1.0 TITLE PAGE

3101-303-002

A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF ATOGEPANT FOR THE PREVENTION OF CHRONIC MIGRAINE (PROGRESS)

STATISTICAL ANALYSIS PLAN – AMENDMENT 1

Date: 10 April 2019

Amendment 1 (Final draft): 12 July 2021

Amendment 1 Signoff: 24 January 2022

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3.0 LIST OF ABBREVIATIONS

AE	adverse event
AIM-D	Activity Impairment in Migraine – Diary
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APAC	Asia-Pacific
ASC-12	allodynia symptom checklist
AST	aspartate aminotransferase
BID	twice daily
BMI	body mass index
bpm	beats per minute
CFB	change from baseline
CI	confidence interval
CM	chronic migraine
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	Diastolic blood pressure
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
ECG	electrocardiogram, electrocardiographic
eDiary	electronic diary
eCRF	electronic case report form
ePRO	electronic Patient Reported Outcome
EQ-5D-5L	European Quality of Life – 5 Dimensional
ET	early termination
EU	European Union
eTablet	electronic tablet
FWER	familywise error rate

GLMM	generalized linear mixed model
HIT-6	Headache Impact Test
INR	international normalized ratio
ITT	intent-to-treat
IWRS	interactive web response system;
K-S	Kolmogorov-Smirnov
LLN	lower limit of normal value
LOCF	last observation carried forward
LS	least square
MAR	missing-at-random
MCMC	Markov chain Monte Carlo
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
NSAID	nonsteroidal anti-inflammatory drug
OL	open label
PCS	potentially clinically significant
PDRS	Protocol Deviation Requirement Specifications
PGIC	Patient Global Impression of Change
PGI-S	Patient Global Impression – Severity
PHQ-9	Patient Health Questionnaire
PID	participant identification
PK	pharmacokinetic
PMM	pattern-mixture model

PRO	patient reported outcomes
PROMIS-PI	Patient-Reported Outcomes Measurement Information Systems Pain Interference – Short Form 6a
PSSM	Patient Satisfaction with Study Medication
Q1	first quartile
Q3	third quartile
QD	once daily
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/(RR)^{1/2}$)
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$)
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SI	*Le Système International d'Unités* (International System of Units)
SoA	Schedule of Activities
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
ULN	upper limit of normal
VAS	visual analogue scale
VCT	verified clinical trial
WHO	World Health Organization
WPAI: MIGRAINE	Work Productivity and Activity Impairment Questionnaire: Migraine Version V2.0

4.0 INTRODUCTION

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of the efficacy and safety data as outlined and/or specified in the final protocol (version dated 13 December 2018), protocol amendment 1 (version dated 08 April 2019), protocol amendment 2 (version dated 23 September 2019), and protocol amendment 3 (version dated 29 May 2020) of Study 3101-303-002. Specifications of tables, figures, and data listings are contained in a separate document.

The analyses of the study for global submissions in various geographic regions (US, Europe, etc.) are documented in the main body of this SAP. Additional analyses for subjects enrolled at study sites in China, Japan, Korea, and Taiwan that will be used to provide additional support for marketing authorization in the above countries or region are documented in region-specific SAP Addenda.

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 study conducted at approximately 110 sites worldwide. Approximately 750 participants will be randomized to 1 of 3 treatment arms (placebo, Atogepant 30 mg twice daily [BID], and Atogepant 60 mg once daily [QD]) in a 1:1:1 ratio.

Participants will be stratified by:

- Randomization will be stratified by use of acute headache medications during the baseline period (acute headache medication overuse Yes or No). Acute headache medication overuse (Yes) will be defined as follows: use of triptans on ≥ 10 days OR use of ergots on ≥ 10 days OR use of simple analgesics (ie, aspirin, nonsteroidal anti-inflammatory drugs [NSAIDs], or acetaminophen) on ≥ 15 days OR use of any combination of triptans, ergots or simple analgesics on ≥ 10 days.

- Approximately 70% of randomized participants will have taken at least 1 prior migraine prevention medication with proven efficacy. Randomization will be stratified based on migraine prevention medication exposure (Current Use, Past Use, or Never Used) with proven efficacy. Participants with current or past use will be further stratified based on the number of medications failed with unique mechanisms of action: "failed 0 medications or failed 1 or more medication(s) with the same mechanism of action" or "failed 2 to 4 medications with different mechanisms of action". Enrollment of participants with current use of a migraine prevention medication will be capped at ~15%.
- Randomization will be stratified by regions: North America, Europe, China, Japan and the Asia-Pacific (APAC).

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 this study 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/ Early Termination (ET) (Week 12), and Visit 8 (follow-up). The Visit 8 (follow-up) must be completed for all participants who take at least 1 dose of study medication, except for participants rolling over into Study 3101-312-002 (long-term safety extension study in regions, excluding Japan and China), Study 3101-306-002 (long-term safety extension study in Japan), or Study 3101-311-002 (open-label safety extension study in China). For these rollover participants Visit 8 of Study 3101-303-002 is not required, because the Follow-up Visit (Visit 8) will be performed after the OL treatment in the respective long-term safety study. For participants who screen fail for the long-term safety study, the Follow-up Visit (Visit 8) of Study 3101-303-002 must be completed.

Due to the COVID-19 pandemic, Section 17.0 is added to specify analyses for evaluating the impact of COVID-19.

Figure 4-1. Study Design

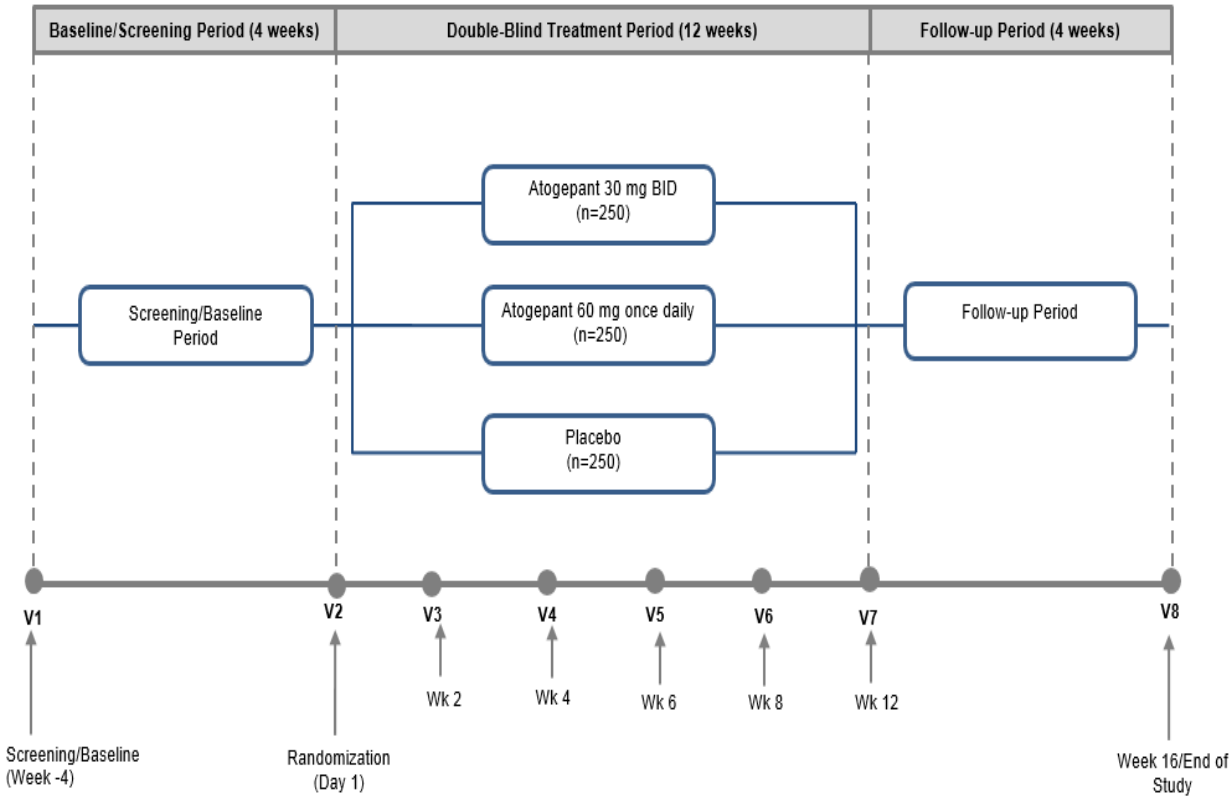


Table 4-1. Schedule of Activities (SoA)

Study Period	**Screening/ Baseline (4 weeks)**	**Double-blind Treatment Period (12 weeks)**						**Follow-up Period (4 weeks)**
Visit #	**Visit 1**	**Visit 2 (Randomization)**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7/ET[a]**	**Visit 8[p] (End of Study)**
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 days	± 3 days	± 3 days	± 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							
Obtain VCT consent and perform verification (United States and Canada only)	X							
Access IWRS	X	X	X	X	X	X	X	X
Assess inclusion/exclusion criteria	X	X						
Collect demographic information	X							
Collect medical history	X							
Collect migraine history	X							
Review prior medications including migraine prophylactic medication use	X							
Perform physical examination	X						X	X
Collect vital sign measurements[d]	X	X	X	X	X	X	X	X
Perform ECG	X				X		X	
Perform urine pregnancy test[e]	X	X	X	X	X	X	X	X
Collect start date (first day) of last menstrual cycle for women having menstrual cycles	X	X	X	X	X	X	X	X
Collect urine drug screen	X							
Collect clinical laboratory determinations[f]	X	X	X	X	X	X	X	X
Collect PK sample (for those participating)[g]		X	X	X	X	X	X	

Study Period	**Screening/ Baseline (4 weeks)**	**Double-blind Treatment Period (12 weeks)**					**Follow-up Period (4 weeks)**
Visit #	**Visit 1**	**Visit 2 (Randomization)**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7/ET[a]**	**Visit 8[p] (End of Study)**
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 days	± 3 days	± 3 days	± 3 days	+ 3 days	± 3 days
Collect blood for future biomedical research (for those participating)	X							
Provide eDiary, and eDiary instructions and training[h]	X							
Participant eDiary data collection	X							
Review of medication compliance			X	X	X	X	X	
Review eDiary data (headache duration, frequency, characteristics and symptoms, acute medication use, AIM-D, activity level and activity limitation) and compliance[i]		X	X	X	X	X	X	
C-SSRS (eTablet)[i]	X	X	X	X	X	X	X	
ASC-12 (eTablet)[k,j]	X							X
HIT-6 (eTablet)[k,l]		X		X		X	X	X
PGIC (eTablet)[k,l]							X	
PGI-S (eTablet)[k,l]		X		X		X	X	
WPAI:MIGRAINE (eTablet)[k,l]		X		X		X	X	
Patient Satisfaction with Study Medication (eTablet)[k,l]				X		X	X	
EQ-5D-5L[m]	X	X	X	X	X	X	X	X[j]
MIDAS (eTablet)[k,l]		X					X	
MSQ v2.1 (eTablet)[k,l]		X		X		X	X	X
PROMIS-PI (eTablet)[k,l]		X		X		X	X	
PHQ-9 (eTablet)[k,l]		X					X	
Collect eDiary		X[k]					X[n]	X[o]
Dispense study intervention		X[l]	X	X	X	X		
Adverse events	X							
Concomitant medications/concurrent procedures	X							

