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

Protocol Date: May 16, 2020

**ALLERGAN**

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

Protocol Number: 3101-301-002

Phase: 3

Name of Study intervention: Atogepant

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

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

**INVESTIGATOR SIGNATURE PAGE**

INVESTIGATOR:

I agree to:

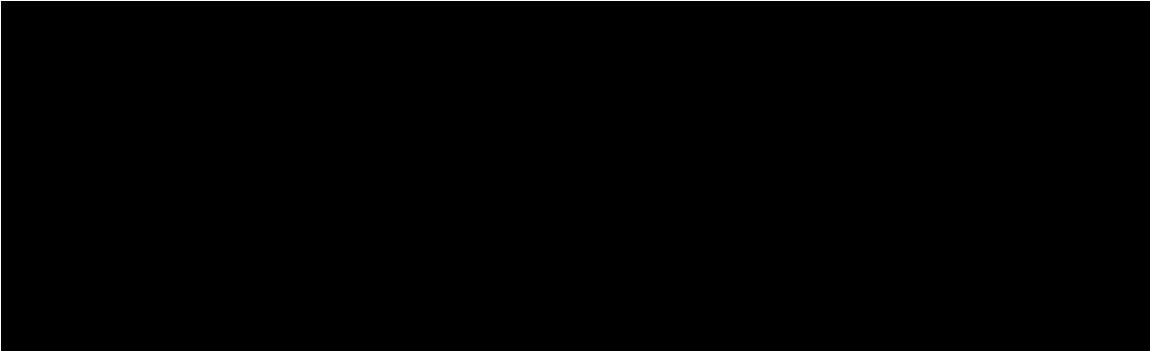

- Implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations.
- Maintain all information supplied by Allergan in confidence and, when this information is submitted to an IRB, IEC or another group, it will be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

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

\_\_\_\_\_  
Investigator Printed Name\_\_\_\_\_  
Signature\_\_\_\_\_  
Date

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## Protocol Summary

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**Study Compound:** Atogepant

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**Phase:** 3

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**Study Objectives:**

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

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

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**Study Design**

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

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

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

*Control:* Atogepant-matching placebo.

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

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

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

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

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

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

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

### Study Population Characteristics

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

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

*Key Inclusion Criteria:*

- Male or female participants age 18 to 80 years, inclusive, at Visit 1.
- At least a 1-year history of migraine with or without aura consistent with a diagnosis according to [ICHD-3, 2018](#).
- Age of the participant at the time of migraine onset < 50 years.

*Key Exclusion Criteria:*

- Has a history of migraine accompanied by diplopia or decreased level of consciousness or retinal migraine as defined by ICHD-3, 2018.
- Has a current diagnosis of chronic migraine, new persistent daily headache, trigeminal autonomic cephalgia (eg, cluster headache), or painful cranial neuropathy as defined by ICHD-3, 2018.

- History of an inadequate response to > 4 medications (2 of which have different mechanisms of action) prescribed for the prevention of migraine (see [Attachment 12.3](#) for classification of inadequate response to migraine-preventive medications).

- Participants with clinically significant hematologic, endocrine, cardiovascular, pulmonary, renal, hepatic, gastrointestinal, or neurologic disease.

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### Response Measures

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

*Health Outcomes:* Activity Impairment in Migraine – Diary (AIM-D);

Migraine-Specific Quality of Life Questionnaire, version 2.1 (MSQ v2.1);

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

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

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

#### **General Statistical Methods and Types of Analyses:**

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

The primary efficacy endpoint is the change from baseline in mean monthly migraine days across the 12-week treatment period.

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

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

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

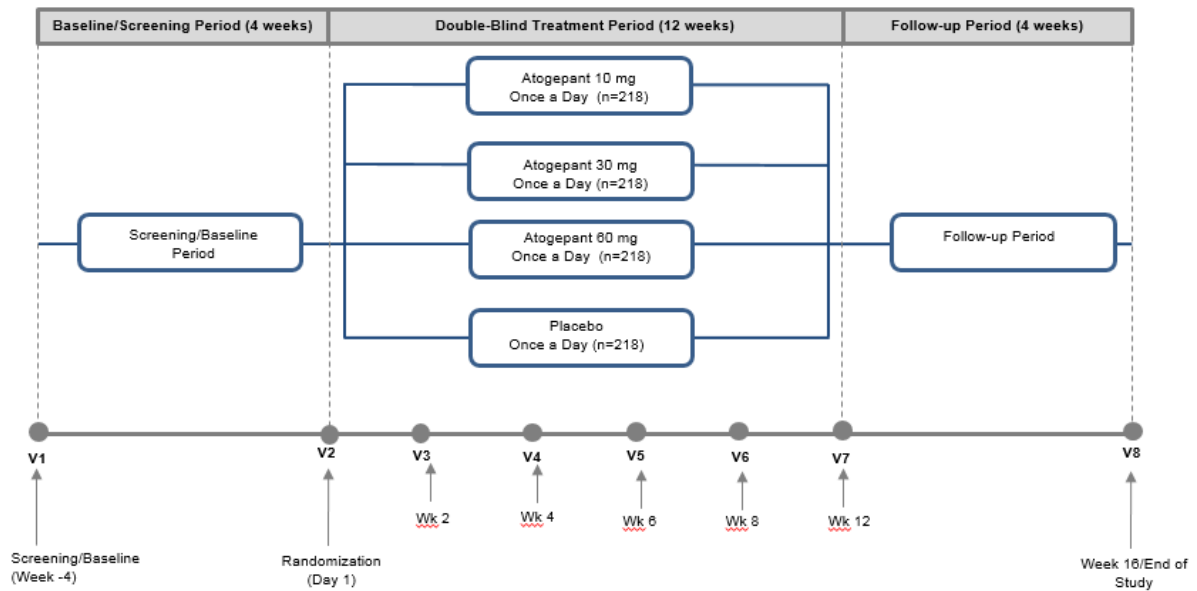
The secondary endpoints for headache days, acute medication use days, MSQ v2.1 Role Function-Restrictive domain score, Performance of Daily Activities domain score of the AIM-D, and Physical Impairment domain score of the AIM-D will be analyzed in the same manner as that used to analyze the primary endpoint.

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

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

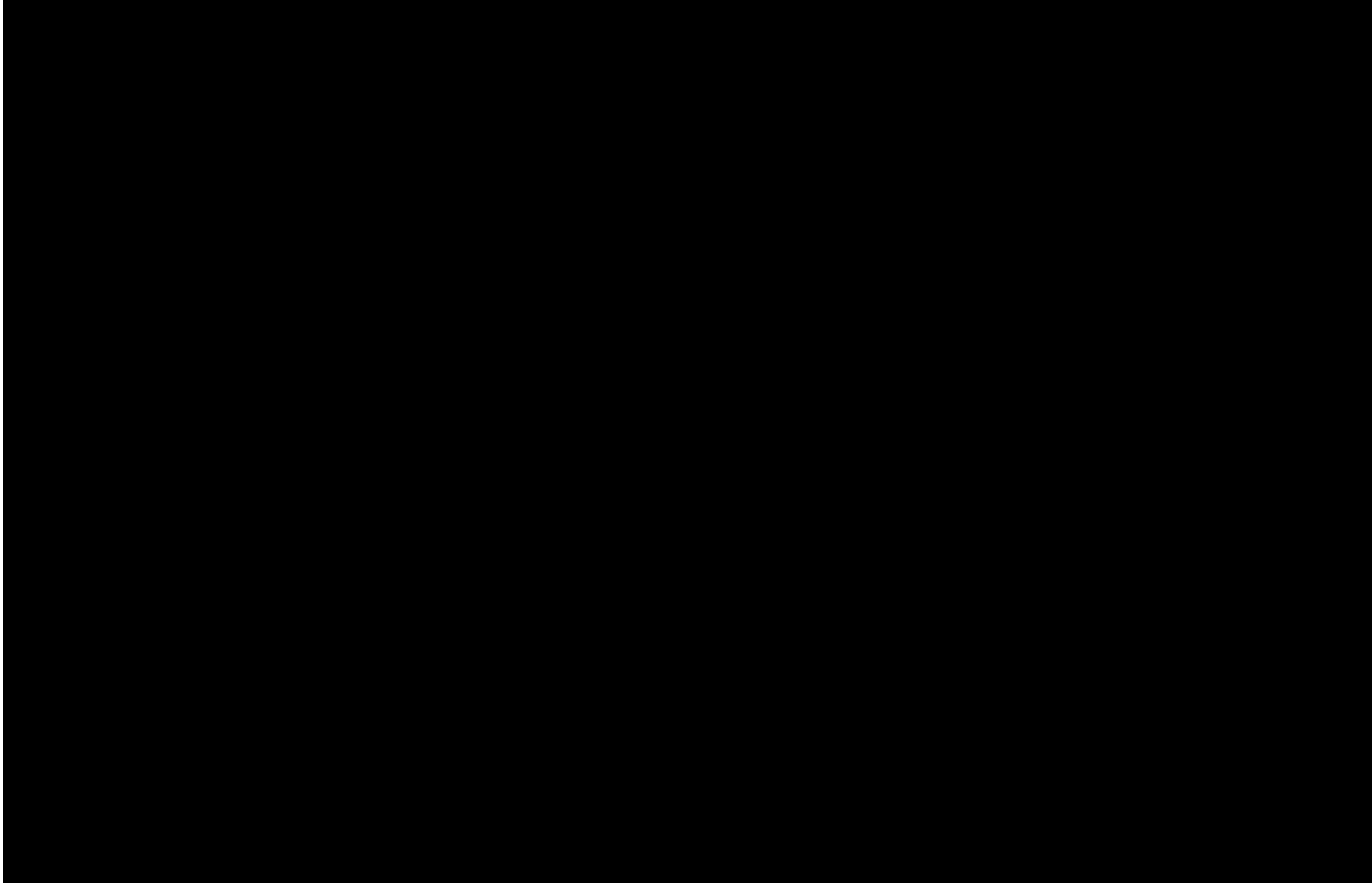
*Sample Size Calculation:* A sample size of 218 randomized participants per treatment group will provide at least 98% power to detect the treatment difference between each of the 3 atogepant doses (assumed equally effective) and placebo for the primary efficacy endpoint. This sample size was selected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

