NCT02848326

Study ID: CGP-MD-01

Title: A PHASE 2/3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF MULTIPLE DOSING REGIMENS OF ORAL AGN-241689 IN EPISODIC MIGRAINE PREVENTION

Protocol Amendment 2 Date: 11 Sept 2017

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A PHASE 2/3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF MULTIPLE DOSING REGIMENS OF ORAL AGN-241689 IN EPISODIC MIGRAINE PREVENTION

Protocol Number:	CGP-MD-01, Amendment 2
Phase:	2/3
Name of Investigational Product:	AGN-241689
Sponsor:	Allergan Pharmaceuticals International Limited Clonshaugh Industrial Estate, Coolock, Dublin 17, Ireland
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Emergency Telephone Number(s):	[redacted]
Serious Adverse Event Reporting Fax Number(s):	[redacted]
Allergan Medical Monitor Contact Information:	Refer to the Study Contacts Page
Allergan Signatory:	[redacted]
Original Protocol Date:	09 May 2016
Protocol Amendment 1 Date:	11 Nov 2016
Protocol Amendment 2 Date:	11 Sep 2017

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 Institutional Review Board (IRB), Independent Ethics Committee (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 investigational product(s), and their trial-related duties and functions.

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

Investigator Printed Name	Signature	Date

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Protocol Summary

Study Compound(s): AGN-241689

Phase: 2/3

Study Objective(s):

To evaluate the safety and tolerability of the following doses and dose regimens of AGN-241689 (10-mg once daily [QD], 30-mg QD, 30-mg twice daily [BID], 60-mg QD, and 60-mg BID for the prevention of episodic migraine.

To characterize the dose/response relationship across the following doses and dose regimens (10-mg QD, 30-mg QD, 30-mg BID, 60-mg QD, and 60-mg BID) for the prevention of episodic migraine.

To prospectively test for superiority of the following doses and dose regimens of AGN-241689 (10-mg QD, 30-mg QD, 30-mg BID, 60-mg QD, and 60-mg BID) versus placebo for the prevention of episodic migraine in this pivotal trial.

Clinical Hypotheses: In individuals with episodic migraine, at least one active treatment arm, 60 mg QD or 60 mg BID is superior to placebo as measured by the change from baseline in mean monthly migraine/probable migraine (MPM) headache days across the 12-week treatment period.

AGN-241689 has an acceptable safety and tolerability profile in patients with episodic migraine.

Study Design

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

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

Test Product: AGN-241689 10-mg tablets, AGN-241689 30-mg tablets, AGN-241689 60-mg tablets. Investigational product will be over-encapsulated to maintain the blind.

Control: AGN-241689 placebo tablets. Placebo tablets will be over-encapsulated to maintain the blind.

Dosage/Dose Regimen: 10-mg AGN-241689 QD, 30-mg AGN-241689 QD, 60-mg AGN-241689 QD, 30-mg AGN-241689 BID, and 60-mg AGN-241689 BID will be administered for 12 weeks duration

Randomization/Stratification: Patients will be randomized to the following 6 arms in a 2:1:2:1:2:1 ratio:

- Placebo (n = 180)
- AGN-241689 10-mg QD (n = 90)
- AGN-241689 30-mg QD (n = 180)
- AGN-241689 30-mg BID (n = 90)
- AGN-241689 60-mg QD (n = 180)
- AGN-241689 60-mg BID (n = 90)

To maintain the blind, investigational product will be over-encapsulated and administered orally for 12 weeks to all patients. Patients, therefore, will receive either placebo twice daily, a morning dose of AGN-241689 with an evening dose of placebo, or AGN-241689 twice daily.

No stratification will be performed.

Visit Schedule: Individual patient participation will begin with a 4-week Screening/Baseline Period. Patients 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 Safety 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 (Safety Follow-up). For details, please see Table 1–1, Schedule of Evaluations.