ASC-12 = 12-item Allodynia Symptom Checklist; AIM-D = Activity Impairment in Migraine–Diary; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; eDiary = electronic diary; EQ-5D-5L = European Quality of Life – 5 Dimensional; ET = early termination; eTablet = electronic tablet; HIT-6 = Headache Impact Test; INR = international normalized ratio; IWRS = interactive web response system; MIDAS = Migraine Disability Assessment; MSQ v2.1 = Migraine Specific Quality of Life Questionnaire, Version 2.1; OL = open-label; PGIC = Patient Global Impression of Change; PGI-S = Patient Global Impression – Severity; PHQ-9 = Patient Health Questionnaire; PK = pharmacokinetic; PRO = patient-reported outcome; PROMIS-PI = Patient-Reported Outcomes Measurement Information System Pain Interference – Short Form 6a; PSSM = Patient Satisfaction with Study Medication; VCT = verified clinical trial; WPAI: MIGRAINE = Work Productivity and Activity Impairment Questionnaire: Migraine V2.0.

a. Visit 1, Visit 2, and either Visit 3 or Visit 4 must be conducted in office. All other visits, should be conducted in office unless it is necessary to conduct remote visits for the safety of participants (eg, COVID-19 or other pandemic): for details please refer to the Remote Visit Schedule of Assessments in Attachment 12.4.
b. Effort should be made by site to not schedule Visit 7 earlier than Day 85 to ensure that participants complete the full 12 weeks of treatment and have eDiary data through Day 84.
c. All participants who take at least 1 dose of study intervention must complete the follow-up period, except for participants rolling over into Study 3101-312-002 (long-term safety extension study in regions excluding Japan and China), participants rolling over into Study 3101-306-002 (long-term safety extension study in Japan), or Study 3101-311-002 (open-label safety extension study in China). For these rollover participants the Follow-up Visit will be performed after the completion of the OL treatment in the respective long-term safety extension study.
d. Vital sign measurements: height, weight, sitting 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.
e. For women of childbearing potential only, a urine pregnancy test will be performed at all visits
f. Clinical laboratory determinations include chemistry, hematology, 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).
g. PK sample should be collected prior to the first dose at Visit 2. One sample should be collected prior to the morning dose during one of the Visits 3 to 7, and the remaining samples should be collected 1 to 10 hours postdose.
h. Participant 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 the site.
i. Participants must bring the eDiary to visits and review with coordinators.
j. Clinicians will complete on eTablet. The screening/baseline assessment of the C-SSRS will be completed. At all other visits, the 'Since Last Visit' C-SSRS will be completed.
k. Participant will complete on eTablet.
l. PRO measures should be administered prior to any tests and/or evaluations unless indicated otherwise in the protocol (eg, during Randomization Visit 2, some tests will be conducted prior to PROs for eligibility).
m. EQ-5D-5L will be given on eDiary during 7 days in the baseline period and during specific time periods for Visit 1 to 7, except at Visit 8 (Week 16) where it will be administered on an eTablet.
n. eDiary will be collected on Visit 2 for screen failures.
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.
q. The first dose of study intervention should be taken at the study site.

5.0 STUDY OBJECTIVES

- To evaluate the safety and tolerability of atogepant 30 mg BID and atogepant 60 mg QD for the prevention of chronic migraine (CM).
- To prospectively test for superiority of atogepant 30 mg BID and atogepant 60 mg QD versus placebo for the prevention of CM.

6.0 PARTICIPANT POPULATIONS

6.1 INTENT-TO-TREAT POPULATION

The Intent-to-Treat (ITT) Population will consist of all randomized participants.

6.2 SAFETY POPULATION

The Safety Population will consist of all participants who received at least 1 dose of study intervention. All safety analyses will be performed using the Safety Population. For safety analyses, the participants will be analyzed according to actual treatment received which is defined as the study treatment received for majority of treatment period (rather than as randomized).

6.3 MODIFIED INTENT-TO-TREAT POPULATION

The Modified Intent-to-Treat (mITT) Population will consist of all randomized participants who received at least 1 dose of study intervention, had an evaluable baseline period of electronic diary (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 0 will be performed using the mITT population. For efficacy analyses, data will be analyzed according to participants' randomization assignments, regardless of actual treatment received.

6.4 OFF-TREATMENT HYPOTHETICAL ESTIMAND POPULATION

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, regardless of whether on study treatment or off study treatment. This population is used for the primary estimand in support of EU filing.

7.0 PARTICIPANT DISPOSITION

The number of participants screened will be summarized overall by study center; the number of participants in the ITT, Safety, mITT, and Off-treatment Hypothetical Estimand Populations will be summarized by treatment group and study center.

The number and percentage of participants in the ITT Population will be summarized by treatment group for the following two categories:

- IWRS randomization stratification: acute headache medication overuse (Yes or No), migraine prevention medication exposure (Current Use, Past Use, or Never Used) and number of medications failed with unique mechanisms of action ("failed 0 medications or failed 1 or more medication(s) with the same mechanism of action" or "failed 2 to 4 medications with different mechanisms of action"). The number and percentage of participants in the ITT Population will also be summarized by treatment group for each randomization stratum of 10 strata (the combination of 2 levels of "acute headache medications during the baseline period" (acute medication overuse Yes/No) and 5 levels of "current and past use of migraine prevention medications and the number of medications failed with unique mechanisms of action" (Current Use and "failed 0 medications or failed 1 or more medication(s) with the same mechanism of action", Current Use and "failed 2 to 4 medications with different mechanisms of action", Past Use only and "failed 0 medications or failed 1 or more medication(s) with the same mechanism of action", Past Use only and "failed 2 to 4 medications with different mechanisms of action", and Never Used) .
- Derived stratification: raw data from the database will be used to re-derive the "actual" stratification based on algorithms detailed in the SAP Section 16.10.

A summary table and list of participants with inconsistent randomization stratum against IWRS will be provided.

Screen-failure participants (ie, participants screened but not randomized) and the associated reasons for failure to randomize will be tabulated overall for 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 double-blind treatment 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 safety follow-up period and estimand follow-up period defined in Figure 2 in Section 8.8.1 of the Protocol. All randomized participants who prematurely discontinue during the double-blind treatment period or the safety follow-up period or the estimand follow-up period will be listed by discontinuation reason. The number of randomized participants who signed informed consent for extension studies will be provided.

8.0 DEMOGRAPHICS 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; region and country [North America, Europe, East Asia]), 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, mITT and Off-treatment Hypothetical Estimand Populations. Continuous variables will be summarized by number of participants and mean, standard deviation (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 histories will be coded using the Medical Dictionary for Regulatory Activities, version 24.0. 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 migraine prevention medication use and the corresponding mechanism or medication failure information will be summarized by treatment group for both ITT and 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.

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 percentage 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, the safety follow-up period and the estimand 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 importance classification. The number and percentage of participants with important protocol deviations will be summarized by treatment group for all categories specified in PDRS for randomized participants.

Baseline efficacy parameters (monthly migraine days, monthly headache days, monthly acute medication use days, monthly performance of daily activities domain score of the Activity Impairment in Migraine - Diary [AIM-D], monthly physical impairment domain score of the AIM-D, Migraine Specific Quality of Life Questionnaire [MSQ] v2.1 Role Function-Restrictive domain score, and Headache Impact Test [HIT-6] total score) will be summarized by treatment group for mITT Population and Off-Treatment Hypothetical Estimand population.

9.0 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 capsules 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: 4 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.

10.0 EFFICACY ANALYSES

10.1 EFFICACY AND HEALTH OUTCOME MEASURES

10.1.1 Efficacy Measures

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.

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. 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).

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) 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

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 participant on a scale from 1 (mild) to 3 (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

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 (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).

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 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 ranging from "Not at all limited - I could do everything" to "Extremely limited."

Headache Impact Test (HIT-6)

The HIT-6 is a 6-question assessment used to measure the impact that 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 participant's 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).

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 3 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.

Patient Satisfaction with Study Medication (PSSM)

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).

Migraine Disability Assessment (MIDAS)

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.

Patient Global Impression of Change (PGIC)

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."

Patient Global Impression - Severity (PGI-S)

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."

Work Productivity and Activity Impairment Questionnaire: Migraine V2.0 (WPAI: MIGRAINE)

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.

Patient Health Questionnaire (PHQ-9)

The PHQ-9 is a concise, self-administered, validated, screening and diagnostic tool for mental health disorder, which has been field-tested in office practice. The screener is quick and user friendly, improves the recognition rate of depression, and facilitates diagnosis and treatment. The PHQ-9 consists of the 9 diagnostic criteria for depressive disorders in the past 2 weeks from the DSM-IV. Participants are asked to indicate the frequency with which they have been bothered by 9 symptoms of depressive disorders over the previous 2 weeks, on a 4-point scale: 0 (not at all), 1 (several days), 2 (more than half the days), and 3 (nearly every day). The total score ranges from 0 to 27 (from best to worst). A score of 15 to 19 is considered as moderately severe depression and 20 to 27 as severe depression.

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

EQ-5D-5L is a generic instrument for use as a measure of health status. As of 2009, the European Quality of Life - 5 Dimension - 5-Level (EQ-5D-5L) has also been available for use; this version was developed to improve the sensitivity of the instrument and to reduce ceiling effects (The EuroQol Group, 2020). The EQ-5D-5L consists of 2 components - the EQ-5D descriptive system and the EQ VAS, but only EQ-5D descriptive system will be summarized in this extension study.

The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). The mobility dimension queries the participant's walking ability. The self-care dimension queries the participant's ability to wash or dress by himself. The

usual activities dimension assesses the participant's performance in "work, study, housework, family or leisure activities". The pain/discomfort dimension measures how much pain or discomfort a participant has. The anxiety/depression dimension assesses how anxious or depressed a participant is. 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 second component of the EQ-5D-5L is a visual analogue scale (EQ-VAS) by which participants can rate their overall health from 0 (worst imaginable health state) to 100 (best imaginable health state).

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 six items ranges from "Not at all" to "Very much." Scores range from 6 to 30, with higher scores indicating greater pain interference.

The detailed algorithms for derivation of the above health outcome measures are presented in Section 16.2.2.

10.1.3 Efficacy Endpoints

All efficacy and health outcome endpoints are summarized in the Table 10.1-1.

Table 10.1-1. Efficacy and Health Outcome Endpoints

	Region	Endpoints
Primary efficacy endpoint	All regions	Change from baseline in mean monthly migraine days across the 12-week treatment period
Secondary efficacy endpoints	All regions except Europe and Canada	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
Secondary efficacy endpoints	Europe, Canada	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 the HIT-6 total score at Week 12 Change from baseline in MSQ v2.1 Role Function-Restrictive domain score at Week 12
Additional Efficacy Endpoints	All regions (with restrictions specified for individual endpoints)	≥ 25%, ≥ 30%, ≥ 50%, ≥ 75%, 100% improvement (decrease) in monthly migraine days at Weeks 1 to 4, 5 to 8, and 9 to 12 ≥ 25%, ≥ 30%, ≥ 75%, 100% improvement (decrease) in 3-month average of monthly migraine days Change from baseline in monthly migraine days at Weeks 1 to 4, 5 to 8, and 9 to 12 Change from baseline in monthly headache days at Weeks 1 to 4, 5 to 8, and 9 to 12 Change from baseline in monthly cumulative headache hours at Weeks 1 to 4, 5 to 8, 9 to 12, and average across the 12-week treatment period Change from baseline in monthly acute medication use days at Weeks 1 to 4, 5 to 8, and 9 to 12 Change from baseline in monthly triptan use days at Weeks 1 to 4, 5 to 8, 9 to 12, and average across the 12-week treatment period Change from baseline in monthly moderate/severe headache days at Weeks 1 to 4, 5 to 8, 9 to 12, and average across the 12-week treatment period Change from baseline in monthly severe headache days at Weeks 1 to 4, 5 to 8, 9 to 12, and average across the 12-week treatment period Change from baseline in weekly migraine days at Weeks 1-4 Participants 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 16 (for Europe and Canada) Change from baseline in the HIT-6 total score at Weeks 4, 8, 12 and 16 (for all regions except Europe and Canada)

	Region	Endpoints
		At least a 5-point improvement (decrease) from baseline in HIT-6 total score at Weeks 4, 8, 12, and 16 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-Restrictive domain score at Weeks 4, 8, and 16 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 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 to 4, 5 to 8, and 9 to 12 Change from baseline in monthly Physical Impairment domain score of the AIM-D at Weeks 1 to 4, 5 to 8, and 9 to 12 Change from baseline in mean monthly Performance of Daily Activities domain score of the AIM-D across the 12-week treatment period (for Europe and Canada) Change from baseline in mean monthly Physical Impairment domain score of the AIM-D across the 12-week treatment period (for Europe and Canada) 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 to 4, 5 to 8, 9 to 12, and average across the 12-week treatment period Change from baseline in monthly activity limitation at Weeks 1 to 4, 5 to 8, 9 to 12, and average across the 12-week treatment period Change from baseline in PHQ-9 score at Week 12 Change from baseline in EQ-5D-5L descriptive system index score at Weeks 1 to 2, at specified windows around Weeks 4, 6, 8, 12, and 16 Change from baseline in the EQ-5D-5L VAS score at Weeks 1 to 2, at specified windows around Weeks 4, 6, 8, 12, and 16 Change from baseline in PROMIS-PI total score at Weeks 4, 8, and 12

10.1.4 Stratification Variables in Modeling

The three stratification variables used in the modeling are listed in the Table 10.1-2.