**Figure 1 Study Diagram**

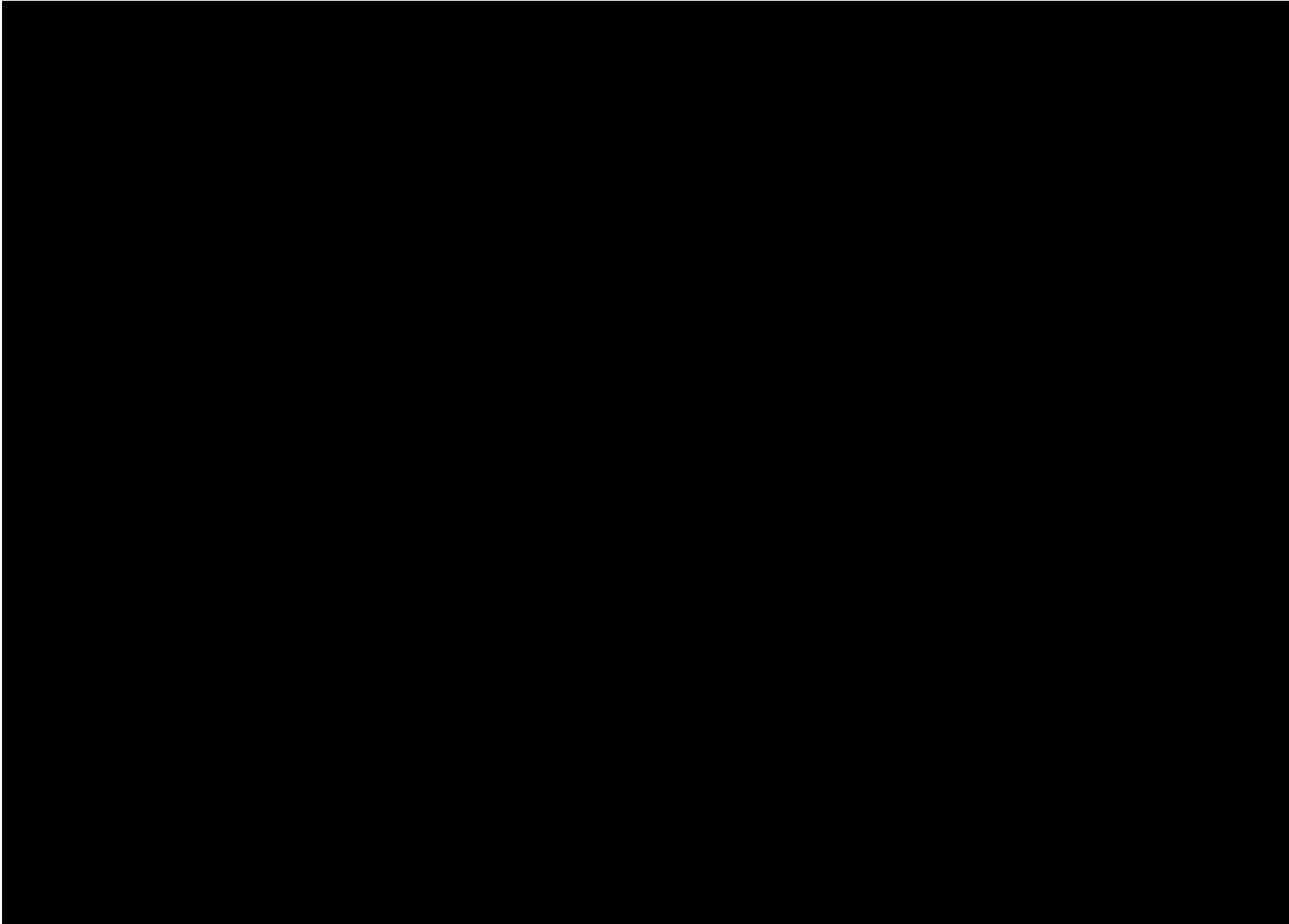




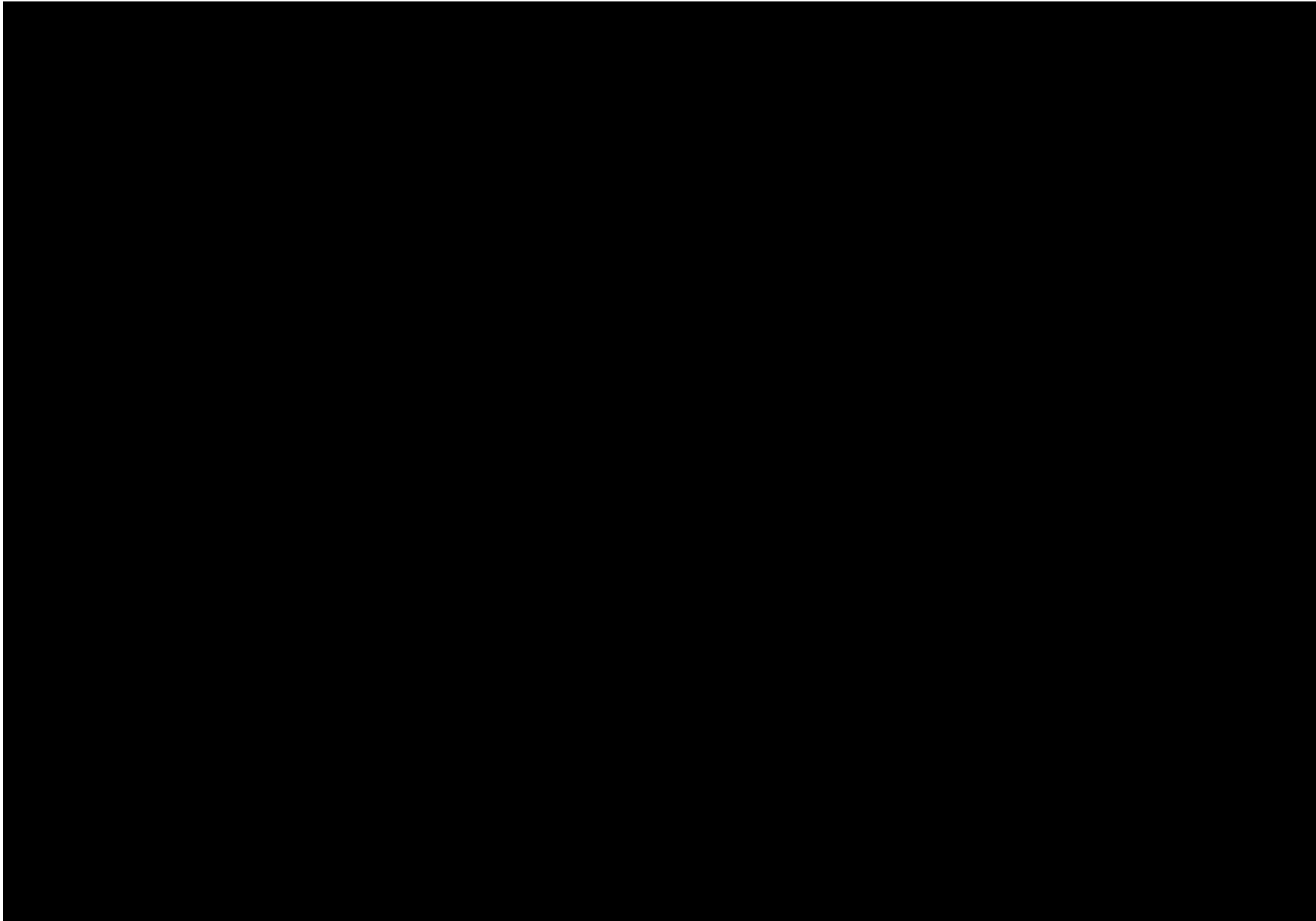
**Table 1 Schedule of Visits and Procedures for In-Person Visits Conducted Prior to or During the COVID-19 Pandemic**



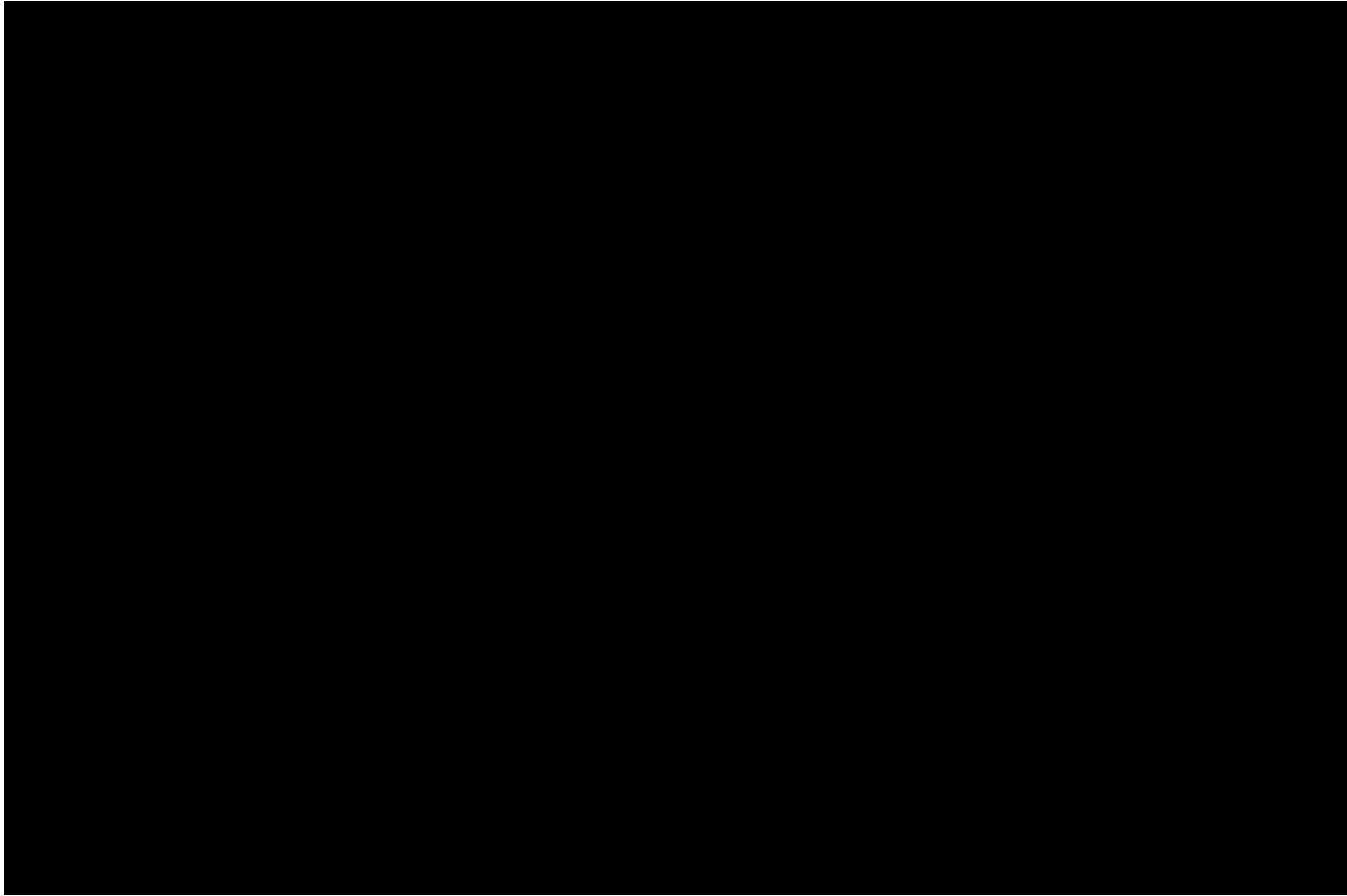
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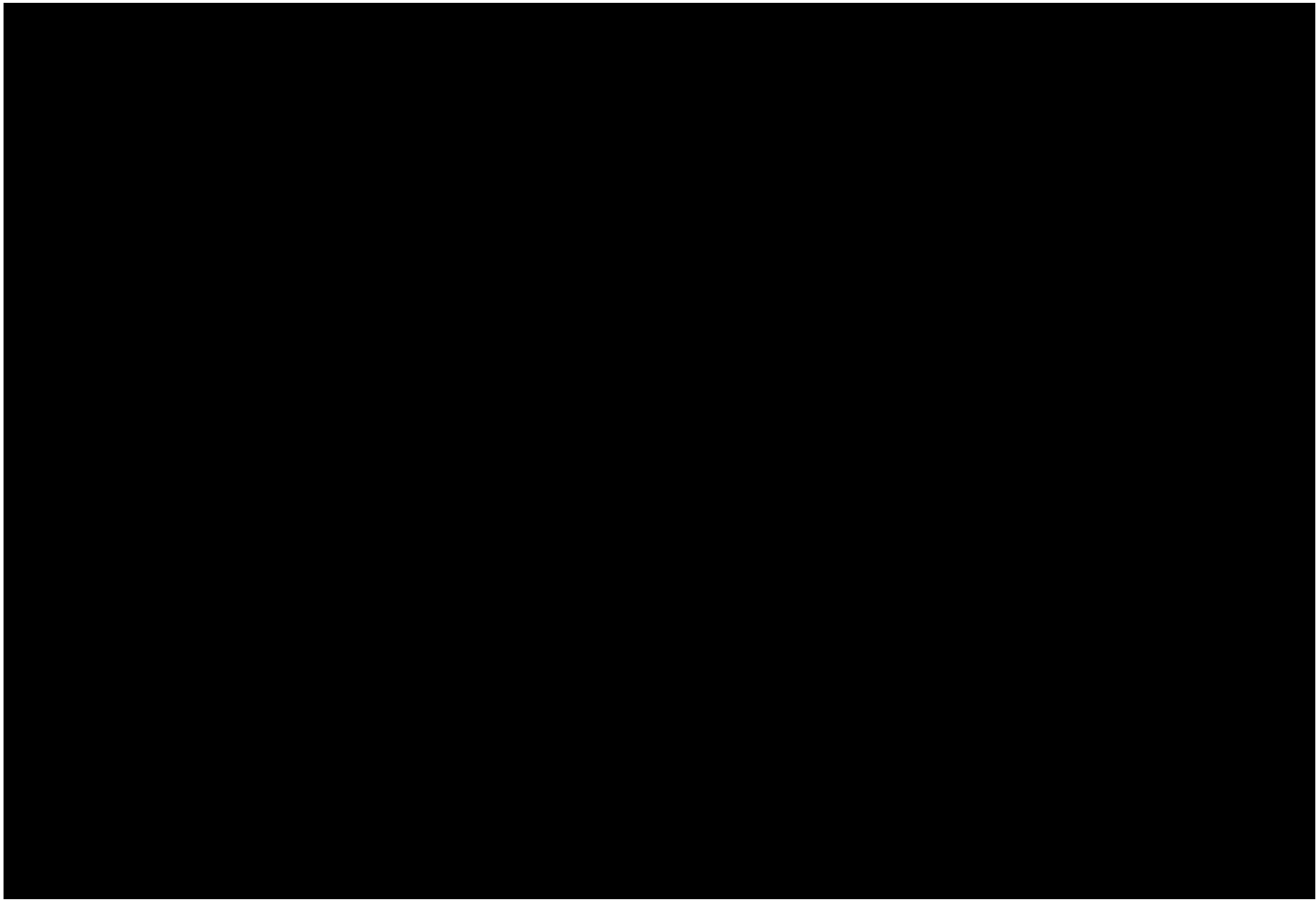




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## 1. Background and Clinical Rationale

### 1.1 Background

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

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

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

### 1.2 Overview of Atogepant

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

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

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

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

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

### 1.3 Study Rationale

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

[REDACTED]

## 2. Study Objectives and Clinical Hypotheses

### 2.1 Study Objectives

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

## 3. Study Design

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

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

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

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

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

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

### **3.1 Data Safety Monitoring Board**

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

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

### 3.2 Adjudication Committee

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

## 4. Study Population and Entry Criteria

### 4.1 Number of Participants

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

### 4.2 Inclusion Criteria

The following are requirements for entry into the study:

1. Written informed consent and participant privacy information (eg, written authorization for use and release of health and research study information) obtained from the participant prior to initiation of any study-specific procedures.
2. Male or female participants ages 18 to 80 years, inclusive, at Visit 1.
3. At least a 1-year history of migraine with or without aura consistent with a diagnosis according to the [ICHD-3, 2018](#).
4. Age of the participant at the time of migraine onset  $< 50$  years.



### 4.3 Exclusion Criteria

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

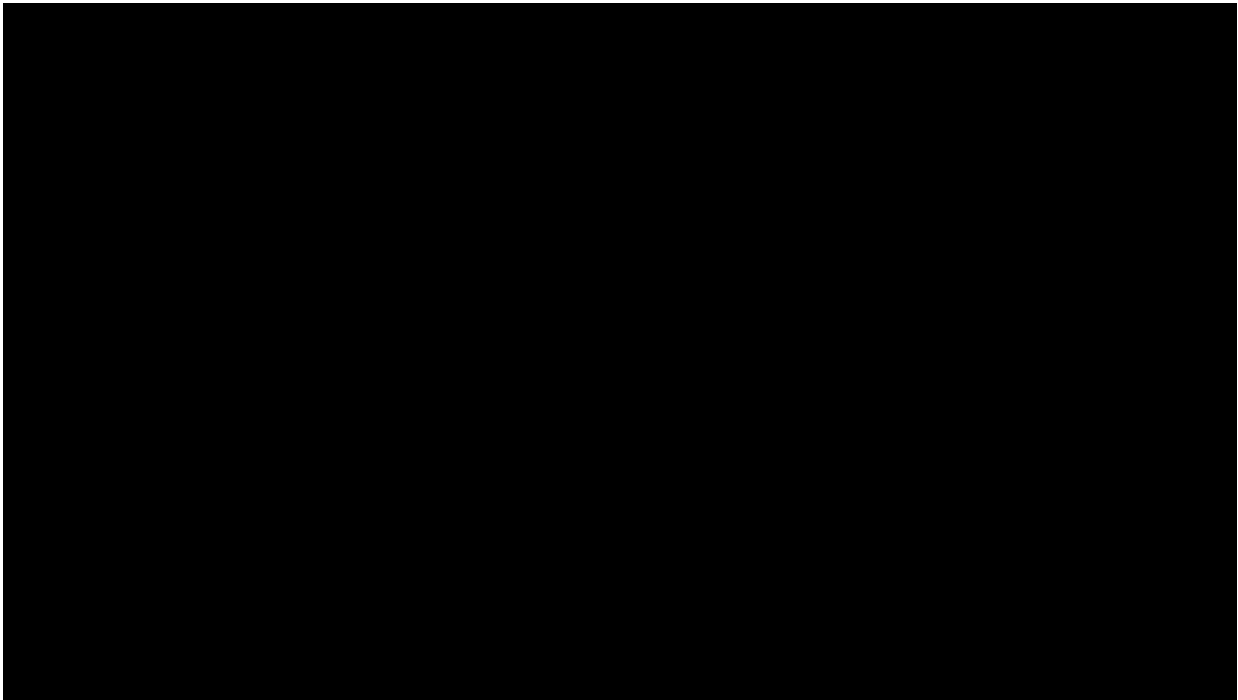
- [REDACTED]
2. Has a history of migraine accompanied by diplopia or decreased level of consciousness or retinal migraine as defined by ICHD-3, 2018.
  3. Has a current diagnosis of chronic migraine, new persistent daily headache, trigeminal autonomic cephalgia (eg, cluster headache), or painful cranial neuropathy as defined by ICHD-3, 2018.

