported in eCRF	Added: According to Appendix 12.3.1 in the protocol, a list of migraine-preventive medications with proven efficacy was identified by clinical team and coding team as shown in Table xx. If a participant has taken medications before the screening visit with preferred names in the provided sheet, and the prior medications are classified as "Migraine Prevention Medication" in the prior and concomitant medications eCRF, then the prior exposure to migraine prevention medications with proven efficacy will be "Yes" for this participant, otherwise, it is set as "No." **Table 17-14 List of Migraine-preventive Medications with Proven Efficacy**	For clarity, since related efficacy analyses are based on this actual stratification .

Section 18, COVID-19 Related Analyses	To eliminate immediate potential hazards to participants and study staff due to the COVID-19 pandemic while ensuring participant safety and maintaining data integrity, the protocol clarification letter and corresponding protocol amendment were sent to sites during the pandemic to allow remote visits (as described in the protocol Table 2 Schedule of Visits and Procedures for Visits Conducted Remotely Due to the COVID-19 Pandemic). This section specifies analyses for evaluating the impact of COVID-19. 1.1 Efficacy Evaluation Efficacy Endpoints Table 18–1 describes the collection devices for primary and key secondary endpoints. The primary endpoint and 5 key secondary endpoints are collected via eDiary according to protocol design. Minimal disruption is expected for these endpoints because participants are expected to complete eDiary at home and submit the responses every day. The endpoint, MSQ v2.1 Role Function Restrictive domain score at Week 12, will be collected using eTablet as one electronic patient reported outcome (ePRO) at site. The remote collection for this endpoint was in production starting from April 20,2020. Participants are required to complete the ePRO measures remotely at Visit 7 (Week 12) according to remote-visit procedure.	For clarity

To evaluate the missing rate for this endpoint at Week 12, the number of participants who missed at least one ePRO assessment due to COVID-19 will be summarized at each visit in the mITT Population (efficacy analyses population).

Table 18-20-4 Summary of Collection Devices for Primary and Key secondary endpoints

Hypothesis Testing	Node	Endpoint	Collection device
Primary	P1	Change from baseline in mean monthly migraine days across the 12-week treatment period	eDiary
Secondary 1	S1	Change from baseline in mean monthly headache days across the 12-week treatment period	eDiary
Secondary 2	S2	Change from baseline in mean monthly acute medication use days across the 12-week treatment period	eDiary
Secondary 3	S3	≥ 50% reduction in 3-month average of monthly migraine days	eDiary
Secondary 4	S4	Change from baseline in MSQ v2.1 Role Function Restrictive domain score at Week 12	eTablet
Secondary 5	S5	Change from baseline in mean monthly Performance of Daily Activities domain score of the AIM-D across the 12-week treatment period.	eDiary
Secondary 6	S6	Change from baseline in mean monthly Physical Impairment domain score of the AIM -D across the 12-week treatment period.	eDiary

Power and Sample Size Evaluation

The study achieved the last participants first visit on January 31, 2020. A total of 910 patients were randomized, and the number of randomized participants exceeded the planned sample size 872. It is expected the missing rate during the pandemic might be slightly higher than the missing rate before the pandemic. No big impact for the power and sample size calculation is anticipated.

1.2 Safety and other evaluations

This section specifies analyses related to COVID-19 pandemic from the following aspects:

- Disposition
- Study visit (missing entire visit due to COVID-19 or missing assessments due to COVID-19)
- Protocol deviation

Section	Revision	Rationale
	• Study drug disruption due to COVID-19 • TEAEs related with COVID-19 Safety Population will be used for the planned analyses described above.The number of participants impacted by COVID-19 during the study will be summarized by treatment group and overall. In addition, the number of participants impacted by COVID-19 and their corresponding disposition status in the double-blind treatment period and the follow-up period will be summarized respectively. The number of participants who missed at least one entire visit due to COVID-19 will be summarized by treatment group and overall. Furthermore, the number of participants who missed at least one assessment due to COVID-19 will be summarized by assessment category (laboratory, C-SSRS, urine pregnancy test, vital signs, ECG, and ePRO) and overall. Similar summaries will be provided by visit. The number of participants with significant protocol deviation due to COVID-19 will be provided. The number of participants with study drug disruption due to COVID-19 will be provided as well. The number of participants with TEAEs related to corona virus infection or coronavirus test positive will be provided. Supporting listings for the described analyses above will be provided.	
Appendix I, Reporting Selected Laboratory Parameters in Conventional Unit	Added: All clinical laboratory parameters will be reported in the International System (SI) units as standard practice. In addition, descriptive statistics for values and changes from baseline in conventional units at all assessed visits will be reported for selected laboratory parameters as listed in Table 20.I-1 below. **Table 20-1 List of Selected Parameters to be Reported in Conventional Units** Patient narratives will also include the values in conventional units for the selected lab parameters (Table 20.I-1). That will be accomplished by presenting the values in conventional units within the parentheses next to the values in SI units. As shown in Table 20.I-2 below for 'Bilirubin, Total' parameter, for which 'umol/L' is the SI unit and 'mg/dL' is the conventional unit. **Table 20-2 Presenting Laboratory Data Using SI and Conventional Units in Narratives**	For clarity