Table 10.1-2. Stratification Variables used in the modeling

Abbreviated Name	Variable	Stratification
Stratification of acute medication overuse	Actual stratification of acute headache medication overuse during the baseline period	• Yes • No
Stratification of migraine prevention medication use and number of failures	Current and past use of migraine prevention medications and the number of medications failed with unique mechanisms of action based on derivation	• Never Used • Current Use • Past Use only and "failed 0 medications or failed 1 or more medication(s) with the same mechanism of action" • Past Use only and "failed 2 or more medications with different mechanisms of action"
Stratification of Region	Region	• North America • Europe • East Asia

10.2 EFFICACY ANALYSES FOR FILINGS EXCEPT EUROPE AND CANADA

10.2.1 Primary Efficacy Analysis

The primary null hypothesis is that atogepant 30 mg BID and 60 mg QD are each equally effective as 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 2 doses of atogepant has a greater effect than placebo.

The primary efficacy endpoint 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 prior to the randomization date. The primary efficacy analyses will be based on the mITT Population.

The primary comparison between treatment groups will be done by a mixed model for repeated measures (MMRM) of the change from baseline. The response variable is the change from baseline to each postbaseline month in monthly migraine days. The statistical model will include treatment group, visit, stratification of region, stratification of acute medication overuse, stratification of

migraine prevention medication use and number of failures, and treatment group-by-visit interaction as categorical fixed effects. The statistical model will also include the baseline monthly migraine days and baseline-by-visit interaction as covariates. The analysis will be performed based on all evaluable post-baseline values using only the observed cases without imputation of missing values. Only data collected during the double-blind treatment 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-participant 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 (Kenward 1997) 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 least square (LS) Means and their differences in LS Means, along with their standard error (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 stratum1 stratum2 stratum3 visit subjid;
  model chg = trt visit stratum1 stratum2 stratum3 trt*visit base
base*visit / s ddfm= kr;
  Repeated visit / type = UN subject = subjid;
  lsmestimate trt*visit
  '30BID vs placebo' -1 -1 -1 1 1 1 0 0 0 divisor = 3,
  '60QD vs placebo'  -1 -1 -1 0 0 0 1 1 1 divisor = 3 / CL;
run;
```

Note: Placebo is the reference for “trt”. Month 1, 2 and 3 are for “visit”.

stratum1 = Stratification of acute medication use.

stratum2 = Stratification of migraine prevention medications use.

stratum3 = Stratification of Region.

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.

10.2.1.1 Sensitivity Analyses in Missing Data Handling

The sensitivity analyses for missing data handling will be conducted and summarized in this section based on the mITT Population. The random seed for all multiple imputation procedures will be 1234.

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 calculated average monthly migraine days during the 12-week treatment period for each participant. The ANCOVA model includes fixed effects for treatment group, stratification of region, stratification of acute medication use, stratification of migraine prevention medication use and baseline monthly migraine days as a covariate. The treatment difference for atogepant doses versus placebo will be estimated and reported along with the corresponding 95% confidence intervals and nominal p-values for superiority testing. This analysis was recommended by FDA at the End of Phase 2 meeting and termed as a 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

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. 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, stratification of region, stratification of acute medication use, stratification of migraine prevention medication use, and baseline monthly migraine days as a covariate.

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

The 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, stratification of region, stratification of acute medication use, stratification of migraine prevention medication use, and baseline monthly migraine days as a covariate. 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 10.2.1. The primary analysis in support of EU filing will serve as one sensitivity analysis in support of US filing.

10.2.1.2 Sensitivity Analysis for Possible Violation of Normality Assumption

The sensitivity analyses for possible violation of normality assumption will be conducted and summarized in this section based on both mITT to support US filling.

Another 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 this 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 (K-S) test for normality is applied to the de-correlated and scaled residuals and normality test is rejected if p-value from the K-S test is less than 0.01.

The 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. 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 complete 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, stratification of region as fixed factors and baseline monthly migraine days as a covariate. The model will also include stratification of acute medication use, stratification of migraine prevention medication prevention

medication use as categorical fixed effects. The mean difference and corresponding SE are estimated from the model comparing each atogepant treatment group with the placebo group.

The robust regression analysis results from 20 complete 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.

10.2.2 Secondary Efficacy Analysis

The secondary efficacy analyses will be based on the mITT Population to support US filling.

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. Some participants may have their MSQ v2.1 assessed at Visit 8, which will not be included in MMRM, and instead the summary statistics will be provided.

The 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 participant. 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, stratification of region and stratification of acute medication use, stratification of migraine prevention medication use as categorical fixed effects; baseline value will be included as a covariate. The analysis will be performed based on only the observed cases without imputation of missing values. The treatment difference in terms of odds ratio between each atogepant group and placebo will be estimated and tested from this model. The sample SAS is given as follows