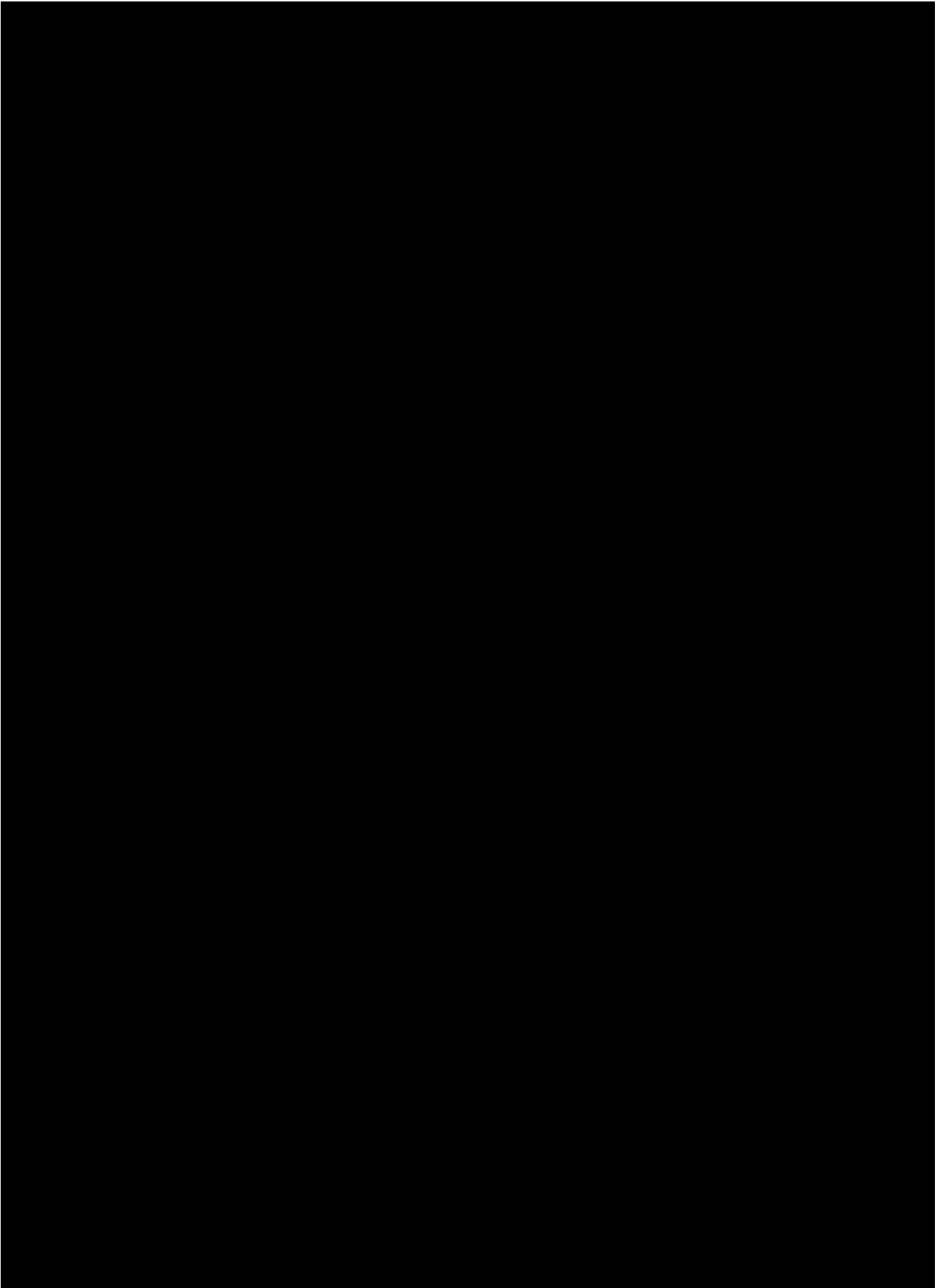
- [REDACTED]
6. History of an inadequate response to > 4 medications (2 of which have different mechanisms of action) prescribed for the prevention of migraine (see Attachment 12.3 for classification of inadequate response to migraine-preventive medications).

- [REDACTED]
12. Clinically significant cardiovascular or cerebrovascular disease [REDACTED]



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



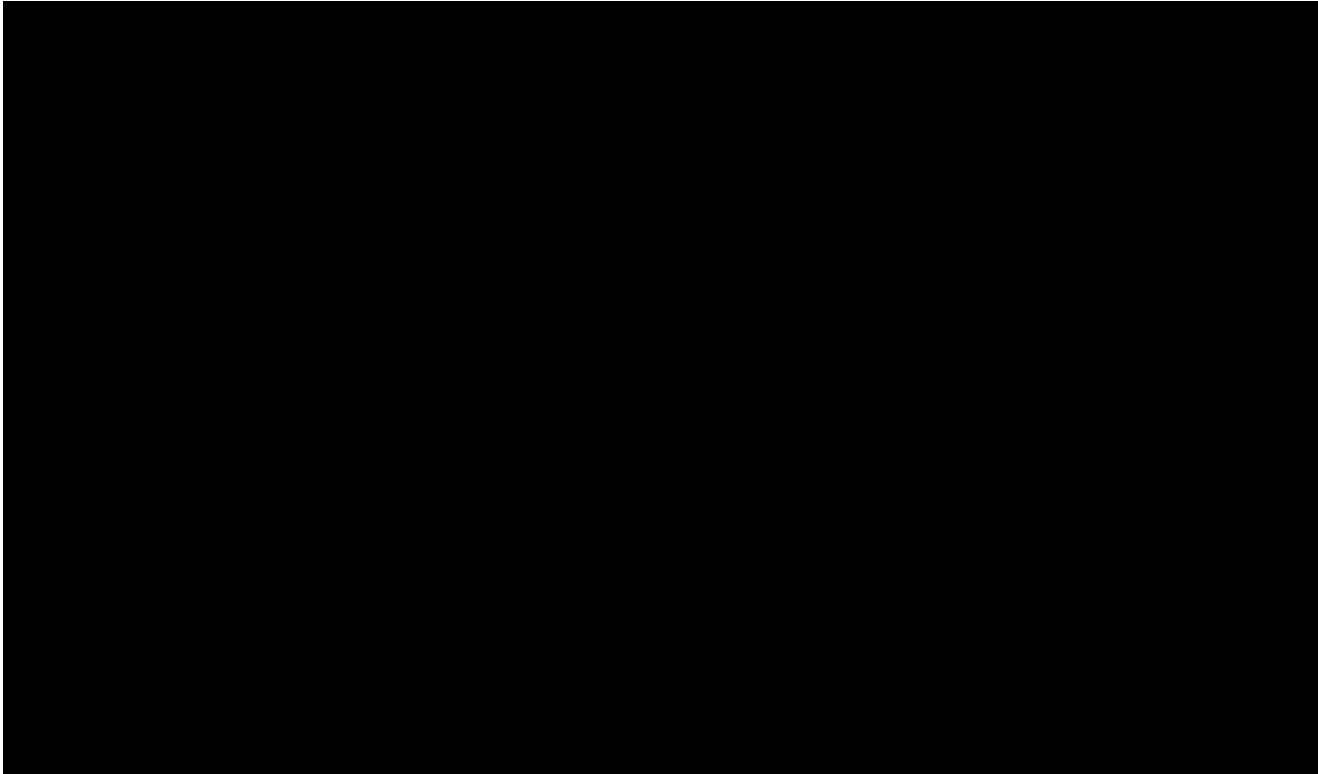


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#### 4.4 Permissible and Prohibited Medications/Treatments

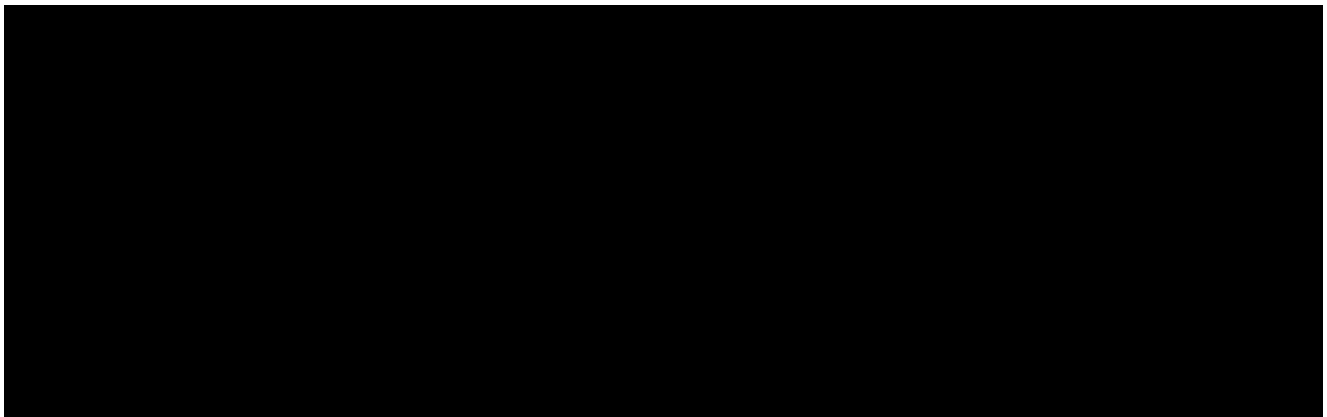
##### 4.4.1 Permissible Medications/Treatments

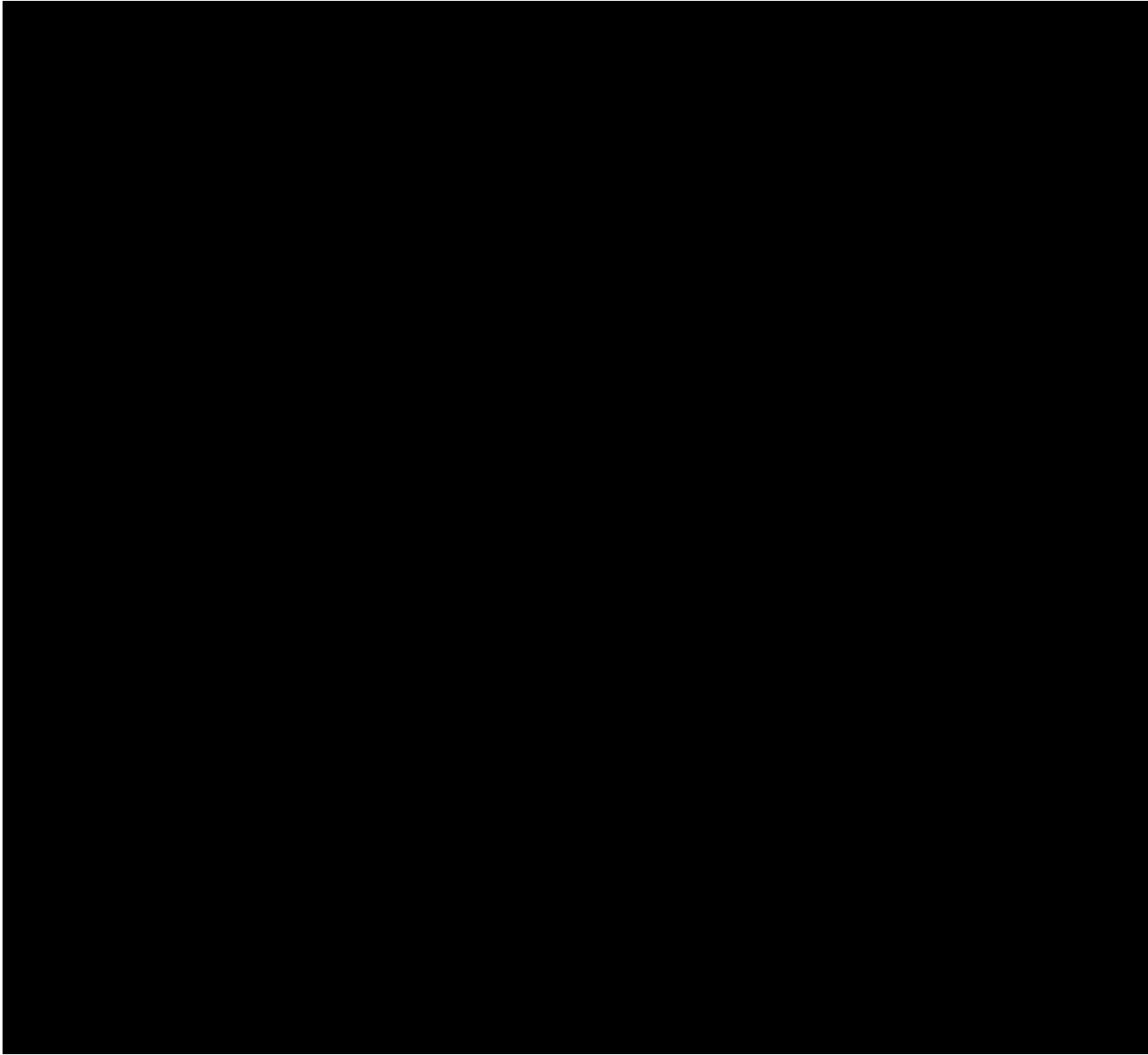
Medications that are not specifically prohibited in Section 4.4.2 are allowed, with the following clarifications and restrictions:



Therapy considered necessary for the participant's welfare may be given at the discretion of the investigator. [REDACTED]

##### 4.4.2 Prohibited Medications/Treatments





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

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

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

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

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

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

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

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

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

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

#### 4.4.4 Special Diet or Activities

#### 4.5 Screen Failures

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

### 5. Study Interventions

#### 5.1 Study Interventions and Formulations

Tablets containing atogepant 10 mg (Formulation [REDACTED]), atogepant 30 mg (Formulation [REDACTED]), and atogepant 60 mg (Formulation [REDACTED]).

#### 5.2 Control Intervention

Atogepant 10 mg matching placebo (Formulation [REDACTED]), atogepant 30 mg matching placebo (Formulation [REDACTED]), and atogepant 60 mg matching placebo (Formulation [REDACTED]).

### 5.3 Methods for Masking/Blinding

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

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

### 5.4 Intervention Allocation Ratio

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

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

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

### 5.5 Method for Assignment to Intervention Groups/Randomization

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

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

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



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

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

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

## 5.6 Study Intervention Regimen and Dosing

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

**Table 5-1 Study Interventions**

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

## 5.7 Storage of Study Interventions

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

## 6. Response Measures and Summary of Data Collection Methods

### 6.1 Efficacy Measures

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

The AIM-D, Activity Level, and Activity Limitation will also be collected daily via an eDiary.