Study Population Characteristics

Number of Patients: Approximately 810 patients will be randomized into the study

Condition/Disease: Migraine with aura or Migraine without aura

Key Inclusion Criteria:

- Male or female patients age 18 to 75 years, inclusive, at Visit 1.
- At least a 1-year history of migraine with or without aura consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd edition, beta version (ICHD-3 beta, 2013; Section 12.1.1)
- Age of the patient at the time of migraine onset < 50 years
- History of 4 to 14 migraine/probable migraine headache days per month (see Section 6.1.1 for definition) in the 3 months prior to Visit 1in the investigator's judgment
- 4 to 14 migraine/probable migraine headache days in the 28-day baseline period per electronic diary (eDiary)

Key Exclusion Criteria:

- Has a history of migraine accompanied by diplopia or decreased level of consciousness, or retinal migraine as defined by ICHD-3 beta version, 2013
- 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 beta version, 2013

[redacted]

- Usage of opioids or barbiturates >2 days/month**,** triptans or ergots ≥ 10 days/month, or simple analgesics (eg, aspirin, non-steroidal anti-inflammatory drugs, acetaminophen) ≥ 15 days/month in the 3 months prior to Visit 1 per investigator's judgment, or during the baseline period (barbiturates are excluded during the baseline period and for the duration of the study [see Section 12.2 Examples of Prohibited Medications])
- Patients with clinically significant hematologic, endocrine, cardiovascular, pulmonary, hepatic, gastrointestinal, or neurologic disease.

Response Measures

Efficacy: Frequency of migraine or probable migraine headache days, headache days, and acute medication use days

[redacted]

General Statistical Methods and Types of Analyses: All safety analyses will be performed using the safety population, consisting of all patients who received at least one dose of the study treatment. For safety analyses, the patients will be analyzed according to the actual treatment received at the first study treatment visit (rather than as randomized). All efficacy analyses will be performed using the modified intent-to-treat (ITT) population, consisting of all randomized patients who received at least 1 dose of study treatment, had an evaluable baseline period of diary data, and had at least 1 evaluable post-baseline 4-week (Weeks 1-4, 5-8, and 9-12) of diary data. For efficacy analyses, the patients will be analyzed according to randomization assignment, regardless of actual treatment received.

The primary efficacy endpoint is the change from baseline in mean monthly MPM headache days across the 12-week treatment period. Comparisons between each dose group and placebo 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 and treatment group by visit interaction as categorical fixed effects. It will also include the baseline score and baseline-by-visit interaction as covariates. Pairwise contrasts in the MMRM model will be used to make the pairwise comparisons of dose to placebo. A sensitivity analysis 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. The sensitivity analysis will be done using a pattern-mixture model (PMM), under which data could be missing-not-at-random (MNAR), with repeated analyses combined via the multiple imputation (MI) procedure. An additional sensitivity, MI in conjunction with robust regression, will be performed in case of non-normality for the primary efficacy endpoint.

Secondary efficacy endpoints include: (1) Change from baseline in mean monthly headache days across the 12-week treatment period; (2) Proportion of patients with at least a 50% reduction in mean monthly MPM days across the 12-week treatment period; (3) Change from baseline in mean monthly acute medication use days across the 12-week treatment period.

Summary tables for each treatment and for each measurement time will include the number of patients and descriptive statistics (mean, standard deviation, median, minimum and maximum) and/or response frequencies.

For continuous variables, pairwise comparisons will be analyzed using MMRM. For variables where data is binary, comparisons between treatment groups will be done by pairwise contrasts using logistic regressions for variables with only one postbaseline assessment or using generalized linear mixed model for variables with multiple postbaseline assessments.

The overall type I error rate for multiple comparisons across active treatment doses and the primary and secondary efficacy parameters will be controlled at the 0.05 level using a graphical approach by Bretz et al (2011). The weighting strategy of the multiple comparisons is designed to allocate initial alpha equally to the QD and BID dose regimens. Within each dosing regimen, individual AGN-241689 doses will be tested in a hierarchical order from high to low dose, i.e. for primary efficacy endpoint, low dose can be tested only if high dose comparison shows statistical significance. In addition, for a given dose comparison versus placebo, the strategy has the primary endpoint as gatekeeper to the secondary endpoints so that secondary endpoints can be tested only if primary hypothesis of the corresponding dose comparison reaches statistical significance. Weighted Bonferroni tests will be used for testing the hypotheses. A complete decision-flow graph and details of the graphical multiple comparison procedure will be presented in the statistical analysis plan of this study.