```
proc logistic data = in_data1;
  class trt stratum1 stratum2 stratum3 subjid/param=glm;
  model responder (event = "1")= trt stratum1 stratum2 stratum3 base;
  lsmeans trt / e diff oddsratio cl;
  ods output diffs = oddsratio;
run;
```

Note: Placebo is the reference for “trt”. stratum1, stratum2, and stratum3 are the same with those in primary analysis.

10.2.2.1 Multiplicity Adjustment

Multiplicity adjustments will be generated based on mITT population and will be generated based on primary and the US set of secondary efficacy endpoints listed in the Table 10.1-1.

The overall familywise error rate (FWER) will be controlled at $\alpha = 0.05$ for each set of primary and secondary endpoint comparisons between each atogepant group vs placebo. Specifically, the overall type I error rate for multiple comparisons across two atogepant groups 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 for primary and secondary efficacy endpoints for US is defined in the Table 10.2-1 and Figure 10.2-1.

In the graph, each of the nodes is corresponding to one null hypothesis, for example, 30 BID/P1 represents the null hypothesis that there is no statistically significant difference comparing 30 mg BID 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 2 primary hypotheses will be 1/2 of the overall significance level for each dose, and no initial α is allocated to the hypotheses for secondary endpoints.

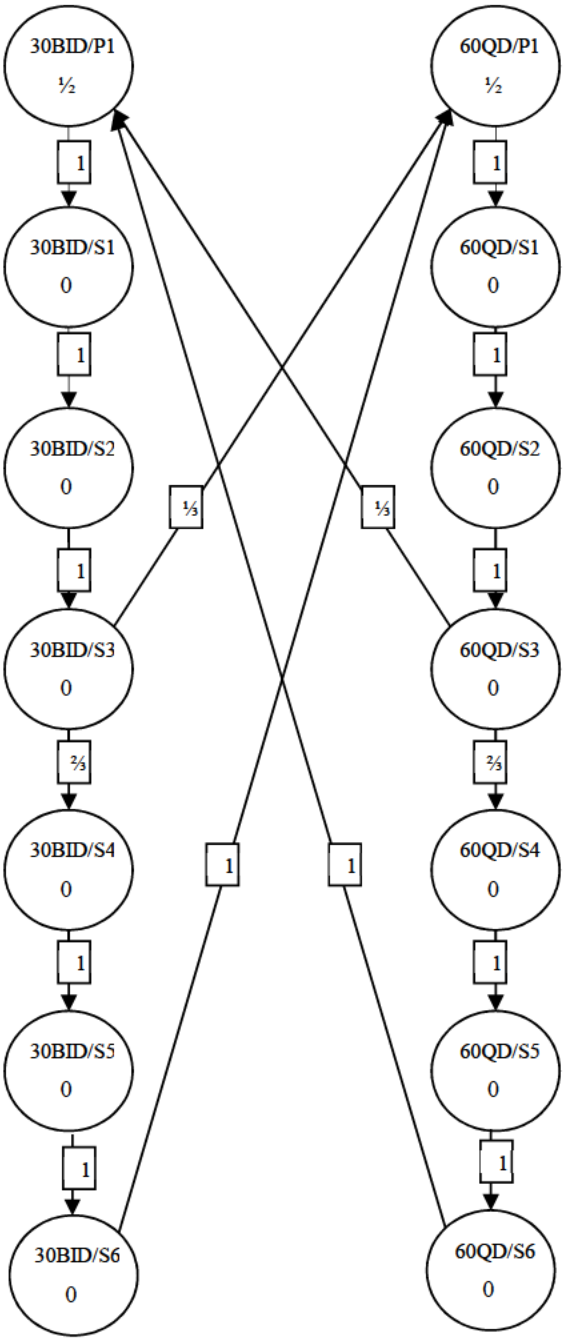
Within each individual dose, testing will start from the primary endpoint, and then test the secondary endpoints in a prespecified order. The order of testing for the first three secondary

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. 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 dose to increase the chances of success for the other dose 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 dose to make full use of the alpha.

Table 10.2-1. Multiple Comparisons Procedure Definitions for the US filing

Nodes	Alternate Hypothesis	Weight	*Initial* Local Significance Level
30mgBID P1	30 mg BID atogepant is significantly different from placebo in change from baseline in mean monthly migraine days across the 12-week treatment period (P1)	1/2	$\alpha\times(1/2) = \alpha/2$
60mgQD P1	60 mg QD atogepant is significantly different from placebo in change from baseline in mean monthly migraine days across the 12-week treatment period (P1)	1/2	$\alpha\times(1/2) = \alpha/2$
30mgBID S1	30 mg BID atogepant is significantly different from placebo in change from baseline in mean monthly headache days across the 12-week treatment period (S1)	0	$\alpha\times0=0$
60mgQD S1	60 mg QD atogepant is significantly different from placebo in change from baseline in mean monthly headache days across the 12-week treatment period (S1)	0	$\alpha\times0=0$
30mgBID S2	30 mg BID atogepant is significantly different from placebo in change from baseline in mean monthly acute medication use days across the 12-week treatment period (S2)	0	$\alpha\times0=0$
60mgQD S2	60 mg QD atogepant is significantly different from placebo in change from baseline in mean monthly acute medication use days across the 12-week treatment period (S2)	0	$\alpha\times0=0$
30mgBID S3	30 mg BID atogepant is significantly different from placebo in proportion of participants with at least a 50% reduction in 3-month average of monthly migraine days (S3)	0	$\alpha\times0=0$
60mgQD S3	60 mg QD atogepant is significantly different from placebo in proportion of participants with at least a 50% reduction in 3-month average of monthly migraine days (S3)	0	$\alpha\times0=0$
30mgBID S4	30 mg BID atogepant is significantly different from placebo in change from baseline in MSQ v2.1 Role Function-Restrictive domain score at Week 12 (S4)	0	$\alpha\times0=0$
60mgQD S4	60 mg QD atogepant is significantly different from placebo in change from baseline in MSQ v2.1 Role Function-Restrictive domain score at Week 12 (S4)	0	$\alpha\times0=0$
30mgBID S5	30 mg BID atogepant 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 (S5)	0	$\alpha\times0=0$
60mgQD S5	60 mg QD atogepant 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 (S5)	0	$\alpha\times0=0$
30mgBID S6	30 mg BID atogepant 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 (S6)	0	$\alpha\times0=0$
60mgQD S6	60 mg QD atogepant 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 (S6)	0	$\alpha\times0=0$

Figure 10.2-1. Multiple Comparisons Procedure for US Filing



10.2.3 Analyses for Additional Efficacy Endpoints and Health Outcome Endpoints

For variables with a continuous response range, analyses will be performed similarly to that used for the primary analysis, focusing 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 PHQ-9, and thus ANCOVA model will be used to analyze MIDAS and PHQ-9 related endpoints with model terms including treatment group, stratification of region, stratification of acute medication use, stratification of migraine prevention medication use, and corresponding baseline score. For the endpoint change from baseline in each MSQ v2.1 domain score and HIT-6 total 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, stratification of region, stratification of acute medication overuse, stratification of migraine prevention medication use and number of failures, 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. 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 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, stratification of region, stratification of acute medication overuse, stratification of migraine prevention medication and number of failures, 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×(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.

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 proportions of participants with at least 25%, at least 30%, at least 50%, at least 75%, and 100% reduction in 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.

The distribution of change from baseline in mean monthly migraine days across the 12-week treatment period in histogram by treatment group in bins of 2-day interval will be presented. The

x-axis will represent the change from baseline in mean monthly migraine days across the 12-week treatment period. Both positive and negative values will be included on the x-axis. The y-axis will represent the relative frequency (% of participants in the mITT population of the treatment group).

Another distribution analysis will be presented as a histogram by treatment group, based on the percentage change from baseline in mean monthly migraine days across the 12-week treatment period with the x-axis displayed as bins of 0 - ≤ 25%, >25% - ≤50%, >50% - ≤75% and > 75% - ≤ 100% reduction from baseline in mean monthly migraine days across the 12-week treatment period. The y-axis would be displayed as % of total participants in the mITT population of the treatment group.

Table 10.2-2 provides a summary of analysis of health outcomes parameters and Table 10.2-3 provides an analysis summary for all additional efficacy endpoints.

Table 10.2-2. Statistical Methodology

Methodology	Description
Categorical descriptive	• Number and percentage of participants in individual categories • Participants with ≥ 1 qualifying event counted once per individual category • N1 if proportion denominator ≠ number of participants in the population (standard percentage denominator) • N1 = participants with non-missing value
Continuous descriptive	N1, mean, standard deviation (SD), median, minimum, maximum N1 = number of participants with non-missing value
CFB MMRM	Continuous descriptive for baseline, postbaseline, and CFB values at each analysis visit o N1 = participants with non-missing values at both baseline and the specified postbaseline analysis visit Analysis of the health outcome endpoints will be performed similarly to the primary analysis using MMRM, as specified in Section 10.2.1. Estimates derived from the MMRM for CFB value controlling for visit as a categorical fixed effect, baseline score, baseline-by-visit interaction as covariates, with an unstructured covariance matrix (Toeplitz or compound symmetry covariance matrix if convergence fails), treatment group, visit, stratification of region, stratification of acute medication overuse, stratification of migraine prevention medication use and number of failures, and treatment group-by-visit interaction as categorical fixed effects. Observed cases without missing value imputation will be used in the analysis.
ANCOVA	The model will include treatment group, stratification of region, actual randomization stratification of acute medication overuse, stratification of migraine prevention medication use and number of failures, and baseline.
Logistic regression model	Similar to the logistic regression model specified for secondary endpoint, the model assumes a binary distribution for the response and uses a logit link. The analysis model will include treatment group, stratification of region and stratification of acute medication overuse, stratification of migraine prevention medication use and number of failures as categorical fixed effects; baseline will be included as a covariate.
Generalized linear mixed model (GLMM	The model assumes a binary distribution for the response and uses a logit link. The model will include treatment group, visit, stratification of region, stratification of acute medication overuse, stratification of migraine prevention medication use and number of failures, and treatment group-by-visit interaction as categorical fixed effects; baseline and baseline-by-visit interaction will be included as covariates. Participants will be included as random effects with unstructured covariance matrix (Toeplitz or compound symmetry covariance matrix if convergence fails) in the model to account for the correlation among repeated measurements.

CFB = change from baseline; MMRM = mixed model for repeated measures

Table 10.2-3. Analysis of Additional Efficacy Endpoints and Health Outcomes

Assessment/ Term	Endpoint	Timing	Methodology
Monthly migraine days	• CFB in monthly migraine days	Weeks 1-4, 5-8, and 9-12	CFB MMRM
	• ≥ 25%, ≥ 30%, ≥ 50%, ≥ 75%, 100% improvement (decrease) in monthly migraine days	Weeks 1-4, 5-8, and 9-12	GLMM
	• ≥ 25%, ≥ 30%, ≥ 75%, 100% improvement (decrease) in monthly migraine days	Average across the 12-week treatment period	Logistic regression model
Monthly headache days	• CFB in monthly headache days	Weeks 1-4, 5-8, and 9-12	CFB MMRM
Monthly cumulative headache hours	• CFB in monthly cumulative headache hours	Weeks 1-4, 5-8, and 9-12, and average across the 12-week treatment period	CFB MMRM
Monthly acute medication use days	• CFB in monthly acute medication use days	Weeks 1-4, 5-8, and 9-12, and average across the 12-week treatment period	CFB MMRM
Monthly triptan use days	• CFB in monthly triptan use days	Weeks 1-4, 5-8, and 9-12, and average across the 12-week treatment period	CFB MMRM
Monthly moderate/severe headache day	• CFB in monthly moderate/severe headache days	Weeks 1-4, 5-8, and 9-12, and average across the 12-week treatment period	CFB MMRM
Monthly severe headache days	• CFB in monthly severe headache days	Weeks 1-4, 5-8, and 9-12, and average across the 12-week treatment period	CFB MMRM
Weekly migraine days	• CFB in weekly migraine days	Week 1-4	CFB MMRM
Migraine day	• Participants having a migraine day on the day of initial dose and on each day of the 6 days post the initial dose		Continuous descriptive
AIM-D	• CFB in monthly Performance Daily Activities domain score at Weeks 1-4, 5-8, and 9-12, and across the 12-week treatment period; • CFB in mean monthly Physical Impairment domain score at Weeks 1-4, 5-8, and 9-12, and across the 12-week treatment period; • CFB in monthly total score at Weeks 1-4, 5-8, and 9-12, and average across the 12-week treatment period	Weeks 1-4, 5-8, 9-12, and average across the 12-week treatment period	CFB MMRM

Assessment/ Term	Endpoint	Timing	Methodology
Activity level and activity limitation	• CFB in monthly activity level at Weeks 1-4, 5-8, and 9-12, and average across the 12-week treatment period; • CFB in monthly activity limitation scores at Weeks 1-4, 5-8, and 9-12, and average across the 12-week treatment period	Weeks 1-4, 5-8, 9-12, and average across the 12-week treatment period	CFB MMRM
HIT-6	• CFB in total score at Weeks 4, 8, 12, and 16 (week 16 summary only) • At least a 5-point improvement (decrease) from baseline in total score at Weeks 4, 8, 12, 16	Weeks 4, 8, 12, 16	CFB MMRM GLMM
MSQ v2.1	• CFB in Role Function-Restrictive domain score at Weeks 4, 8, and 16 (week 16 summary only); • CFB in Role Function-Preventive domain score at Weeks 4, 8, 12, and 16 (week 16 summary only); • CFB in Emotional Function domain score at Weeks 4, 8, 12, and 16 (week 16 summary only).	Weeks 4, 8, 16	CFB MMRM
Patient Satisfaction with Study Medication (PSSM)	Participants response as "satisfied" or "extremely satisfied" with study medication for migraine prevention at Weeks 4, 8, and 12	Weeks 4, 8, 12	GLMM
MIDAS	• CFB in total score at Weeks 12 • CFB in absenteeism score (questions 1, 3, 5) at Weeks 12 • CFB in presenteeism score (questions 2, 4) at Weeks 12	Weeks 12	ANCOVA
PGIC	Participant assessed as "much better" or "very much better" at Week 12	Weeks 12	Logistic regression model
WPAI: MIGRAINE	CFB in percent work time missed, percent impairment while working, percent overall work impairment, and percent activity impairment due to migraine at Week 12	Week 4, 8, 12	CFB MMRM
PGI-S	CFB (as categorical in levels) in score at Weeks 4, 8, and 12	Weeks 4, 8, 12	MMRM
PHQ-9	CFB in PHQ-9 score at Week 12	Week 12	ANCOVA

Assessment/ Term	Endpoint	Timing	Methodology
EQ-5D-5L	• CFB in descriptive system index score US-based values at Weeks 1 to 2, at specified windows around Weeks 4, 6, 8, and 12 • CFB in descriptive system index score US-based values at Week 16 (follow-up visit)	Double-blind treatment period	CFB MMRM
		Week 16	Continuous descriptive
	• CFB in the VAS score at Weeks 1 to 2, at specified windows around Weeks 4, 6, 8, and 12	Double-blind treatment period	CFB MMRM
	• CFB in the VAS score at Week 16 (follow-up visit)	Week 16	Continuous descriptive
PROMIS-PI	CFB in total score at Weeks 4, 8 and 12	Weeks 4, 8, 12	CFB MMRM

10.3 EFFICACY ANALYSES FOR EUROPEAN MEDICIANS AGENCY

The section defines an estimand, termed as "off-treatment hypothetical estimand", which will be the primary estimand in support of EU filing.

10.3.1 Attributes of Off-treatment Hypothetical Estimand

The attributes of the estimand corresponding to the primary efficacy endpoint are summarized as following:

Treatment Condition of Interest

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

- Participants are allowed to take acute migraine medications (Section 4.4.1 of Protocol) to keep the participants in the study