#### 6.1.1 Migraine Day

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

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

#### **OR**

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

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

### **6.1.2 Headache Day**

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

### **6.1.3 Acute Medication Use Day and Triptan Use Day**

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

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

## **6.2 Health Outcomes Measures**

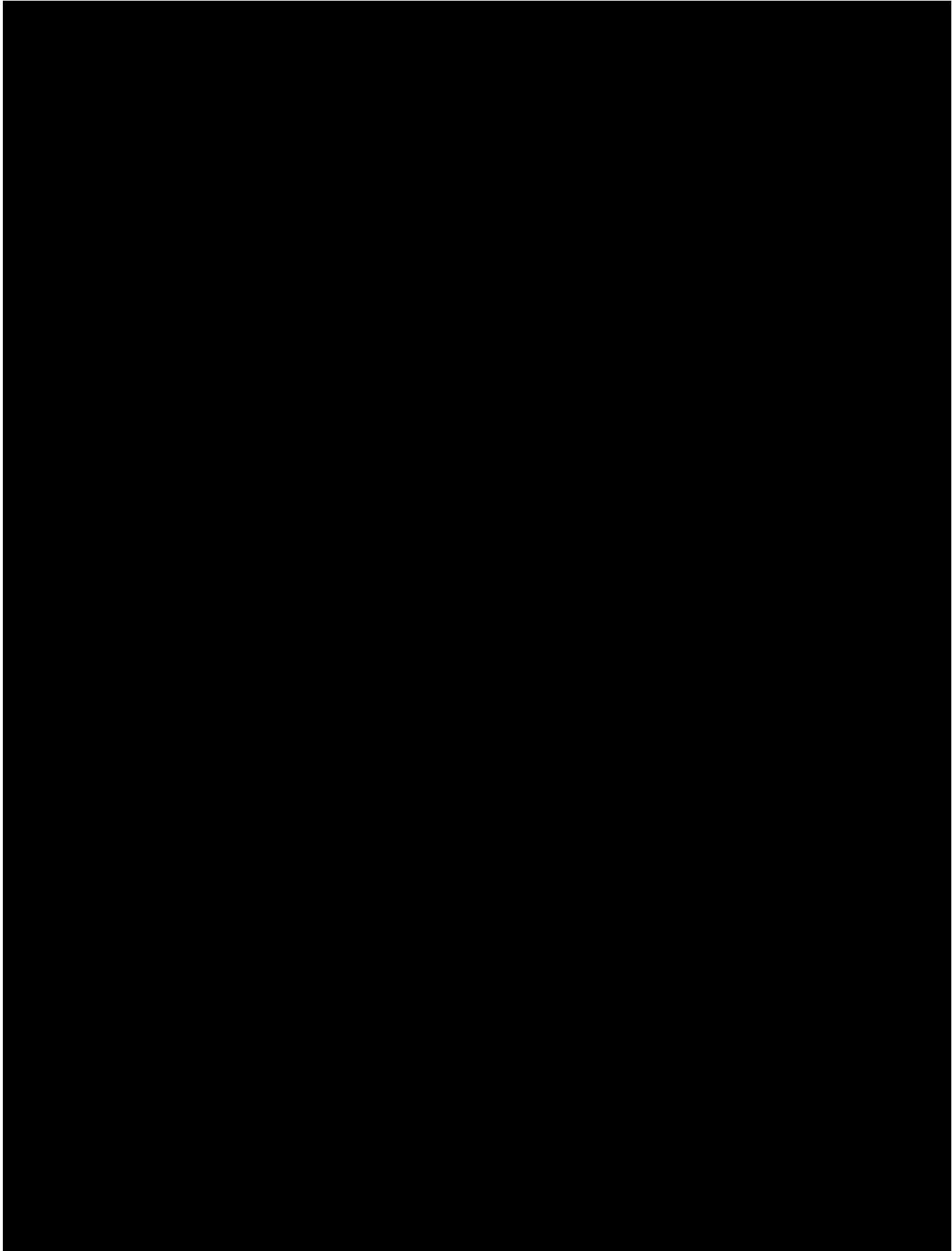
### **6.2.1 Activity Impairment in Migraine – Diary (AIM-D)**

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

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

### **6.2.2 Activity Level and Activity Limitation**

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

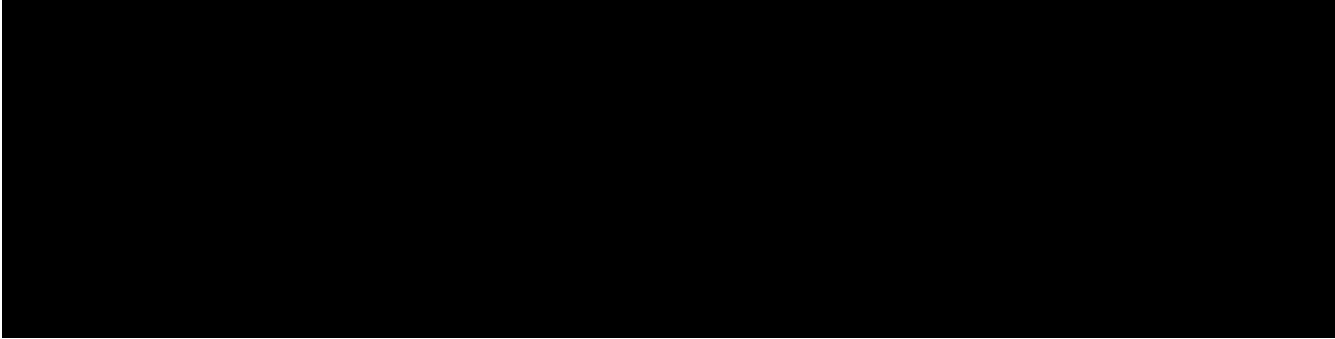


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### **6.2.10 Migraine Specific Quality of Life Questionnaire, Version 2.1 (MSQ v2.1)**

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



### **6.3 Pharmacokinetic Measures**



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

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

#### **6.4 Future Biomedical Research**

## 6.5 Safety Measures

### 6.5.1 Adverse Events

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

### 6.5.2 Adverse Events of Special Interest

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

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

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

### 6.5.3 Clinical Laboratory Determinations

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



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

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

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

The clinical laboratory parameters to be measured are shown in [Table 6-1](#).

**Table 6-1 Clinical Laboratory Parameters**

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

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

#### 6.5.4 Vital Signs

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

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

### **6.5.5 Physical Examination**

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

### **6.5.6 Electrocardiograms (ECG)**

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

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

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

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

## 6.6 Other Study Supplies

The following will be provided by Allergan or Allergan designee:

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

## 6.7 Summary of Methods of Data Collection

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

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

## **7. Statistical Procedures**

### **7.1 Analysis Populations**

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

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

### **7.2 Collection and Derivation of Efficacy Assessments**

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

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

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

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

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

### **7.2.1 Primary Efficacy Variable**

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

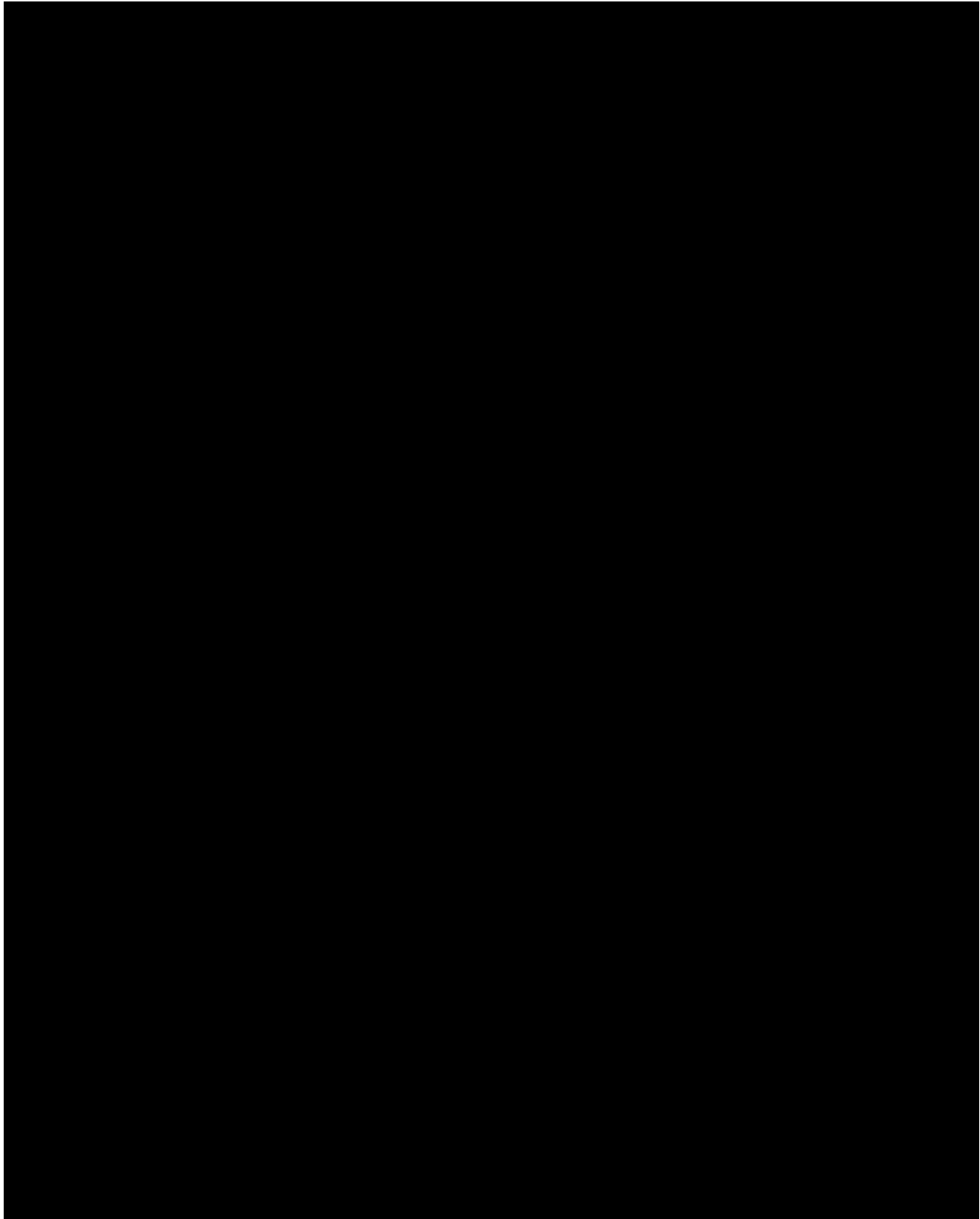
### **7.2.2 Secondary Efficacy Variables**

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

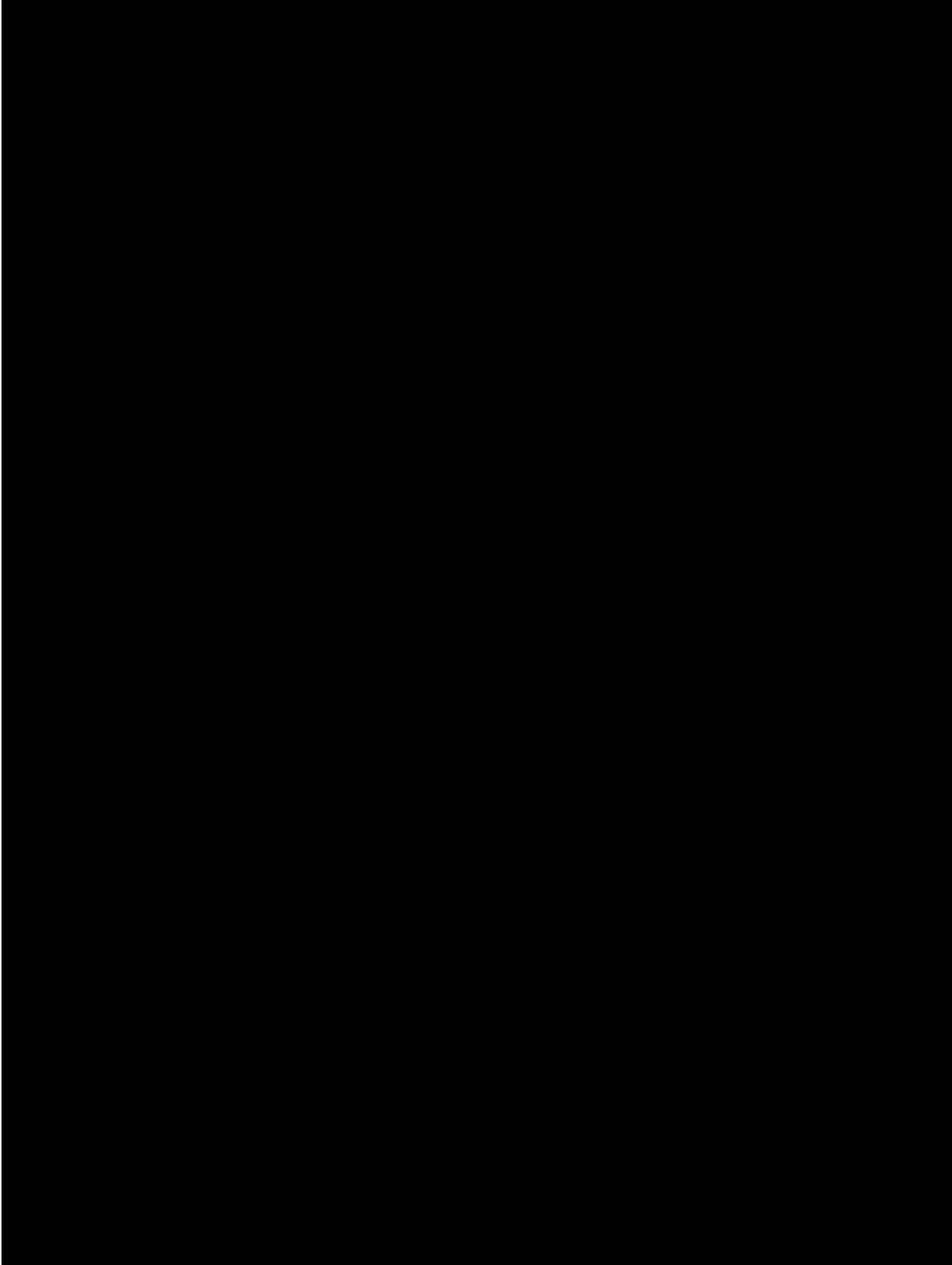
- Change from baseline in mean monthly headache days across the 12-week treatment period.
- Change from baseline in mean monthly acute medication use days across the 12-week treatment period.
- At least a 50% reduction in 3-month average of monthly migraine days.

- Change from baseline in MSQ v2.1 Role Function-Restrictive domain score at Week 12
- Change from baseline in mean monthly Performance of Daily Activities domain score of the AIM-D across the 12-week treatment period.
- Change from baseline in mean monthly Physical Impairment domain score of the AIM-D across the 12-week treatment period.

### 7.2.3 Additional Efficacy Variables



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### 7.3 Hypothesis and Methods of Analysis

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

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

#### 7.3.1 Primary Efficacy Analyses

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

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

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

### **7.3.1.1 Sensitivity Analyses in Missing Data Handling**

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

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

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

#### **Within-group Imputation Based on Observed Data**

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

#### **Copy-reference Approach**

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

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

The details for this analysis are provided in Section 7.4.