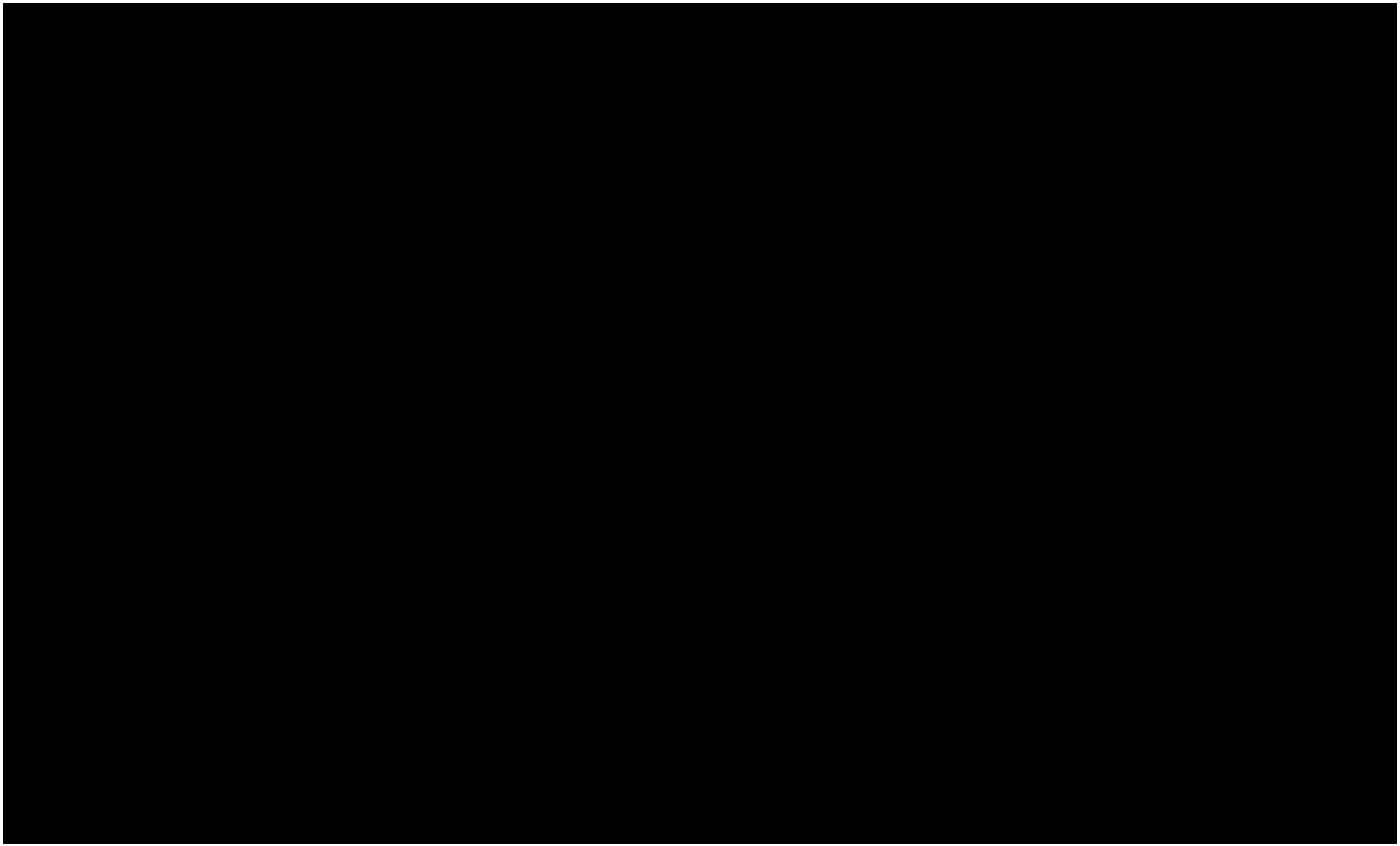
Sample Size Calculation:

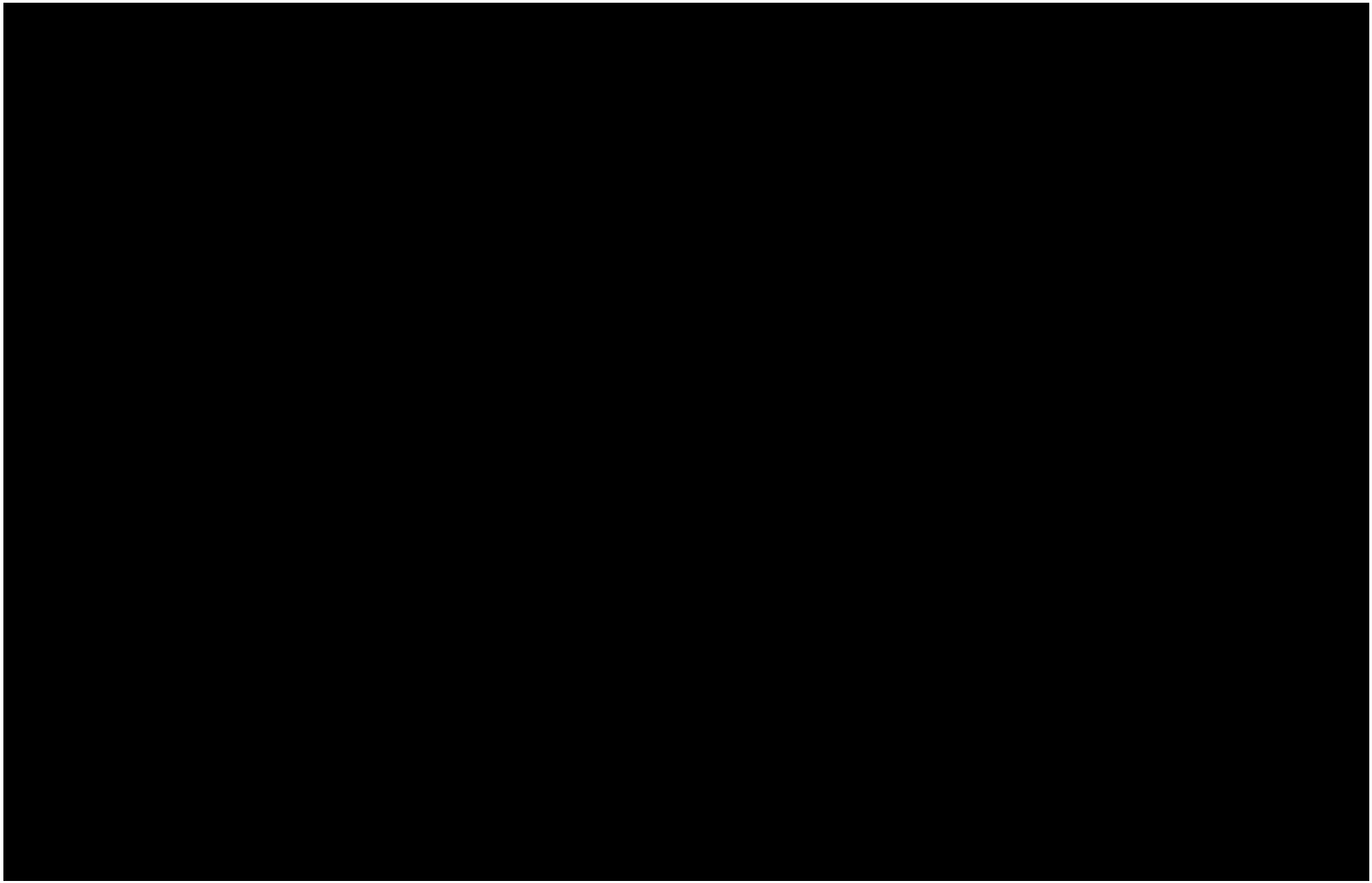
The assumptions and corresponding power assessments for the primary efficacy endpoint are shown in the table below. The treatment difference assumption is based on results from other episodic migraine prevention studies: the placebo-adjusted reduction in monthly migraine days ranged from 1.1 to 2 days (topiramate [Silberstein et al, 2004 and Brandes et al, 2004], telcagepant [Ho et al, 2014], and CGRP monoclonal antibodies Ph2 studies

[Dodick et al, 2014; Dodick et al, 2014; Bigal et al, 2015; Sun et al, 2016], and their Ph3 studies results reported from American Headache Society & American Academy of Neuroscience 2017). Common standard deviation is estimated based on blinded interim data assessments of this study. Power is calculated via 10,000 simulations based on multiplicity adjustment.