- Medications with demonstrated efficacy for the prevention of migraine (e.g., amitriptyline, propranolol, topiramate) are prohibited when used for any indication other than migraine prevention
    - Participants taking one medication with demonstrated efficacy for the prevention of migraine may be randomized provided that in the opinion of the investigator:

- Dose has been stable and the medication has been well-tolerated for at least 12 weeks prior to Visit 1, and
- Participant is willing and able to maintain at a stable dose and dosage regimen during the study, which should be assessed to ensure compliance at each study visit
- Enrollment of participants with current use of a migraine prevention medication will be capped at ~15%

Population

The target population is patients suffering from CM satisfying the inclusion and exclusion criteria as specified in Section 4 of the 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, or 9 to 12) of eDiary data, regardless of whether on study treatment or off study treatment.

On study treatment is from the first dose till the last dose of study intervention. As the analysis-visit mapping window (Table 16.1-2) 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 this estimand approach is greater than or equal to the number of participants in the mITT Population for the primary analysis.

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.

Accounting of Intercurrent Events

Intercurrent events and their handling rules are as follows:

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

Population-level Summary

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

10.3.2 Primary Efficacy Analysis

The primary efficacy endpoint 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 prior to the randomization date. The primary efficacy analyses will be based on the Off-treatment Hypothetical Estimand Population.

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 without imputation before switching to other prophylaxis treatment during the follow up periods. The model terms include treatment group, visit (derived as month), stratification of region, stratification of acute medication overuse, stratification of migraine prevention medication use and number of failures, treatment-by-visit interaction, the baseline monthly migraine days and baseline-by-visit interaction. The analysis will be performed based on all evaluable post-baseline values using only the observed cases without imputation of missing values. Participants are always analyzed based on the treatment group assigned by randomization.

10.3.2.1 Sensitivity Analyses in Missing Data Handling

The sensitivity analyses for missing data handling will be conducted and summarized in this section based on the Off-treatment Hypothetical Estimand Population.

Multiple Imputation

The following multiple imputation sensitivity analysis cannot be completed and has been eliminated from the final SAP due to the low number of participants observed in some of the pattern groups.

If a participant provides less than 14 days of efficacy data during a monthly period regardless on or off study treatment, 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, if the number of days with available efficacy data while on study treatment is no less than the one while off study treatment, then he/she is considered to have efficacy data on study treatment during that monthly period; otherwise, he/she is considered to have efficacy data off study treatment during that monthly period.

Missing data are assumed to follow monotone pattern. Any intermediate missing values will be imputed first by the same method discussed in Section 10.2.1.1. Possible monotone missing data patterns are discussed below, and a summary is provided in Table 10.3-1.

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 month on study treatment and two months off study treatment (pattern group 3)
- Three months off study treatment (pattern group 4)

Participants may provide two-month efficacy data in the following patterns:

- Two months on study treatment (pattern group 5)
- One month 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 10.3.1.

Table 10.3-1. Monotone Missing Data Patterns

Pattern Group	Month 1	Month 2	Month 3
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 10.2.1), 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.

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 20 times, then we have 20 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.

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 calculated 3-month average of the monthly migraine days including both on- and off-treatment data during the 12-week treatment period for each participant.

The ANCOVA model includes fixed effects for treatment group, stratification of region, stratification of acute medication use, stratification of migraine prevention medication use and baseline monthly migraine days as a covariate. The treatment difference for atogepant doses versus placebo will be estimated and reported along with the corresponding 95% confidence intervals and nominal p-values for superiority testing. 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).

10.3.3 Secondary Efficacy Analysis

The Secondary efficacy endpoints are listed in the Table 10.1-1. The secondary efficacy analyses will be based on the Off-treatment Hypothetical Estimand Population to support EU filling.

The secondary endpoints for headache days and acute medication use days, , will be analyzed in the same manner as that used to analyze the primary endpoint.

For HIT-6 total score and 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. Some participants may have their HIT-6 total score or MSQ v2.1 assessed at Visit 8, which will not be included in MMRM, and instead the summary statistics will be provided.

The secondary endpoint of 50% responders are derived as at least a 50% reduction from baseline in the 3-month average of monthly migraine days based on the observed on- and off-treatment data collected throughout the study before switching to other prophylaxis treatment during the follow-up period. The similar logistic regression model as described in 10.2.2 will be used for analysis.

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, stratification of region, stratification of acute medication overuse, stratification of migraine prevention medication and number of failures, and treatment group as fixed factors.

The graphical approach to control the overall Type I error rate described in Section 10.3.3 (Table 10.3-1 and Figure 10.3-1) will be conducted for primary and secondary efficacy endpoints based on the off-treatment hypothetical estimand analysis population.

10.3.3.1 Multiplicity Adjustment

Multiplicity adjustments will be generated based on Off-treatment Hypothetical Estimand Population for Europe. The multiplicity adjustments will be applied to primary endpoint and the European set of the Secondary efficacy endpoints listed in Table 10.1-1.

The overall graphic approach procedure for primary and secondary efficacy endpoints for Europe is defined in the Table 10.3-2 and Figure 10.3-1.

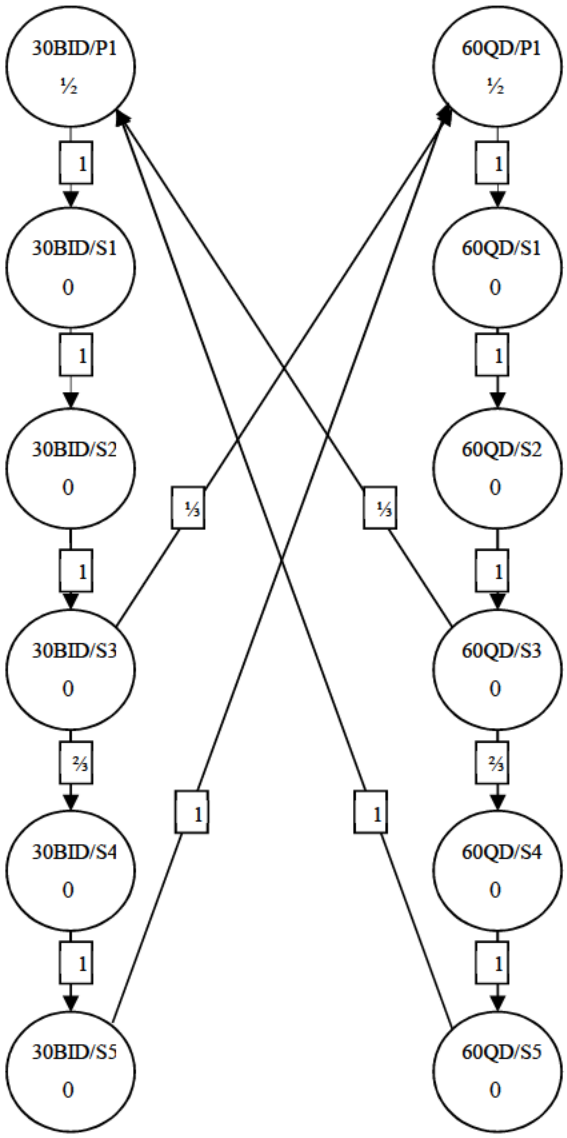
The initial allocation of the overall significant level to 2 primary hypotheses will be 1/2 of the overall significance level for each dose, and no initial α is allocated to the hypotheses for secondary endpoints.

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 HIT-6 and MSQ v2.1 are placed in the last two positions in the testing hierarchy. 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 dose to increase the chances of success for the other dose 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 two HO endpoints are rejected within a dose based on remaining alpha, the alpha for this dose will be propagated to the other dose to make full use of the alpha.

Table 10.3-2. Multiple Comparisons Procedure Definitions for EU Filing

Nodes	Alternate Hypothesis	Weight	*Initial* Local Significance Level
30mgBID P1	30 mg BID atogepant is significantly different from placebo in change from baseline in mean monthly migraine days across the 12-week treatment period (P1)	1/2	$\alpha\times(1/2) = \alpha/2$
60mgQD P1	60 mg QD atogepant is significantly different from placebo in change from baseline in mean monthly migraine days across the 12-week treatment period (P1)	1/2	$\alpha\times(1/2) = \alpha/2$
30mgBID S1	30 mg BID atogepant is significantly different from placebo in change from baseline in mean monthly headache days across the 12-week treatment period (S1)	0	$\alpha\times0=0$
60mgQD S1	60 mg QD atogepant is significantly different from placebo in change from baseline in mean monthly headache days across the 12-week treatment period (S1)	0	$\alpha\times0=0$
30mgBID S2	30 mg BID atogepant is significantly different from placebo in change from baseline in mean monthly acute medication use days across the 12-week treatment period (S2)	0	$\alpha\times0=0$
60mgQD S2	60 mg QD atogepant is significantly different from placebo in change from baseline in mean monthly acute medication use days across the 12-week treatment period (S2)	0	$\alpha\times0=0$
30mgBID S3	30 mg BID atogepant is significantly different from placebo in proportion of participants with at least a 50% reduction in 3-month average of monthly migraine days (S3)	0	$\alpha\times0=0$
60mgQD S3	60 mg QD atogepant is significantly different from placebo in proportion of participants with at least a 50% reduction in 3-month average of monthly migraine days (S3)	0	$\alpha\times0=0$
30mgBID S4	30 mg BID atogepant is significantly different from placebo in change from baseline in the HIT-6 total score at Week 12 (S4)	0	$\alpha\times0=0$
60mgQD S4	60 mg QD atogepant is significantly different from placebo in change from baseline in the HIT-6 total score at Week 12 (S4)	0	$\alpha\times0=0$
30mgBID S5	30 mg BID atogepant is significantly different from placebo in change from baseline in MSQ v2.1 Role Function-Restrictive domain score at Week 12 (S5)	0	$\alpha\times0=0$
60mgQD S5	60 mg QD atogepant is significantly different from placebo in change from baseline in MSQ v2.1 Role Function-Restrictive domain score at Week 12 (S5)	0	$\alpha\times0=0$

Figure 10.3-1. Multiple Comparisons Procedure for Europe and Canada



10.3.4 Additional Efficacy Endpoints and Health Outcomes Analysis

In general, all additional efficacy endpoint analyses are performed at the nominal significance level, without adjusting for multiplicity and will be based on the Off-treatment Hypothetical Estimand Population.

The additional endpoints are described in Section 10.1.3 and the analysis methods are the same with those analysis methods in support of US filing, which are described in Section 10.2.3.

10.4 EFFICACY ANALYSIS FOR HEALTH CANADA

10.4.1 Primary Efficacy Analysis

The primary efficacy analyses in support of Canadian filing will be based on the mITT Population. The primary endpoint, change from baseline in mean monthly migraine days across the 12-week treatment period, will be analyzed in the same manner as that used to analyze the primary endpoint in support of US filing.

10.4.2 Secondary Efficacy Analysis

The secondary efficacy analyses will be based on the mITT Population.

The secondary efficacy endpoints are listed in the Table 10.1-1. All secondary endpoints will be handled using the same approaches defined in the Section 10.2.2. The analysis of HIT-6 total score is similar to that of MSQ v2.1 role function restrictive domain score.

Multiplicity adjustments will be generated based on mITT population and will be generated based on primary and the Canadian set of secondary efficacy endpoints listed in the Table 10.1-1. The overall graphic approach procedure for primary and secondary efficacy endpoints for Canada is the same with that used in the Section 10.3.3.

10.4.3 Additional Efficacy Endpoints and Health Outcomes Analysis

In general, all additional efficacy endpoint analyses are performed at the nominal significance level, without adjusting for multiplicity and will be based on the mITT Population.

The additional endpoints are described in Section 10.1.3 and the analysis methods are the same with those analysis methods in support of US filing, which are described in Section 10.2.3.

11.0 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 each safety parameter of the clinical laboratory, vital sign, and ECG, the last nonmissing safety assessment before the first dose of study 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 21.1.

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. However, 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 with a new AE onset date for any AE that worsens. Therefore, TEAEs can simply be identified as those AEs 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. TEAEs that started after the date of last dose of study treatment will be considered as newly emergent.

Only AEs captured in study 3101-303-002 will be considered for TEAEs in this study. For participants rolling over into studies 3101-306-002, 3101-311-002 or 3101-312-002 (extension studies) who start the first dose on Visit 1 or beyond, AEs captured in those studies will be summarized in those studies although some AEs might occur within 30 days after the last dose from study 3101-303-002.

Overall summary of AEs will be provided on a per-participant basis for categories of TEAEs, treatment-related TEAEs, serious adverse events (SAEs), deaths, and AEs leading to study intervention discontinuation.

The number and percentage of participants reporting TEAEs in each treatment group will be tabulated by descending percentage in Atogepant 60 mg QD group, by system organ class and preferred term, and further categorized by severity and causal relationship to the study treatment. If more than 1 AE is coded to the same preferred term for the same participant, the participant will be counted only once for that preferred term using the greatest severity and strictest causality for the summarization by severity and causal relationship.

For "current use" of migraine prevention medication participants, the number and percentage of participants reporting 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 for the safety follow-up period.

The total number of TEAEs by severity and causal relationship to the study treatment will be summarized by treatment group.

The incidence of common (≥ 2% of participants [after rounding] in any treatment group) TEAEs will be summarized by preferred term and treatment group and sorted by decreasing frequency in the Atogepant 60 mg QD group. A similar 5% table will be provided as well.

An AE will be considered a treatment-emergent serious adverse event (TESAE) if it is a TEAE that additionally meets any SAE criterion.