### **7.3.1.2 Sensitivity Analysis for Possible Violation of Normality Assumption**

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

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

### **7.3.2 Secondary Efficacy Analyses**

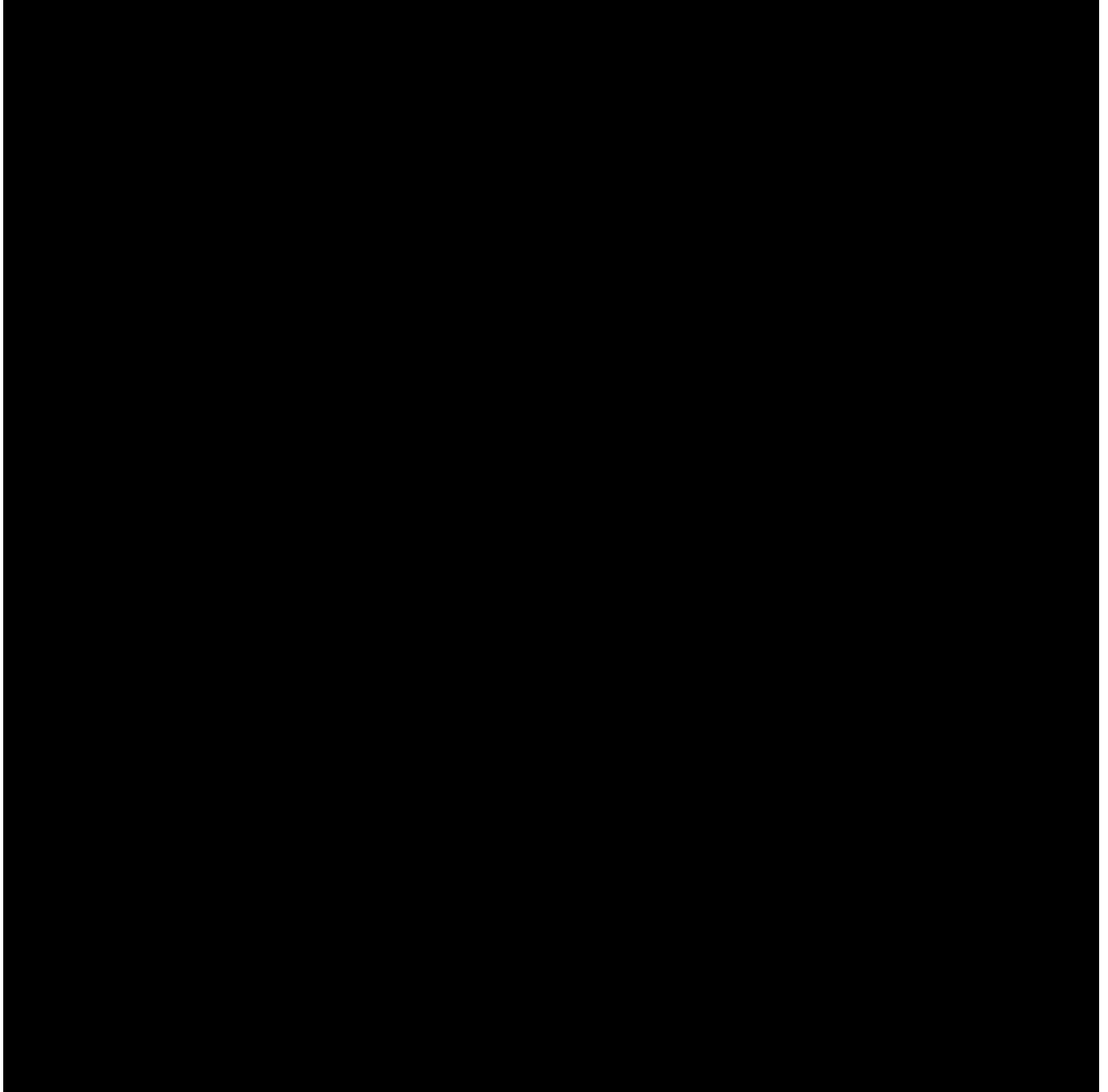
The secondary efficacy variables are identified in Section 7.2.2.

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

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

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

### 7.3.3 Additional Efficacy Analyses



### 7.3.4 Safety Analyses

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

## 7.4 Off-treatment Hypothetical Estimand

This section defines an estimand, termed as off-treatment hypothetical estimand, [REDACTED]  
[REDACTED]  
[REDACTED]

### 7.4.1 Treatment Condition of Interest

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

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

### 7.4.2 Population

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

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

### 7.4.3 Variable

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

#### **7.4.4 Accounting of Intercurrent Events**

Intercurrent events and their handling rules are as follows:

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

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

#### **7.4.5 Population-level Summary**

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

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

#### **7.4.6 Off-treatment Hypothetical Estimand Approach for the Secondary Endpoints**

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

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

#### **7.5 Subgroup Analyses**

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

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

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

## 7.6 Sample Size Calculation

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

- 1) The treatment difference from placebo will be similar to the average value across the migraine prevention studies for atogepant (Phase 2/3 Study CGP-MD-01), telcagepant ([Ho 2014](#)) and monoclonal antibodies ([Dodick 2014a](#); [Dodick 2014b](#); [Bigal 2015](#)). The standard deviation of each endpoint was estimated from an internal study that randomized approximately 800 participants. In particular, the assumed treatment difference from placebo in change from baseline in mean monthly migraine days across the 12-week treatment period is -1.5 days, and the standard deviation is 3.5 days. Detailed treatment difference and standard deviation assumptions are listed in [Table 7-1](#).
- 2) The study statistical testing plan controls the overall type I error at 5%. The power calculations of the primary and secondary endpoints have taken the multiple comparisons into consideration by testing each dose versus placebo at a 0.0167 significance level, 2-sided.

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

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

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

<sup>a</sup> Standard deviations observed in an internal study that randomized approximately 800 participants

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

## 7.7 Pharmacokinetics and Exposure-response Analyses

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

## 7.8 Interim Analyses

No interim analysis is planned.



## **8. Study Visit Schedule and Procedures**

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

### **8.1 Participant Entry Procedures**

#### **8.1.1 Overview of Entry Procedures**

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

#### **8.1.2 Informed Consent and Participant Privacy**

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

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

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

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

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

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

## 8.2 Washout Intervals

This study will not include a washout period.

## 8.3 Procedures for Final Study Entry

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

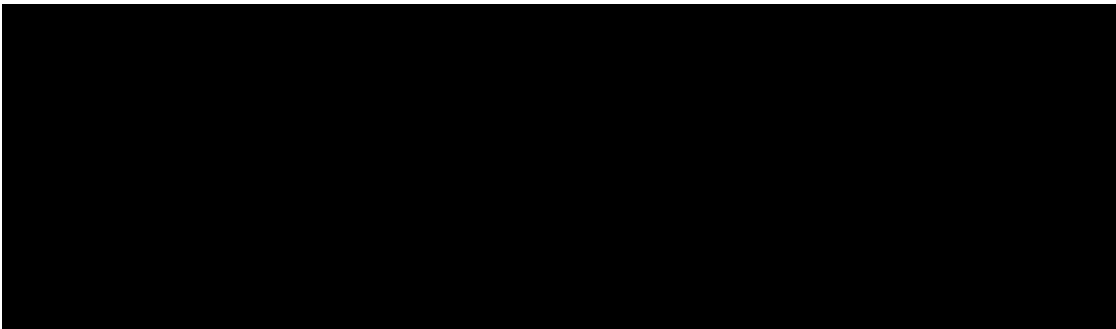
Prior to randomization, it must be confirmed that the participant had 4 to 14 migraine days and < 15 headache days during the 28-day baseline period (see Section 6.1.1 for definition) and completed the eDiary for at least 20 of the 28 days.

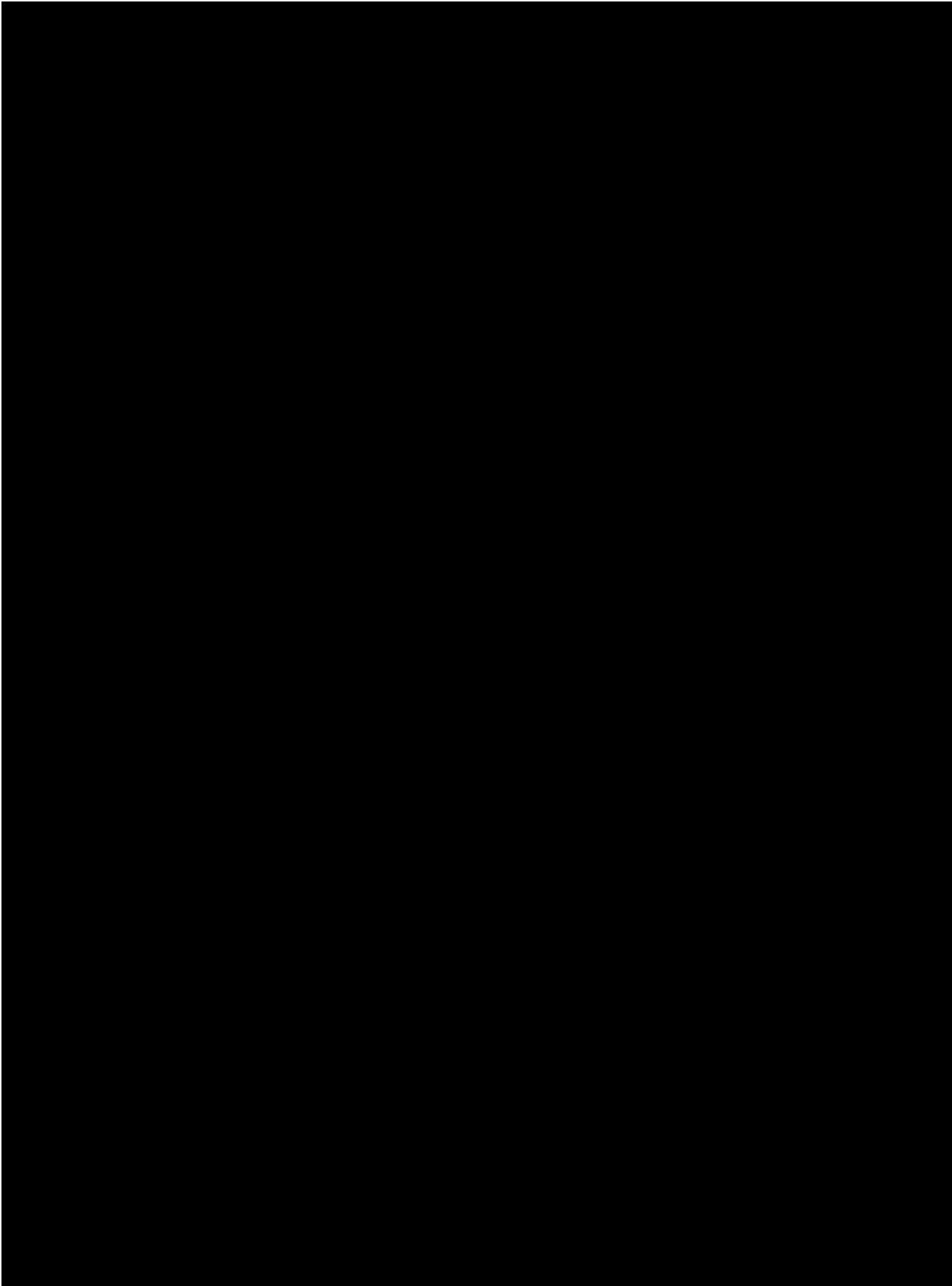
See Section 5.5 for the method for assignment to treatment groups/randomization.

## 8.4 Visits and Associated Procedures

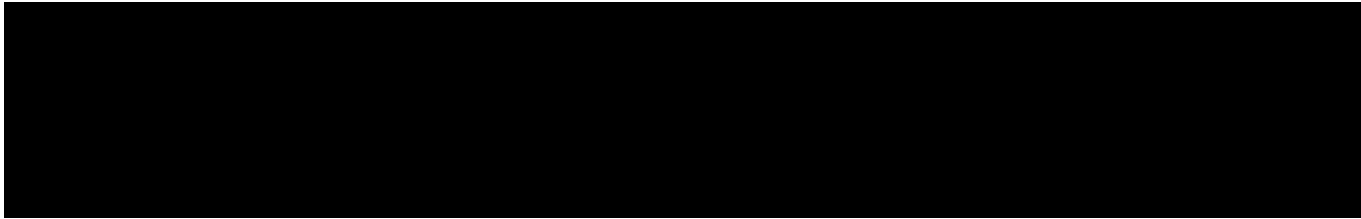
There will be 8 scheduled clinic visits: Visit 1 (Screening/Baseline), Visit 2 (Randomization), Visit 3 (Week 2), Visit 4 (Week 4), Visit 5 (Week 6), Visit 6 (Week 8), Visit 7/ET (Week 12), and Visit 8 (Follow-up). For details, please see Table 1 Schedule of Visits and Procedures for In-Person Visits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