The number and percentage of participants who have TESAEs will be summarized by system organ class and preferred term by treatment group. In addition, the incidence of on-therapy SAEs that led to death will be summarized separately by preferred term for each treatment group.

The number and percentage of participants in the Safety Population who have TEAEs and TESAEs leading to premature discontinuation of the study intervention will be summarized by system organ class, preferred term and treatment group.

The number and percentage of participants reporting newly emergent SAEs and those that led to death will be summarized respectively by preferred term and treatment group for the safety follow-up period.

For all screened participants, separate tabular displays will be presented for participants who died, participants with SAEs, and participants with AEs leading to study intervention discontinuation.

11.2 CLINICAL LABORATORY PARAMETERS

Descriptive statistics for clinical laboratory values (in International System of units [SI]) 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, white blood cell count differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), and 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, estimated glomerular filtration rate

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 20.1. A description of reporting the lab values in conventional units in participant narratives (along with the standard reporting in SI units) is presented at the end of Appendix 0.

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 11.2-1. 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 participant identification (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 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 lab vendor.

Participants 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 11.2-1. Criteria for Potentially Clinically Significant Laboratory Results

Parameter	***SI Unit***	***Lower Limit***	***Higher Limit***
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
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 mL/min/1.73m^2	—
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
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).

The number and percentage of participants meeting each of the following criteria for postbaseline hepatic laboratory abnormalities listed in Table 11.2-2 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 11.2-2. 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 × ULN and/or AST ≥ 3 × 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 × ULN or AST ≥ 3 × 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 × ULN or AST ≥ 3 × 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.

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 as listed in Table 11.3-1. The number and percentage of participants who have PCS postbaseline vital sign values will be tabulated by study treatment. 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. 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 11.3-1. 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 ELECTROCARDIOGRAM

Descriptive statistics for ECG parameters (heart rate, RR interval, PR interval, QRS interval, QT interval, and QT interval corrected for heart rate [QTc]) at baseline, postbaseline, and changes from baseline values at each assessment time point to the end of study will be presented by treatment group. The QTc will be calculated using both the Bazett and Fridericia corrections (if the vendor does not provide).

ECG parameter values are considered PCS if ECG values meet either the actual value or change from baseline PCS high criteria listed in Table 11.4-1. The number and percentage of participants with PCS postbaseline values will be tabulated by treatment group. 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.

Table 11.4-1. Criteria for Potentially Clinically Significant Electrocardiograms

Parameter	Unit	Actual Value
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-baseline QTcF >450 msec, >480 msec, or >500 msec will be tabulated by treatment group. A supportive listing of participants with postbaseline clinical interest will be provided. A listing of all AEs for participants with postbaseline clinical interest will also be provided.

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 safety 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. A listing of all AEs occurring in participants who have suicidal ideation or suicidal behavior will also be provided.

12.0 SUBGROUP ANALYSES

12.1 SUBGROUP ANALYSES FOR EVALUATING THE CONSISTENCY OF TREATMENT EFFECTS ACROSS REGIONS AND SUBPOPULATIONS

To estimate the treatment effect on the primary efficacy endpoint for regions (North America, Europe, and East Asia [China, Japan and APAC including Korea and Taiwan]), the same model as that of the primary MMRM model in primary efficacy analysis in Section 10.2.1 will be utilized based on mITT population in support of US filing and on the Off-treatment Hypothetical Estimand Population in support of EU filing. In addition, the model will include region, region by treatment (2-way interaction) and region by treatment by visit (3-way interaction) as categorical fixed effects. An unstructured covariance matrix will be used to model the covariance of within participant repeated measurements. Pairwise contrasts in the MMRM model will be used to compare each atogepant dose to placebo for treatment effect in patients enrolled in each region.

The estimate of the between-group treatment effect (with a 95% CI) for each atogepant dose versus placebo for the primary efficacy endpoint for each region and overall treatment effect will be plotted in the forest plot to visualize the consistency of treatment effect across regions.

For key efficacy endpoints (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, and at least a 50% reduction in 3-month average of monthly migraine days), the estimate of the between-group treatment effect (with 95% CI) for each atogepant dose versus placebo will be summarized overall and for each region in a table to facilitate the comparison. The test of treatment-by-region interaction will be provided as recommended in ICH E17 Section 2.2.7 on Examination of Consistency across Regions and Subpopulations.

12.2 OTHER SUBGROUP ANALYSES

The subgroup analyses will be based on mITT population in support of US filing and the Off-treatment Hypothetical Estimand Population in support of EU filing.

The subgroup analysis will be based on the following four endpoints and ten subgroup categories.

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
- At least a 50% reduction in 3-month average of monthly migraine days

Subgroup Categories:

- Age group: < 40 years; 40 to <65 years; >=65 years
- Sex: Male; Female
- Race: White; Asian; All other races
- BMI: Underweight or normal (<25); Overweight (>=25- <30); Obese (>=30)
- Baseline monthly migraine days: <18 days; > =18 days
- Acute medication overuse: Yes; No
- Preventive medication current use: Yes; No
- Prior exposure to a migraine prevention medication with proven efficacy: Yes; No
- Migraine prevention medication use and number of failures:
    - Current use
    - Past Use only and "failed 0 medications or failed 1 or more medication(s) with the same mechanism of action"
    - Past Use only and "failed 2 or more medications with different mechanisms of action
    - Never used

- Number of migraine prevention medication failures:
    - Current use or past use and "failed 0 medication"
    - Current use or past use and "failed 1 or more medication(s) with the same mechanism of action"

- Current use or past use and "failed 2 or more medications with different mechanisms of action"
- Never used

Within each subgroup category, data will be divided into mutually exclusive subsets and then a separate analysis will be performed for each subset (e.g., for the "Sex" category, a separate analysis will be performed for all Male participants and the same analysis will be performed for all Female participants). For efficacy endpoints, point estimates along with corresponding confidence intervals will be provided for parameters of interests in tables.

If models do not converge, descriptive statistics for subgroups will be provided.

13.0 INTERIM ANALYSIS

No interim analysis is planned for this study.

14.0 DETERMINATION OF SAMPLE SIZE

A total sample size of 250 participants will be randomized per treatment group and that will provide at least 96% power to detect the treatment difference between each of the 2 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 first 3 secondary endpoints as shown in Table 12.2-1. The power calculations are based on the following assumptions:

1) The treatment difference from placebo will be similar to the average value across the CM prevention studies for Botox (Aurora 2010, Diener 2010) and TEV-48125 (Bigal 2015, Silberstein 2017). In particular, the assumed treatment difference from placebo in change from baseline in mean monthly migraine days across the 12-week treatment period is -2 days, and the standard deviation is 5.5 days. Detailed treatment difference and standard deviation assumptions are listed in Table 12.2-1.

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 0.025 significance level, 2-sided. Once the primary endpoint for each dose is significant at 0.025, 2-sided, the secondary endpoints will be tested sequentially in Section 10.2.

Table 12.2-1. 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	–2	5.5	96%
Secondary 1	Change from baseline in mean monthly headache days across the 12-week treatment period	–2	6.0	93% [a]
Secondary 2	Change from baseline in mean monthly acute medication use days across the 12-week treatment period	–1.8	5.5	92% [a]
Secondary 3	At least a 50% reduction in mean monthly migraine days across the 12-week treatment period	33% Placebo Rate	49% Atogepant Rate	92% [a]

[a] Statistical powers 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.

15.0 STATISTICAL SOFTWARE

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

16.0 DATA HANDLING CONVENTIONS

16.1 VISIT TIME WINDOWS

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

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

Table 16.1-1. 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	Treatment Day [1, 28]
	Weeks 5 – 8	Treatment Day [29, 56]
	Weeks 9 – 12	Treatment Day [57, min (end of the double-blind treatment period, 84)]

The analysis visit windows for monthly efficacy endpoints based on daily eDiary data for Off-treatment Hypothetical Estimand Population are defined as follows.

Table 16.1-2. Efficacy Analysis Visit Definitions in the Off-treatment Hypothetical 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, min(end of the last visit, 84)]

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

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

Table 16.1-3. 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 for mITT population are defined as follows:

Table 16.1-4. 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 and HIT-6 for mITT Population and Off-treatment Hypothetical Estimand Population are defined as follows:

Table 16.1-5. Efficacy Analysis Visit Definitions for MSQ v2.1 and HIT-6

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, min(end of last study visit, 115)]

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

Table 16.1-6. Efficacy Analysis Visit Definitions in the Off-Treatment Hypothetical Estimand Approach for MSQ v2.1 and HIT-6

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, 97]
	Week 16	Treatment Day [98, end of 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.

The analysis visit windows for EQ-5D-5L for mITT Population and Off-treatment Hypothetical Estimand Population are defined as follows:

Table 16.1-7. Efficacy Analysis Visit Definitions for EQ-5D-5L

Analysis Phase	Analysis Visit (Derived)	Scheduled Study Visit (eCRF)	Window
Pretreatment	Baseline	Visit 2 (Randomization)	Treatment Day [-7, -1]
Double-Blind Treatment Period	Week 1-2	Visit 3	Treatment Day [1, 14]
	Week 4	Visit 4	Treatment Day [25, 31]
	Week 6	Visit 5	Treatment Day [39, 45]
	Week 8	Visit 6	Treatment Day [53, 59]
	Week 12	Visit 7/ET	Treatment Day [77, minimum(end of the double-blind treatment period, 83)]
Follow-up	Week 16 (Follow-up)	Visit 8	Treatment Day [end of the double-blind treatment period +1, min(end of last study visit, 115)]

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

Table 16.1-8. Efficacy Analysis Visit Definitions in the Off-Treatment Hypothetical Estimand Approach for EQ-5D-5L

Analysis Phase	Analysis Visit (Derived)	Window
Pretreatment	Baseline	Treatment Day [-7, -1]
On or after the first dose of study intervention	Week 1-2	Treatment Day [1, 14]
	Week 4	Treatment Day [25, 31]
	Week 6	Treatment Day [39, 45]
	Week 8	Treatment Day [53, 59]
	Week 12	Treatment Day [77, 83]
	Week 16	Treatment Day [98, end of last study visit]

The analysis visit windows for PGI-S, WPAI: MIGRAINE, and PROMIS-PI for mITT Population and Off-treatment Hypothetical Estimand Population are defined as follows:

Table 16.1-9. Efficacy Analysis Visit Definitions for PGI-S, WPAI: MIGRAINE, and PROMIS-PI

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.

Table 16.1-10. Efficacy Analysis Visit Definitions in the Off-treatment Hypothetical Estimand Approach for PGI-S, WPAI: MIGRAINE, and PROMIS-PI

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, end of last study visit]

The analysis visit windows for PGIC for mITT Population and Off-treatment Hypothetical Estimand Population are defined as follows:

Table16.1-11. 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.

Table 16.1-12. Efficacy Analysis Visit Definitions in the Off-treatment Hypothetical Estimand Approach for PGIC

Analysis Phase	Analysis Visit (Derived)	Window
On or after the first dose of study intervention	Week 12	Treatment Day [2, end of last study visit]

The analysis visit windows for Patient Satisfaction with Study for mITT Population and Off-treatment Hypothetical Estimand Population are defined as follows:

Table 16.1-13. 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.

Table 16.1-14. Efficacy Analysis Visit Definitions in the Off-Treatment Hypothetical Estimand Approach for Patient Satisfaction with Study

Analysis Phase	Analysis Visit (Derived)	Window
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, end of last study visit]

The analysis visit windows for MIDAS and PHQ for mITT Population and Off-treatment Hypothetical Estimand Population are defined as follows:

Table 16.1-15. Efficacy Analysis Visit Definitions for MIDAS and PHQ

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]

Table 16.1-16. Efficacy Analysis Visit Definitions in the Off-Treatment Hypothetical Estimand Approach for MIDAS and PHQ

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

The analysis visit windows for safety endpoints are defined as follows:

Table 16.1-17. Safety Data 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 Double-blind Treatment Period		Last available assessment during double-blind treatment period
	Week 16 (Safety follow-up)	Visit 8	Treatment Day [end of double-blind treatment period +1, end of safety follow-up period]
	Estimand Follow-up		Treatment Day [end of safety follow-up 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

Safety follow-up visit will be presented in analysis tables for clinical laboratory values and vital signs.
End of Double-blind Treatment Period is defined as the last available assessment during double-blind treatment period. End of Double-blind Treatment Period results will be presented in analysis tables for clinical laboratory values and vital signs.
End of Study is defined as the last available assessment during the study, including double-blind and safety follow-up period. End of Study results will be presented in analysis tables for safety parameters, including but not limited to electrocardiograms, 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 periods 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 Visit 2 to Visit 7 for participants who entered the safety follow-up period; or ends with the latest date of the last study medication date, and last assessment date for participants who did not enter the safety follow-up period. The safety follow-up period starts with the 1 day after the end of the double-blind period and ends with the last scheduled assessment date of Visit 8 for participants who entered the estimand follow-up period;

or ends with the last assessment date for participants who did not enter the estimand follow-up period. The estimand follow-up period starts with the 1 day after the end of the safety follow-up period and ends with the last assessment date for participants who entered the estimand follow-up period.

16.2 DERIVED EFFICACY AND HEALTH OUTCOME DATA

16.2.1 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 study, 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 diary" 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 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"

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 as 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. A minimum of 14 days' eDiary data during a postbaseline monthly treatment period is required for the migraine days to be evaluable for that particular period. 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 headache day pain intensity, 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.

16.2.2 Derivation of Health Outcome Endpoints Based on eDiary Data

A separate SAP will be provided for additional efficacy endpoints related to health outcome. Details regarding derivation for those endpoints are provided in that document. This section covers health outcome endpoints which are related to primary and secondary efficacy 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 16.2-1.

Table 16.2-1. 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, precoded item values and final item values for each item response are shown in Table 16.2-2. 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 16.2-2. 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.

PHQ-9 Depression Severity

The PHQ-9 consists of the 9 diagnostic criteria for depressive disorders in the past 2 weeks from the DSM-IV. Participants are asked to indicate the frequency with which they have been bothered by 9 symptoms of depressive disorders over the previous 2 weeks, on a 4-point scale: 0 (not at all), 1 (several days), 2 (more than half the days), and 3 (nearly every day). The total score ranges from 0 to 27 (from best to worst). A score of 15 to 19 is considered as moderately severe depression and 20 to 27 as severe depression.

Patient-Reported Outcomes Measurement Information System Pain Interference - Short Form 6a (PROMIS-PI) Related Endpoints Derivation

The PROMIS-PI measures self-reported interference of pain on relevant aspects of daily life (i.e., social, cognitive, emotional, physical, recreational) over the past 7 days. A 5-level response scale for all 6 items ranges from 1 to 5, corresponding to item response of "Not at all" to "Very much." The raw score of PROMIS-PI is the sum of all 6 items, ranging from 6 to 30. If one or more items

are missing, the raw score will be set to missing. A raw score can be standardized into a T-score with a mean of 50 and standard deviation of 10 using the table as follows. Higher raw or T-scores indicate greater pain interference.

Table 16.2-3. PROMIS-PI Raw Score Transformation

Raw score	T-score	Raw score	T-score	Raw score	T-score	Raw score	T-score	Raw score	T-score
6	41.1	11	54.5	16	59.5	21	63.8	26	68.7
7	48.6	12	55.6	17	60.4	22	64.8	27	69.8
8	50.7	13	56.6	18	61.2	23	65.7	28	71.0
9	52.2	14	57.6	19	62.1	24	66.7	29	72.6
10	53.4	15	58.6	20	63.0	25	67.6	30	76.3

The PROMIS-PI will be completed by the participants at Day 1 (randomization), Weeks 4, 8 and 12.

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

EQ-5D-5L is a generic instrument for use as a measure of health status. As of 2009, the EQ-5D-5L has also been available for use; this version was developed to improve the sensitivity of the instrument and to reduce ceiling effects (The EuroQol Group, 2020). The EQ-5D-5L consists of 2 components - the EQ-5D descriptive system and the EQ VAS, but only EQ-5D descriptive system will be summarized in this extension study.

The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). The mobility dimension queries the participant's walking ability. The self-care dimension queries the participant's ability to wash or dress by himself. The usual activities dimension assesses the participant's performance in "work, study, housework, family or leisure activities". The pain/discomfort dimension measures how much pain or discomfort a participant has. The anxiety/depression dimension assesses how anxious or depressed a participant is. 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 second component of the EQ-5D-5L is a visual analogue scale (EQ-VAS) by which participants can rate their overall health from 0 (worst imaginable health state) to 100 (best imaginable health state).

With the EQ-5D-5L, rating levels can be coded as numbers 1, 2, 3, 4 or 5 which correspond to having no problems, having slight problems, having moderate problems, having severe problems, and being unable to do/having extreme problem. As a result, a participant's health state can be defined by a 5-digit number by combining the numeric levels from the 5 dimensions, ranging from 11111 (having no problems in all 5 dimensions) to 55555 (having extreme problem in all 5 dimensions). The US-based value set for the EQ-5D-5L will be derived using an international standardized protocol (Pickard et al., 2019).

EQ-5D-5L will be captured on eDiary during 7 days in the screening/baseline period and during specific time periods for Visit 1 to 7, except at Visit 8 (Week 16) where it will be administered on an eTablet. The index score and VAS score for a specific period will be calculated as the average of available scores in that period respectively if at least 50% of daily scores are available; otherwise, the scores will be set as missing. For example, for a period of 14 days, at least 7 assessments are required; and for a period of 7 days, at least 4 assessments are required.

16.3 REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY PARAMETERS

If a participant has repeated assessments before the start of the first treatment, the results from the final nonmissing assessment made prior to the start of the study treatment will be used as baseline. If a participant has 2 or more visits within the same window, the last visit with a nonmissing value will be used for summary over time. If end-of-study assessments are repeated or if unscheduled visits occur, the last nonmissing 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.

16.4 MISSING DATE OF THE LAST DOSE OF STUDY TREATMENT

When the date of the last dose of study treatment is missing for a participant in the Safety Population, all efforts should be made to obtain the date from the Investigator. If after all efforts are made it is still missing, the last available dosing record date will be used as the last dose date.

16.5 MISSING SEVERITY ASSESSMENT FOR ADVERSE EVENTS

If severity is missing for an AE that started before the date of the first dose of 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 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.

16.6 MISSING CAUSAL RELATIONSHIP TO STUDY DRUG FOR ADVERSE EVENTS

If the causal relationship to the study treatment is missing for an AE that started on or after the date of the first dose of study treatment, a causality of yes will be assigned. The imputed values for causal relationship to study treatment will be used for the incidence summary; the values will be shown as missing in the data listings.

16.7 MISSING DATE INFORMATION FOR ADVERSE EVENTS

The following imputation rules only apply to cases in which the start date for AEs is incomplete (ie, partly missing).

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of study treatment, the month and day of the first dose of 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 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 study treatment, *January 1* will be assigned to the missing fields

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

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 study treatment, the day of the first dose of 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 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 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 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 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 study treatment, the date of the first dose of study treatment will be assigned to the missing start date

- If the stop date is before the date of the first dose of study treatment, the stop date will be assigned to the missing start date

16.8 MISSING DATE INFORMATION FOR PRIOR OR CONCOMITANT MEDICATIONS

For prior or concomitant medications, including rescue medications, incomplete (ie, 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.

16.8.1 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.

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of study treatment, the month and day of the first dose of 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 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 study treatment, *January 1* will be assigned to the missing fields

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

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 study treatment, the day of the first dose of 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 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 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 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 study treatment, the first day of the month will be assigned to the missing day

16.8.2 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, impute it as descripted in Section 16.4. 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.

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

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

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

16.9 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.

16.10 ACTUAL RANDOMIZATION STRATIFICATION DERIVATION

As mentioned in the current SAP Section 7.0, 'derived stratification' will be used in the statistical models rather than IWRS.

Per study design and IWRS, the participants are stratified into 10 following strata:

1. Acute medication overuse (Yes) and Migraine prevention medication past use and not current use, Failed 0 to 1 or more with the same mechanism of action;
2. Acute medication overuse (Yes) and Migraine prevention medication past use and not current use, Failed 2 to 4 with different mechanisms of action;
3. Acute medication overuse (Yes) and Migraine prevention medication Current use regardless of past use, Failed 0 to 1 or more with the same mechanism of action;
4. Acute medication overuse (Yes) and Migraine prevention medication Current use regardless of past use, Failed 2 to 4 with different mechanisms of action;

5. Acute medication overuse (Yes) and Migraine prevention medication Never used;
6. Acute medication overuse (NO) and Migraine prevention medication past use and not current use, Failed 0 to 1 or more with the same mechanism of action;
7. Acute medication overuse (NO) and Migraine prevention medication past use and not current use, Failed 2 to 4 with different mechanisms of action;
8. Acute medication overuse (NO) and Migraine prevention medication Current use regardless of past use, Failed 0 to 1 or more with the same mechanism of action;
9. Acute medication overuse (NO) and Migraine prevention medication Current use regardless of past use, Failed 2 to 4 with different mechanisms of action;
10. Acute medication overuse (NO) and Migraine prevention medication Never used;

To derive the actual participant stratification, the algorithm will be as follows:

- First, the acute headache medication overuse *during the baseline period* will be derived as Yes or No, based on eDiary data. Acute headache medication overuse is defined as Yes, when use of triptans on ≥ 10 days OR use of ergots on ≥ 10 days OR use of simple analgesics (ie, aspirin, nonsteroidal anti-inflammatory drugs [NSAIDs], or acetaminophen) on ≥ 15 days OR use of any combination of triptans, ergots or simple analgesics on ≥ 10 days. The baseline period is defined here as all 28 days prior to the randomization visit;
- Next, migraine prevention medication exposure (Current Use, Past Use, or Never Used) will be derived based on concomitant data from eCRF (and Excel spreadsheet with prevention medication list provided by Clinical team). For participants who took medications before/at the screening visit with the preferred names in excel spreadsheet with prevention medication list provided by Clinical team and those medications were classified as "Migraine Prevention Medication" in the prior and concomitant medications eCRF, these participants were further classified as participants with current use (ongoing at the screening visit) or past use (stopped prior to screening), the number of migraine prevention medications failed with unique mechanisms of action: "failed 0 medications or failed 1 or more medication(s) with the same mechanism of action" or "failed 2 or more medications with different mechanisms of action". If both start and end date for a migraine prevention medication are missing, it will be considered when determining the number of migraine prevention medications failed and the number of mechanisms of action. If the medication is noted as "ongoing" it will be considered current use, and if it is not noted as "ongoing" then it will be considered past use. Otherwise,