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



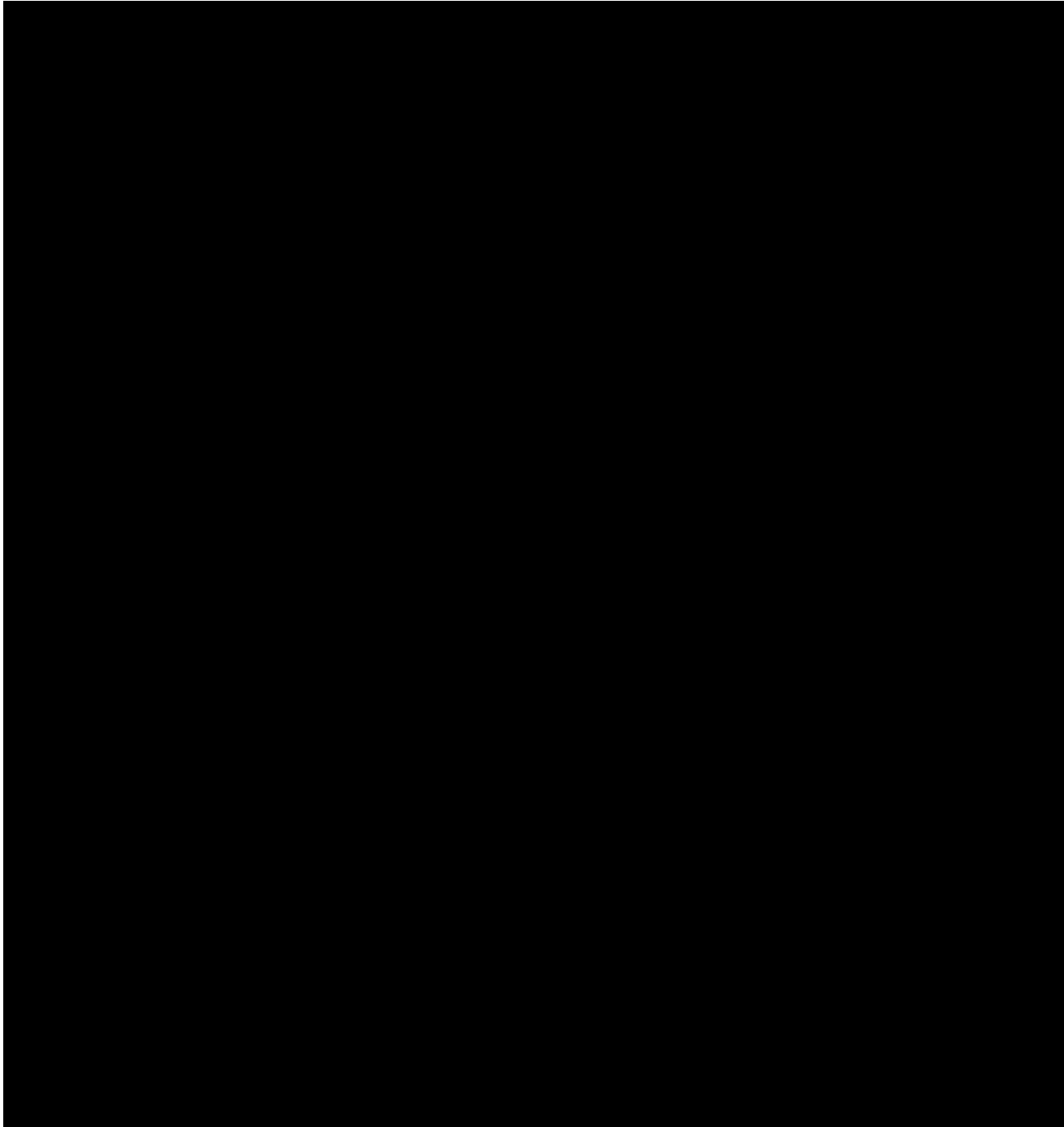


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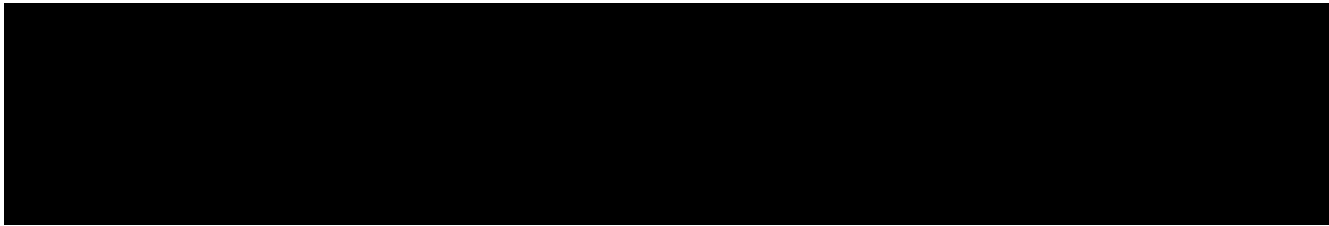


**8.4.2 Double-blind Treatment Phase (12 Weeks)**

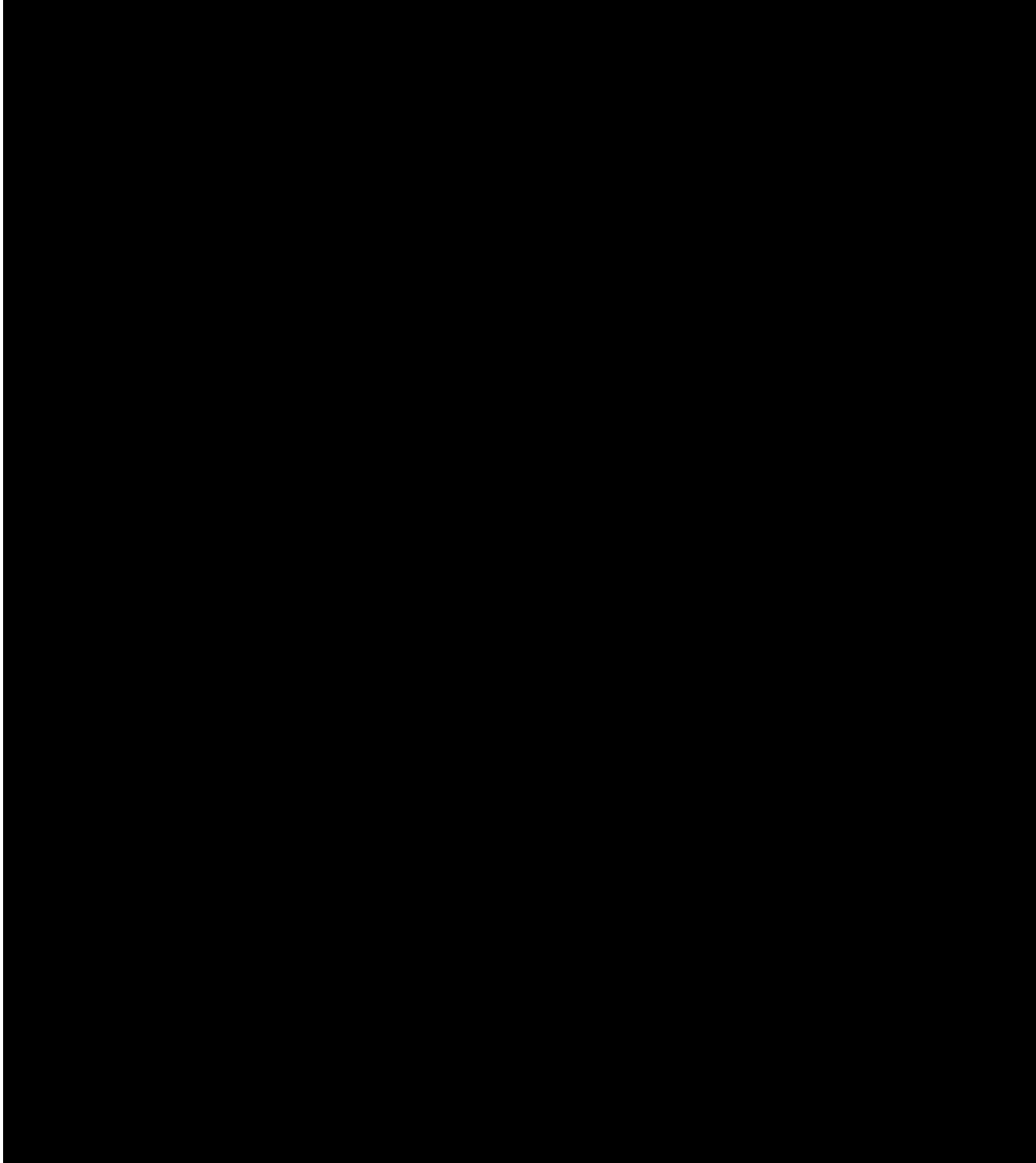
**8.4.2.1 Visit 2 (Randomization) Day 1**



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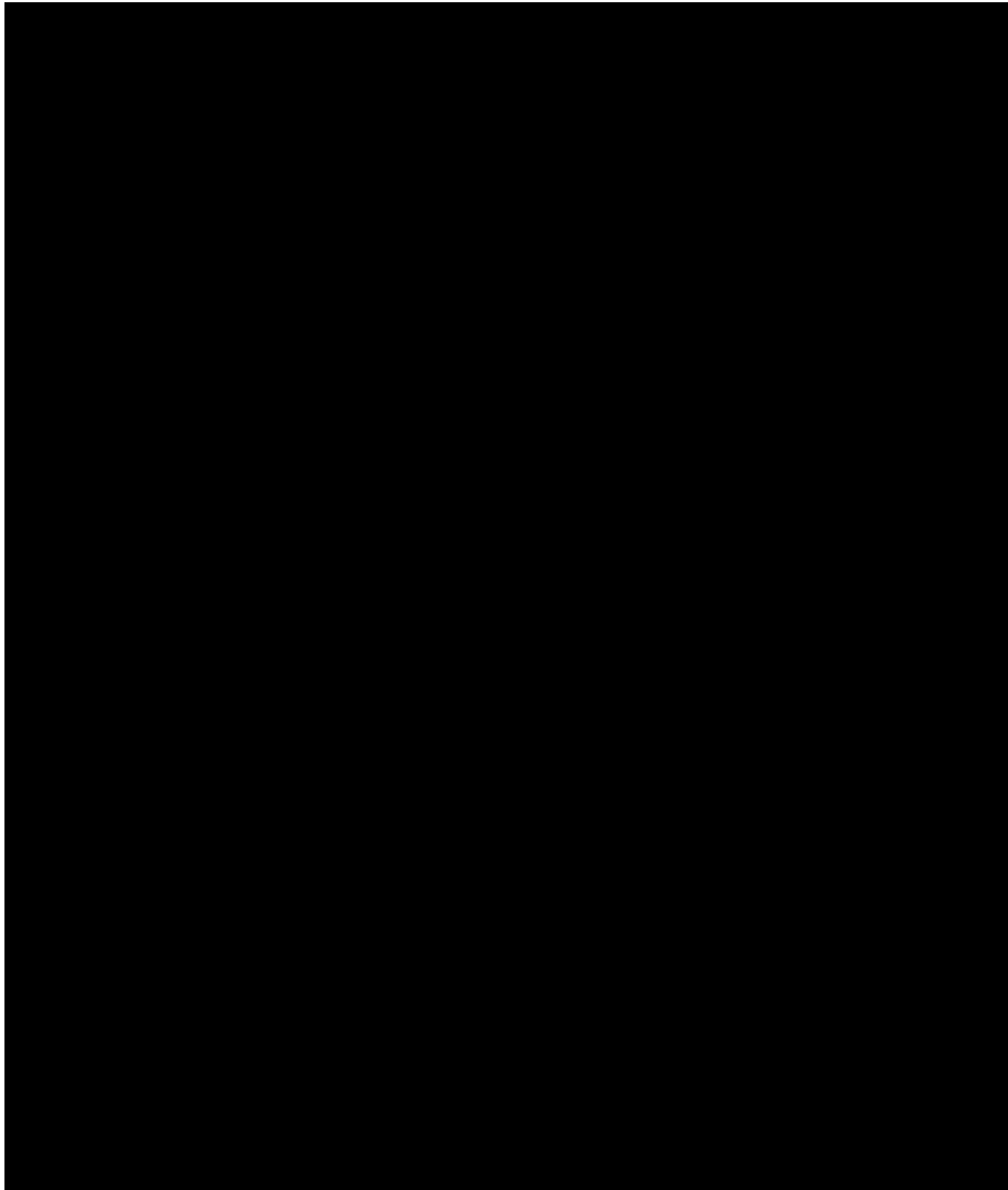


**8.4.2.2 Visits 3 to 6 (Weeks 2 to 8)**



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**8.4.2.3 Visit 7/Early Termination (Week 12)**



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### **8.4.3 Follow-up Period (4 weeks)**

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

During the COVID-19 pandemic, Visit 8 (Follow-up/End of Study) should be conducted remotely for all participants in all cases. [REDACTED]

[REDACTED]

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





## 8.5 Instructions for the Participants



### 8.6 Unscheduled Visits

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

### 8.7 Compliance with Protocol

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

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



## 8.8 Early Discontinuation of Participants

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

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

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

## 8.9 Withdrawal Criteria

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

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

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

### **8.10 Withdrawal from Future Biomedical Research**

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

### **8.11 Study Termination**

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

## **9. Adverse Events**

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

### **9.1 Definitions**

#### **9.1.1 Adverse Event (AE)**

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

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

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

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

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

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

### 9.1.2 Serious Adverse Event (SAE)

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

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

involving at least an overnight stay) at the hospital or emergency ward for observation and/or intervention that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

Hospitalization for elective intervention of a pre-existing condition that did not worsen from baseline is not considered an AE.

**d. Results in persistent disability/incapacity**

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

**e. Is a congenital anomaly/birth defect**

**f. Other situations:**

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

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

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

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

### 9.1.3 Intensity

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

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

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

### 9.1.4 Assessment of Causality

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

### 9.1.5 Follow-up of Adverse Events and Serious Adverse Events

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

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Allergan to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- Prior to database lock, new or updated information will be recorded in the originally completed eCRF. If the event is an SAE, it will also need to be reported on the SAE reporting form. Post database lock, new or updated SAE information will only be reported on the SAE reporting form.
- The investigator will submit any updated SAE data to Allergan within 24 hours of receipt of the information.

## **9.2 Procedures for Reporting Adverse Events**

Any AE must be recorded on the appropriate eCRF.

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

## **9.3 Procedures for Reporting a Serious Adverse Event**

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

### **9.3.1 Regulatory Reporting Requirements for Serious Adverse Events**

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

- Allergan has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. Allergan will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Allergan's policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from Allergan will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

#### 9.4 Exposure to Study Intervention During Pregnancy

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

#### 9.5 ALT or AST Elevations

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



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

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

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

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

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

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

### 9.5.1 Potential Hy's Law Cases

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

- ALT or AST  $\geq 3$  x ULN **AND**
- Total bilirubin  $\geq 2$  x ULN **AND**
- Alkaline phosphatase  $< 2$  x ULN

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

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

### 9.6 Procedures for Unmasking of Study Intervention

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

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

## **10. Administrative Items**

### **10.1 Protection of Human Participants**

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

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

The following process will be followed:

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

### **10.1.2 Compliance with IRB or IEC Regulations**

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

### **10.1.3 Compliance with Good Clinical Practice**

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

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

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

## **10.3 Changes to the Protocol**

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

## **10.4 Data Protection**

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

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

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

## **10.5 Participant Confidentiality**

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

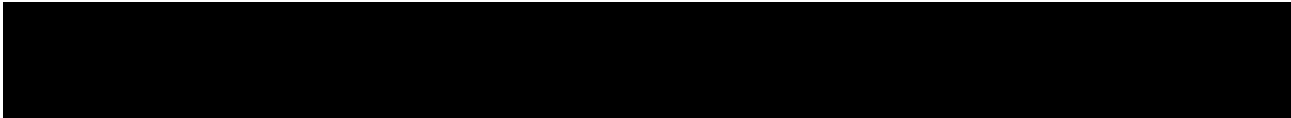
### **10.5.1 Participant Privacy**

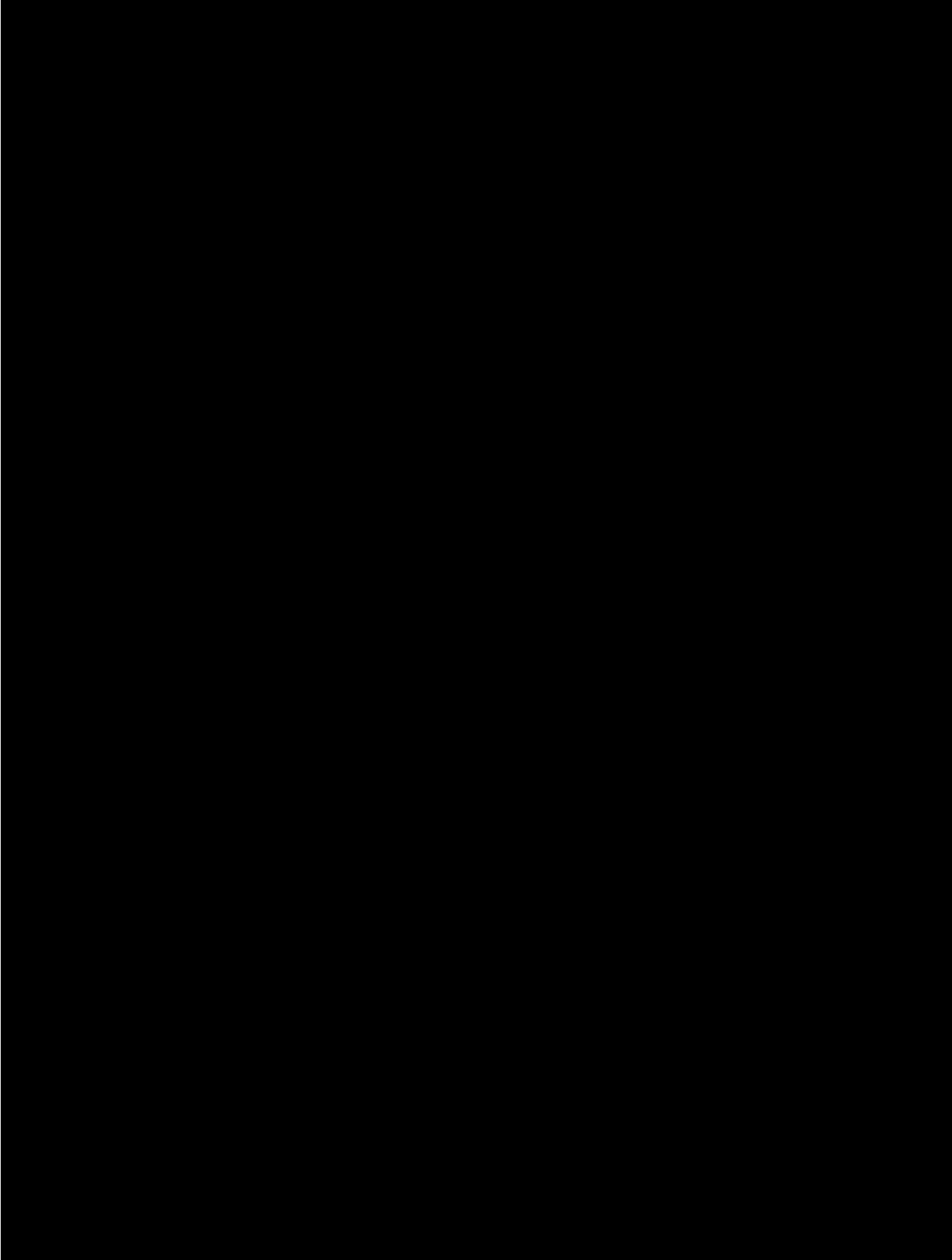
Written authorization and other documentation in accordance with local privacy requirements (where applicable) is to be obtained from each participant prior to enrollment into the study, and/or from the participant's legally authorized representative in accordance with the applicable privacy requirements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

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

## **10.6 Documentation**

### **10.6.1 Source Documents**





Approval Date: 15-May-2020 16:33:54 (GMT)

### **10.6.2 Case Report Form Completion**

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

### **10.6.3 Study Summary**

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

### **10.6.4 Retention of Documentation**

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

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

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

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

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

### **10.7.1 Labeling/Packaging**

### **10.7.2 Clinical Supply Inventory**

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

### **10.7.3 Return or Disposal of Study Intervention and/or Supplies**

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

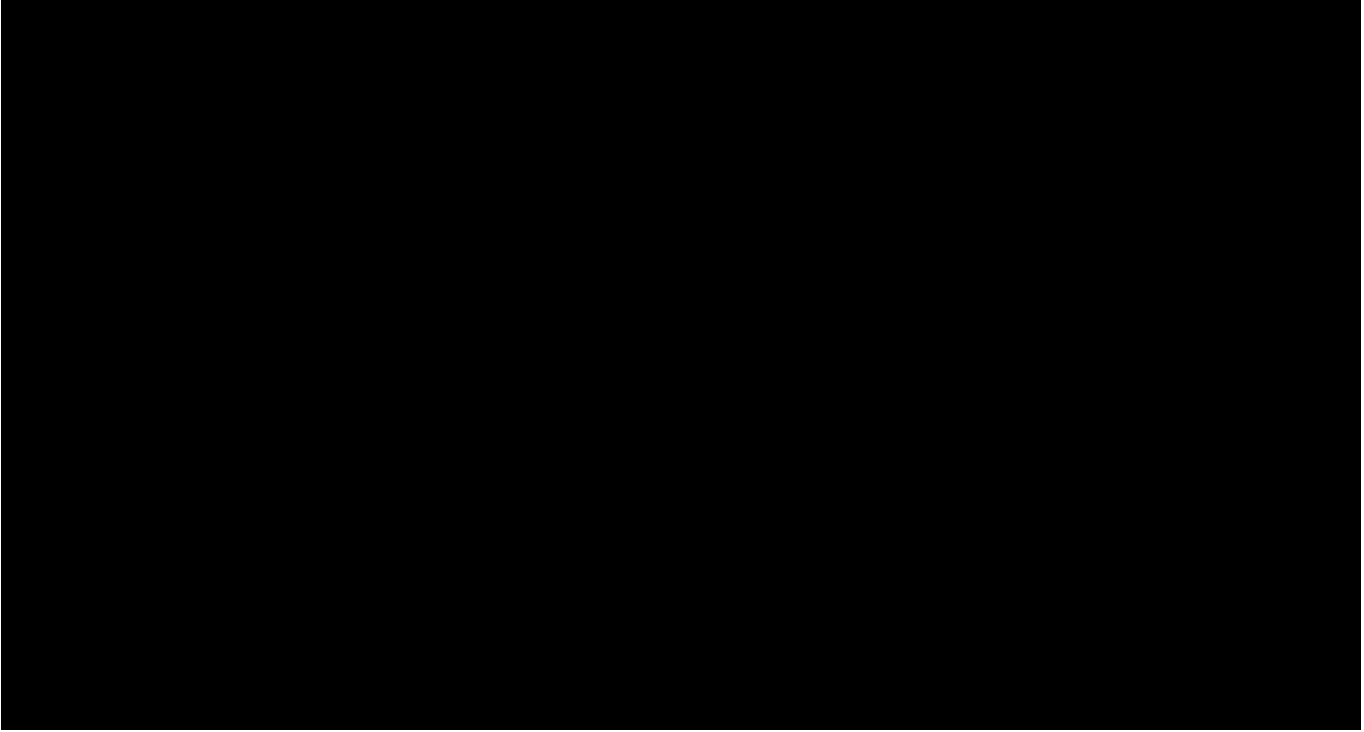
## **10.8 Monitoring by the Sponsor**

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

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



## 10.9 Handling of Biological Specimens



## 10.10 Publications

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

## 10.11 Coordinating Investigator

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

## 11. References

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## **12. Attachments**

### **12.1 International Classification of Headache Disorders, 3<sup>rd</sup> Edition**

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

#### **Coded elsewhere:**

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

#### **General comment**

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

1. When a *new headache with the characteristics of migraine* occurs for the first time in close temporal relation to another disorder known to cause headache, or fulfils other criteria for causation by that disorder, the new headache is coded as a secondary headache attributed to the causative disorder.
2. When *pre-existing migraine* becomes *chronic* in close temporal relation to such a causative disorder, both the initial migraine diagnosis and the

secondary diagnosis should be given. 8.2 *Medication-overuse headache* is a particularly important example of this: both the migraine diagnosis (episodic or chronic) and the diagnosis 8.2 *Medication-overuse headache* should be given when medication overuse is present.

3. When *pre-existing migraine* is made *significantly worse* (usually meaning a twofold or greater increase in frequency and/or severity) in close temporal relation to such a causative disorder, both the initial migraine diagnosis and the secondary headache diagnosis should be given, provided that there is good evidence that the disorder can cause headache.

#### **Introduction**

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

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

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

#### **1.1 Migraine without aura**

*Previously used terms:* Common migraine; hemicrania simplex

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

*Diagnostic criteria:*

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

*Notes:*

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

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

follow resolution of the headache, persisting for up to 48 hours; these are less well studied.

Migraine attacks can be associated with cranial autonomic symptoms and symptoms of cutaneous allodynia.

In young children, photophobia and phonophobia may be inferred from their behaviour.

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

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

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

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

### 1.2 *Migraine with aura*

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

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

#### *Diagnostic criteria:*

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

#### *Notes:*

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

3. Scintillations and pins and needles are positive symptoms of aura.

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

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

The aura is the complex of neurological symptoms that occurs usually before the headache of 1.2 *Migraine with aura*, but it may begin after the headache phase has commenced or continue into the headache phase.

Visual aura is the most common type of aura, occurring in over 90% of patients with 1.2 *Migraine with aura*, at least in some attacks. It often presents as a fortification spectrum: a zigzag figure near the point of fixation that may gradually spread right or left and assume a laterally convex shape with an angulated scintillating edge, leaving absolute or variable degrees of relative scotoma in its wake. In other cases, scotoma without positive phenomena may occur; this is often perceived as being of acute onset but, on scrutiny, usually enlarges gradually. In children and adolescents, less typical bilateral visual symptoms occur that may represent an aura. A visual aura rating scale with high specificity and sensitivity has been developed and validated. Next in frequency are sensory disturbances, in the form of pins and needles moving slowly from the point of origin and affecting a greater or smaller part of one side of the body, face and/or tongue. Numbness may occur in its wake, but numbness may also be the only symptom.

Less frequent are speech disturbances, usually aphasic but often hard to categorize. Systematic studies have demonstrated that many patients with visual aura occasionally have symptoms in the extremities and/or speech symptoms. Conversely, patients with symptoms in the extremities and/or speech or language symptoms almost always also experience visual aura symptoms at least during some attacks. A distinction between migraine with visual aura, migraine with hemiparaesthetic aura and migraine with speech and/or language aura is probably artificial, and therefore not recognized in this classification: they are all coded as 1.2.1 *Migraine with typical aura*.

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

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

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

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

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

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

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

#### 1.2.1 *Migraine with typical aura*

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

*Diagnostic criteria:*

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

##### 1.2.1.1 *Typical aura with headache*

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

*Diagnostic criteria:*

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

##### 1.2.1.2 *Typical aura without headache*

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



*Diagnostic criteria:*

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

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

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

*1.2.2 Migraine with brainstem aura*

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

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

*Diagnostic criteria:*

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

*Notes:*

1. Dysarthria should be distinguished from aphasia.
2. Vertigo does not embrace and should be

distinguished from dizziness.

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

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

There are typical aura symptoms in addition to the brainstem symptoms during most attacks. Many patients who have attacks with brainstem aura also report other attacks with typical aura and should be coded for both 1.2.1 *Migraine with typical aura* and 1.2.2 *Migraine with brainstem aura*.

Many of the symptoms listed under criterion B1 may occur with anxiety and hyperventilation, and are therefore subject to misinterpretation.

*1.2.3 Hemiplegic<sup>1</sup> migraine*

*Description:* Migraine with aura including motor weakness.

*Diagnostic criteria:*

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

*Notes:*

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

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

*1.2.3.1 Familial hemiplegic migraine (FHM)*

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

*Diagnostic criteria:*

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

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

It has been shown that 1.2.3.1 *Familial hemiplegic migraine* very often presents with brainstem symptoms in addition to the typical aura symptoms, and that headache almost always occurs. Rarely, during FHM attacks, disturbances of consciousness (sometimes including coma), confusion, fever and cerebrospinal fluid (CSF) pleocytosis can occur.

1.2.3.1 *Familial hemiplegic migraine* may be mistaken for epilepsy and treated (unsuccessfully) as such. FHM attacks can be triggered by (mild) head trauma. In approximately 50% of FHM families, chronic progressive cerebellar ataxia occurs independently of the migraine attacks.

*1.2.3.1.1 Familial hemiplegic migraine type 1 (FHM1)**Diagnostic criteria:*

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

*1.2.3.1.2 Familial hemiplegic migraine type 2 (FHM2)**Diagnostic criteria:*

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

*1.2.3.1.3 Familial hemiplegic migraine type 3 (FHM3)**Diagnostic criteria:*

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

*1.2.3.1.4 Familial hemiplegic migraine, other loci**Diagnostic criteria:*

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

*1.2.3.2 Sporadic hemiplegic migraine (SHM)*

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

*Diagnostic criteria:*

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

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

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

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

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

#### 1.2.4 Retinal migraine

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

*Diagnostic criteria:*

- A. Attacks fulfilling criteria for 1.2 *Migraine with aura* and criterion B below
- B. Aura characterized by both of the following:
  1. fully reversible, monocular, positive and/or negative visual phenomena (e.g. scintillations, scotomata or blindness) confirmed during an attack by either or both of the following:
    - a. clinical visual field examination
    - b. the patient's drawing of a monocular field defect (made after clear instruction)
  2. at least two of the following:
    - a. spreading gradually over  $\geq 5$  minutes
    - b. symptoms last 5–60 minutes
    - c. accompanied, or followed within 60 minutes, by headache
- C. Not better accounted for by another ICHD-3 diagnosis, and other causes of amaurosis fugax have been excluded.

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

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

### 1.3 Chronic migraine

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

*Diagnostic criteria:*

- A. Headache (migraine-like or tension-type-like<sup>1</sup>) on  $\geq 15$  days/month for  $>3$  months, and fulfilling criteria B and C
- B. Occurring in a patient who has had at least five attacks fulfilling criteria B–D for 1.1 *Migraine without aura* and/or criteria B and C for 1.2 *Migraine with aura*
- C. On  $\geq 8$  days/month for  $>3$  months, fulfilling any of the following<sup>2</sup>:
  1. criteria C and D for 1.1 *Migraine without aura*
  2. criteria B and C for 1.2 *Migraine with aura*
  3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
- D. Not better accounted for by another ICHD-3 diagnosis.<sup>3–5</sup>

*Notes:*

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

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

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

#### 1.4 *Complications of migraine*

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

##### 1.4.1 *Status migrainosus*

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

*Diagnostic criteria:*

- A. A headache attack fulfilling criteria B and C
- B. Occurring in a patient with 1.1 *Migraine without aura* and/or 1.2 *Migraine with aura*, and typical of previous attacks except for its duration and severity
- C. Both of the following characteristics:
  1. unremitting for >72 hours<sup>1</sup>
  2. pain and/or associated symptoms are debilitating<sup>2</sup>
- D. Not better accounted for by another ICHD-3 diagnosis.

*Notes:*

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

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

##### 1.4.2 *Persistent aura without infarction*

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

*Diagnostic criteria:*

- A. Aura fulfilling criterion B
- B. Occurring in a patient with 1.2 *Migraine with aura* and typical of previous auras except that one or more aura symptoms persists for  $\geq 1$  week
- C. Neuroimaging shows no evidence of infarction
- D. Not better accounted for by another ICHD-3 diagnosis.

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

##### 1.4.3 *Migrainous infarction*

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

*Diagnostic criteria:*

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

*Note:*

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

*Comments:* Ischaemic stroke in a migraine sufferer may be categorized as cerebral infarction of other cause coexisting with 1. *Migraine*, cerebral infarction of other cause presenting with symptoms resembling 1.2 *Migraine with aura*, or cerebral infarction occurring during the course of a typical attack of 1.2 *Migraine with aura*. Only the last fulfils criteria for 1.4.3 *Migrainous infarction*.

1.4.3 *Migrainous infarction* mostly occurs in the posterior circulation and in younger women. A twofold increased risk of ischaemic stroke in patients with 1.2 *Migraine with aura* has been demonstrated in several population-based studies. However, it should be noted that these infarctions are not migrainous infarctions. The mechanisms of the increased risk of ischaemic stroke in migraine sufferers remain unclear; likewise, the relationship between increased risk and frequency of aura and the nature of aura symptoms denoting the increase in risk are unknown. Most studies have shown a lack of association between 1.1 *Migraine without aura* and ischaemic stroke.

1.4.4 *Migraine aura-triggered seizure*

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

*Diagnostic criteria:*

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

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

1.5 *Probable migraine*

*Previously used term:* Migrainous disorder.

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

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

*Diagnostic criteria:*

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

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

1.5.1 *Probable migraine without aura Diagnostic criteria:*

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



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

#### 1.5.2 Probable migraine with aura

##### Diagnostic criteria:

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

### 1.6 Episodic syndromes that may be associated with migraine

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

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

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

#### 1.6.1 Recurrent gastrointestinal disturbance

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

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

##### Diagnostic criteria:

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

#### 1.6.1.1 Cyclic vomiting syndrome

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

##### Diagnostic criteria:

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

##### Note:

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

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

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

#### 1.6.1.2 Abdominal migraine

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

*Diagnostic criteria:*

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

*Note:*

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

*Comments:* Pain of 1.6.1.2 *Abdominal migraine* is severe enough to interfere with normal daily activities.

In young children, the presence of headache is often overlooked. A careful history of presence or absence of headache must be taken and, when headache or head pain during attacks is identified, a diagnosis of 1.1 *Migraine without aura* should be considered.

Children may find it difficult to distinguish anorexia from nausea. Pallor is often accompanied by dark shadows under the eyes. In a few patients, flushing is the predominant vasomotor phenomenon.

Most children with abdominal migraine will develop migraine headache later in life.

*1.6.2 Benign paroxysmal vertigo*

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

*Diagnostic criteria:*

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

*Notes:*

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

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

*1.6.3 Benign paroxysmal torticollis*

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

*Diagnostic criteria:*

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

*Notes:*

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

*Comments:* The child's head can be returned to the neutral position during attacks: some resistance may be encountered but can be overcome.

These observations need further validation by patient diaries, structured interviews and longitudinal data collection.

1.6.3 *Benign paroxysmal torticollis* may evolve into

1.6.2 *Benign paroxysmal vertigo* or 1.2 *Migraine with aura* (particularly 1.2.2 *Migraine with brainstem aura*) or cease without further symptoms.

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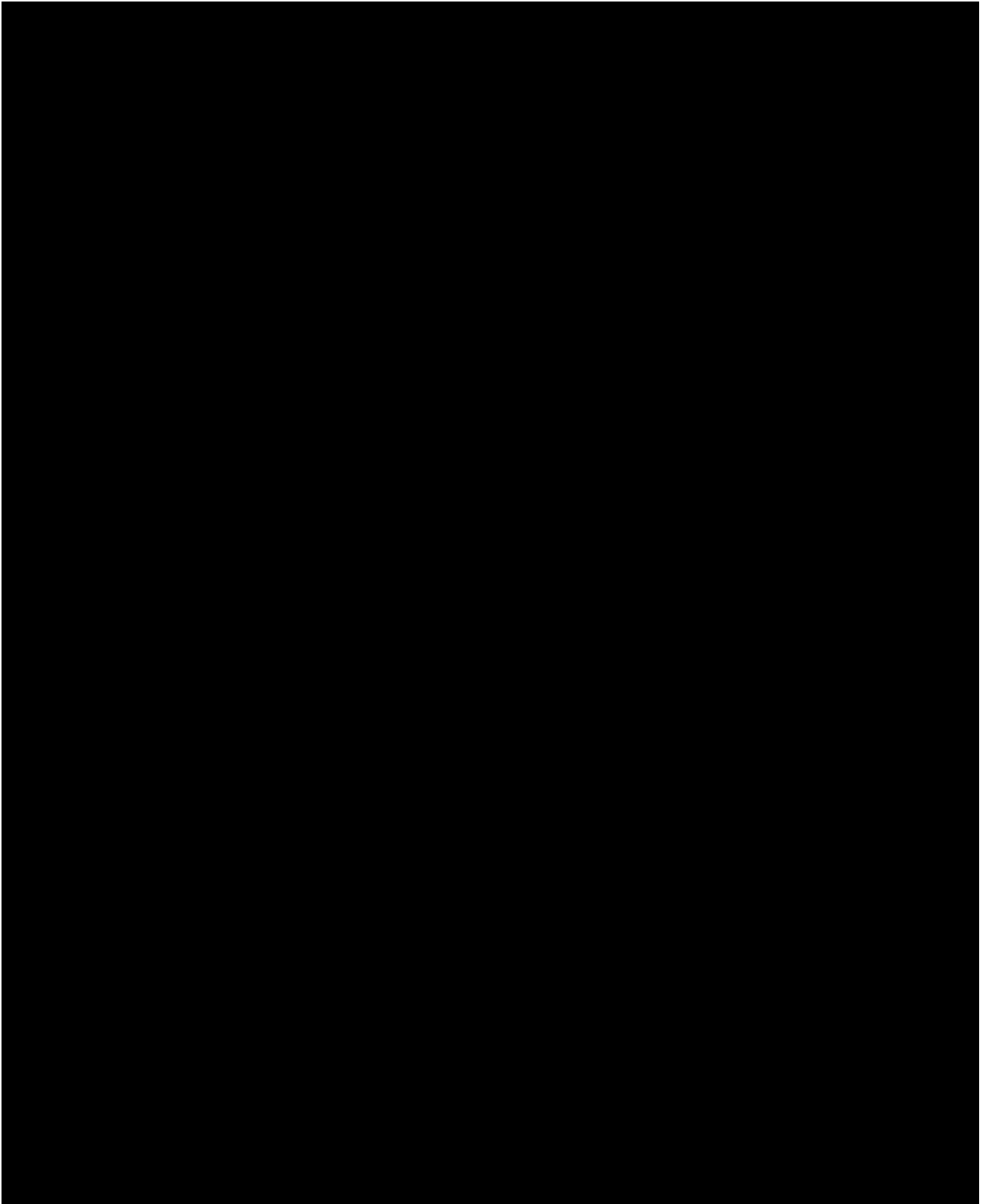
### 1.6.3 Benign paroxysmal torticollis

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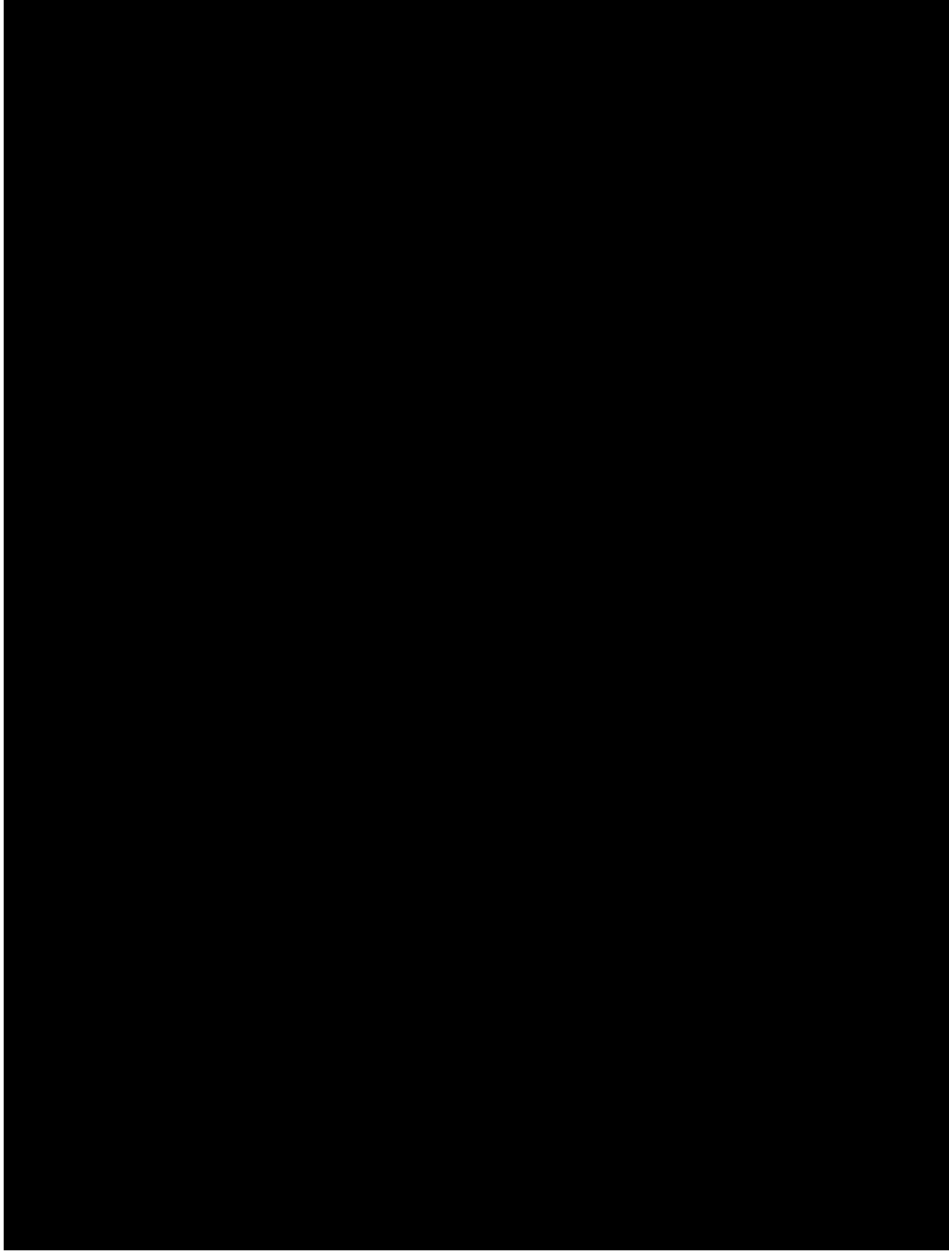
Giffin NJ, Benton S and Goadsby PJ. Benign paroxysmal torticollis of infancy: four new cases and linkage to CACNA1A mutation. *Dev Med Child Neurol* 2002; 44: 490–493.

Rosman NP, Douglass LM, Sharif UM, et al. The neurology of benign paroxysmal torticollis of infancy: report of 10 new cases and review of the literature. *J Child Neurol* 2009; 24: 155–160.

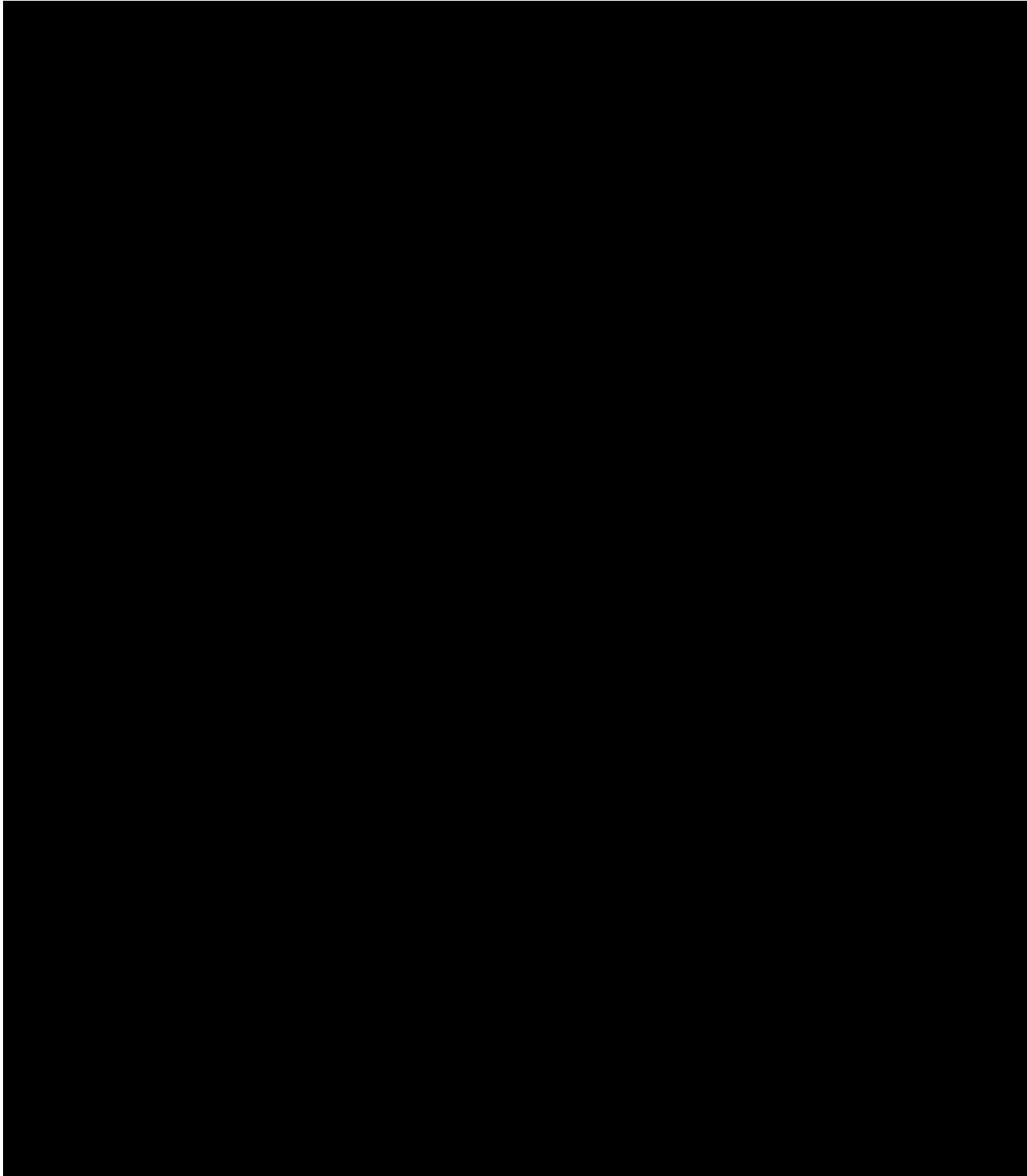
## 12.2 Examples of Prohibited Medications



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

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

For efficacy:

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

For tolerability:

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

## 12.4 Glossary of Abbreviations

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

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

**Protocol Approval Form**

**Protocol Number:** 3101-301-002 Amendment 3

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

*Approver:*

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May 14, 2020

[Redacted Name]

Date

Vice President, Neuroscience Development

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