participants who did not took qualified medications as specified above were classified into the category "Never used".

- The study will be conducted in 5 regions: North America, Europe, China, Japan and APAC. The regions used as a stratification factor in the analysis are North America, Europe, and East Asia (includes China, Japan, and APAC).

16.11 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 10.3.1 (Attributes of Off-treatment Hypothetical Estimand), the following criteria are used: A participant has taken prophylaxis medications during the double-blind or follow-up period with preferred names, and the concomitant medications are classified as "Migraine Prevention Medication" in concomitant medications eCRF.

17.0 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 1 Schedule of Visits and Procedures).

This section specifies analyses for evaluating the impact of COVID-19.

17.1 EFFICACY EVALUATION

Efficacy Endpoints

Table 17.1-1 describes the collection devices for primary and key secondary endpoints. The primary endpoint and most of key secondary endpoints are collected via eDiary according to the protocol. Minimal disruption is expected for these endpoints because participants are expected to complete eDiary at home and submit the responses everyday.

The endpoints, "MSQ v2.1 Role Function-Restrictive domain score at Week 12" and "HIT-6 total score at Week 12", will be collected using eTablet as one electronic patient reported outcome (ePRO) at site. Participants are required to complete the ePRO measures remotely at Visit 7 (Week 12) according to remote-visit procedure. 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 17.1-1. Summary of Collection Devices for Primary and Key secondary endpoints

Endpoint	Collection Device
Change from baseline in mean monthly migraine days across the 12-week treatment period	eDiary
Change from baseline in mean monthly headache days across the 12-week treatment period	eDiary
Change from baseline in mean monthly acute medication use days across the 12-week treatment period	eDiary
≥ 50% reduction in 3-month average of monthly migraine days	eDiary
Change from baseline in mean monthly Performance of Daily Activities domain score of the AIM-D across the 12-week treatment period	eDiary
Change from baseline in mean monthly Physical Impairment domain score of the AIM -D across the 12-week treatment period	eDiary
Change from baseline in MSQ v2.1 Role Function-Restrictive domain score at Week 12	eTablet
Change from baseline in the HIT-6 total score at Week 12	eTablet

17.2 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 and supplemental signs and symptoms
- COVID-19 status (COVID-19 testing results or contact with a COVID-19 positive person)

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 coronavirus infection or coronavirus test positive will be provided. Supporting listings for the described analyses above will also be provided.

18.0 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

All health outcome endpoints have been added to this SAP.

19.0 REFERENCES

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20.0 APPENDICES

All laboratory parameters are reported in the International System (SI) units as standard practice. In addition, selected laboratory parameters (listed in Table 20.1-1) will be reported in conventional units to facilitate interpretation and reporting for the CSR and future labeling.

20.1 LIST OF PARAMETERS REPORTED IN CONVENTIONAL UNIT

The list of selected parameters required to be reported in conventional unit is provided in Table 20.1-1.

Table 20.1-1. List of Selected Parameters Reported in Conventional Unit

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
19	Uric Acid	mg/dL	1
20	Hemoglobin	g/dL	1

20.2 ANALYSIS AND REPORTING FORMAT IN CONVENTIONAL UNITS

1) For individual clinical study reports for the CNS projects, the descriptive statistics for the selected laboratory parameters (Table 20.2-1) will be reported in conventional units using the similar layout for the summary table in SI unit.

2) Patient narratives generated by the statistical programming team will also include the values in conventional units for the selected lab parameters (Table 20.2-1). That will be accomplished by presenting the values in conventional units within the parentheses next to the values in SI units. An example is provided in Table 20.2-1. for lab parameter 'Bilirubin, Total', for which 'umol/L' is the SI unit and 'mg/dL' is the conventional unit.

Table 20.2-1. 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)
…						

3) Details of reporting the selected laboratory parameters in conventional units as detailed in this document should be included in SAP for various CNS projects.

20.3 SUMMARY OF CHANGES FROM FINAL SAP TO SAP AMENDMENT 1

Date	Section	Description
December 3, 2019	4.0	• Added protocol amendment 2 information • Added Japan related appendix 2 in text • Replaced SoA table • Clarified the stratification method by adding another bullet of "region"
December 3, 2019	6.2	Further clarified mITT definition by adding "while on study treatment……".
December 3, 2019	6.4	Added estimand population definition
December 3, 2019	8.0	• Added "Other" in region definition • Added "off-treatment hypothetical estimand" population for demographic summary • Changed the population of ASC-12 summary to "safety and mITT" • Updated AIM-D endpoint definition in baseline efficacy summary
December 3, 2019	10.1.2	Updated AIM-D endpoint definition
December 3, 2019	10.3	• Updated region definition for secondary efficacy endpoints • Updated definitions for binary endpoints • Updated definition of 50% responder to be the "3-month average" • Updated AIM-D endpoint definition • Further clarified and added details for analyses for secondary efficacy endpoints (i.e., use logistic regression model instead of generalized linear mixed model) • Updated multiplicity control figures and tables due to AIM-D's new definition; also added another edge after testing S5 • Clarified that the multiplicity control for Europe and Canada will be based on the analysis population for off-treatment hypothetical estimand
December 3, 2019	10.4	• Updated definitions for binary endpoints • Added a new endpoint of "weekly migraine days" • Added week 16 for HIT-6 • Updated AIM-D endpoint definition • Added two more graphical analyses as detailed in the last two paragraphs of this section
December 3, 2019	10.5.1	Further clarified and added details for estimand population
December 3, 2019	10.5.3	Added a new sensitivity analysis
December 3, 2019	10.5.5	Further clarified and added details for estimand approach for secondary efficacy endpoints
December 3, 2019	11.1	• Used "study intervention discontinuation" for AE as the default instead of "study discontinuation" • Clarified "after rounding" and also the sorting order for the "2%" table

Date	Section	Description
December 3, 2019	11.2	• Deleted "conventional units" • Updated "Higher Limit" in Urinalysis
December 3, 2019	11.4	Added new criteria
December 3, 2019	13.0	• Updated definitions for binary endpoints • Added "if model does not converge……" • Added section 13.1 to align with protocol and renumbered section 13.2
December 3, 2019	17.1	• Updated table 17.1-1 • Added new windows for estimand and weekly endpoint • Updated table of "safety data analysis" for clarity and consistency across atogepant program
December 3, 2019	17.2.1	Added a new endpoint of "weekly migraine days"
December 3, 2019	17.2.2	Updated AIM-D endpoint definition
December 3, 2019	Appendix 1	• Added "Other" in region definition • Added consistency criterion for key secondary efficacy endpoints • Added a test for treatment-by-region interaction • Added "if model does not converge……" • Clarified sample size calculation
December 3, 2019	Appendix 2	Created it newly for Japan
December 3, 2019	Appendix 3	Added a new column of "decimal places"
January 17, 2020	11.2	Updated shift table to "Shift tables from baseline to end of double-blind treatment period for clinical laboratory parameters will be presented"
February 25, 2020	11.2	Updated eGFR's PCS lower limit in Table 11.2–1 since central lab did not provide the lower level of normal
February 25, 2020	Appendix 3	Updated unit of Albumin and Hemoglobin for CDISC compliance purpose
March 24, 2020	9.2	Clarified double blind treatment period and algorithm
March 24, 2020	Throughout	• Re-updated all AIM-D related sections to go back to 2 domains • Updated algorithms of all HEOR endpoints
March 24, 2020	7.0 10.2, 10.3, 10.5 17.10	• Added "region" stratification factor into the primary analysis model • Added "actual randomization stratification" related summary • Clarified "actual randomization stratification" will be used in the models rather than IWRS • Updated responder endpoint definition
September 1, 2020	4.0	• Added protocol amendment 3 related information (e.g., extension studies, COVID-19, etc.) • Updated the stratification regarding "current use" as per protocol amendment 3
September 1, 2020	6.2, 6.4	Updated population definitions for mITT and estimand
September 1, 2020	10.1.1	Updated "headache day" definition

Date	Section	Description
September 1, 2020	10.2, 10.3	• Restrucured and clarified to align with the entire atogepant program • Updated the entire sensitivity analysis section
September 1, 2020	10.4	Clarified to align with the entire atogepant program
September 1, 2020	10.5	• Added a new element as per final ICH E9 R1 • Updated the entire section of intercurrent events • Updated the estimand approach for secondary endpoints
September 1, 2020	17	• Updated all visit time windows to align with the entire atogepant program • Clarified and provided more details regarding eDiary data derivation for efficacy endpoints • Added 17.11 for intercurrent event handling
September 1, 2020	18	Newly added for COVID-19 impact
By 17May 2021		• Added all HO endpoints • Added Appendix 3 for subgroup • updated visit time windows • Added Actual randomization startification algorithm in Section 17.10.
20May2021	17.11	• Added Sections 17.11 and 17.12
By July 12, 2021	1	• Delete the wording about stand-alone pharmacometrics analysis plan. • Update the wording about regional statistical analysis
By July 12, 2021	10.1.2	• Update the wording about AIM-D
By July 12, 2021	10.1.3	• Add the Section 10.1.3 to list all efficacy endpoints
By July 12, 2021	10.1.4	• Add the Section 10.1.4 to describe the stratification variables in the modeling
By July 12, 2021	10.2	• Update the Section 10.2 for efficacy analysis for filing except Europe and Canada, including the primary efficacy analysis, secondary efficacy analysis, and analysis for additional efficacy endpoints and health outcome endpoints
By July 12, 2021	10.3	• Update the Section 10.3 for efficacy analysis for European Medication Agency filing
By July 12, 2021	10.4	• Update the Section 10.4 for efficacy analysis for Health Canada filing
By July 12, 2021	12	• Delete the original Section 12 for additional efficacy endpoints and other health outcomes analysis
By July 12, 2021	12	• Update the subgroup analysis
By July 12, 2021	16.1	• Delete the Table 17.1.7
By July 12, 2021	16.10	• Update the wording for stratification of migraine prevention medication exposure
By July 12, 2021	16.11	• Add the Section 16.11to identify the participants who started a new migraine prophylaxis treatment
By January 24, 2022		• Minor typos corrected and clarifications made throughout
By January 24, 2022	3.0	• Added missing abbreviations

Date	Section	Description
By January 24, 2022	7.0	• A summary table of participants with inconsistent randomization strata will also be produced
By January 24, 2022	8.0, 12.1	• Region summary "other" updated to "East Asia"
By January 24, 2022	8.0	• Updated MedDRA version to 24.0
By January 24, 2022	10.1.4, 10.2.1, 10.2.3, Table 10.2-2, 10.3.2, 10.3.3, 12.2, 16.10	• Updated abbreviated names of derived strata to more closely match protocol • Updated "failed 2 to 4 medications with different mechanisms of action" to "failed 2 or more medications with different mechanisms of action"
By January 24, 2022	10.2.1.1	• Specify random seed for multiple imputation sensitivity analyses
By January 24, 2022	10.2.1.2	• Robust regression will be presented of results of K-S test for normality
By January 24, 2022	10.2.3, Table 10.2-2	• Specify covariance structures to be used in the event that the model does not converge with an unstructured covariance matrix • Specified that PHQ-9 would be analyzed using an ANCOVA as it is collected at one post-baseline time point • Specified that HIT-6 total score change from baseline analysis would not include Week 16 in the MMRM
By January 24, 2022	Table 10.2-2	• Changed "GLIMMIX" (SAS procedure name) to "GLMM" (statistical analysis abbreviation) • ≥ 25%, ≥ 30%, ≥ 50%, ≥ 75%, 100% improvement (decrease) in monthly migraine days at each 4 week interval will be analyzed with a GLMM • WPAI is collected at weeks 4, 8, and 12 and will be analyzed using an MMRM • Deleted "Only data collected during the double-blind treatment period will be included in the analysis" which applies only to the analysis for the mITT population. For the off-treatment estimand, data will be included as noted in section 10.3.1.
By January 24, 2022	10.3.2	• Deleted "Only data collected during the double-blind treatment period will be included in the analysis". For the off-treatment estimand, data will be included as noted in section 10.3.1.
By January 24, 2022	10.3.2.1	• Due to the low number of subjects in several of the monotone missing data pattern categories, the multiple imputation sensitivity analysis for the off-treatment estimand cannot be completed and has been eliminated.
By January 24, 2022	10.3.3	• AIM-D removed from second paragraph as it is an exploratory, not secondary, endpoint in the EU
By January 24, 2022	11.1	• Noted TESAEs will be summarized by SOC and PT
By January 24, 2022	11.4	• Corrected typo – changed "post-treatment" to "post-baseline"

Date	Section	Description
By January 24, 2022	16.1	• Analysis windows for the mITT and off-treatment estimand clarified throughout and specified where not previously done so
By January 24, 2022	16.2.1	• Defined what it means for baseline to be evaluable
By January 24, 2022	16.2.2	• Specified method of data collection and rules for analysis of the EQ-5D-5L
By January 24, 2022	16.10	• Stratification of region used in the analysis specified as noted in Table 10.1-2