	60mg BID (n=90)	**30mg BID (n=90)**	**60mg QD (n=180)**	**30mg QD (n=180)**	**10mg QD (n=90)**
Assumed Treatment difference vs. placebo (placebo n = 180)	-1.6	-1.5	-1.5	-1.4	-1.2
Effect size (Common SD = 3.0)	0.53	0.5	0.5	0.47	0.4
Power	**97.0%**	**91.4%**	**99.3%**	**98.1%**	**80.3%**

QD = once daily; BID = twice daily; SD = standard deviation.





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 25-55 years. Approximately one-third of these migraineurs have 3 or more migraine headaches per month, and over half report severe impairment or the need for bed rest (Lipton et al, 2005, Lipton et al, 2007). In the US alone, work loss due to migraine is estimated to cost ~ $13 billion annually (Hu et al, 1999). Prevalence is similar in Europe, with migraine headache affecting on average 17.6% of women and 8% of men (Stovner, 2010). It is currently ranked by the World Health Organization (WHO) as 19th among causes of disability (Katsarava et al, 2012).

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, exam, and the exclusion of other headache disorders. Physicians apply clinical criteria to guide diagnoses and subsequent treatment. Episodic migraine (EM) is a syndrome diagnosis applied to patients with migraine (with or without aura) who have 1-14 headache days per month. Chronic migraine (CM) is a specific ICHD-3 beta version diagnosis applied to a subset of patients with ≥15 headache days per month (Katsarava et al, 2011; Olesen et al, 2006; ICHD-3 beta version, 2013). This study will evaluate the efficacy, safety and tolerability of AGN-241689 in patients with episodic migraine.

1.2 Overview of AGN-241689

AGN-241689 is a potent, selective oral calcitonin gene-related peptide (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 (i.e, external jugular vein) are increased during a migraine attack and exogenously administered CGRP has been shown to trigger migraine-like headache in migraineurs. The majority (80 to 90%) of trigeminal Aδ fibers that innervate the dura contain CGRP, suggesting that these fibers may be involved in sterile neurogenic inflammation and migraine pain transmission. Furthermore, the CGRP receptor is present on human meningeal and cerebral blood vessels. These observations suggest that activation of the trigeminovascular system, with release of

CGRP, may play a key role in migraine pathogenesis and that inhibition of CGRP may yield a novel therapeutic approach to treating migraine.

The ability of CGRP inhibition to induce pain relief in the acute treatment of migraine was initially observed with an intravenous (IV) formulation of olcegepant (Olesen et al, 2004), and replicated by Merck & Co., Inc with an oral formulation of MK-0974 (telcagepant), a highly selective CGRP receptor antagonist (CGRP RA). 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 alanine aminotransferase (ALT) increases were observed with telcagepant. For this reason, the development of these oral CGRP antagonists was stopped.

Recently, several phase 2 trials have been published that further establish proof-of-concept of CGRP as a therapeutic target in the prevention of episodic and chronic migraine (Dodick DW, Goadsby PJ, Silberstein SD, et al, 2014; Bigal et al, 2015; Dodick DW, Goadsby PJ, Spierings EL, et al, 2014). Specifically, TEV-48125, LY-2951742, and ALD-403 are injectable monoclonal antibodies shown to be efficacious in the prevention of migraine that act by targeting CGRP and blocking the CGRP pathway thought to be involved in migraine pathophysiology. AGN-241689 was chemically designed to minimize the potential for reactive metabolites, thereby reducing the risk of liver toxicity that has been observed with telcagepant, and MK-3027. An extensive Phase 1 program, including a 28-day multiple dose study of doses up to 170 mg QD, has been conducted to assess hepatic effects of AGN-241689. To date, no safety signal in hepatic lab parameters has been observed in either preclinical or clinical studies conducted with AGN-241689.

The purpose of this study is to prospectively assess the safety, tolerability and efficacy of 10-, 30- and 60-mg once daily (QD) and 30- and 60-mg twice daily (BID) doses of AGN-241689 compared with placebo in the prevention of episodic migraine, in a randomized, double-blind, placebo-controlled Phase 2/3 study. This study is designed to be a pivotal trial, and will be used to support registration applications.

Additional information on non-clinical pharmacology, toxicology, and pharmacokinetic properties of AGN-241689 can be found in the Investigator's Brochure.

1.3 Rationale For Doses and Dose Regimens Selected

The ability of a CGRP antagonist to block capsaicin induced increases in dermal blood flow has been used as a pharmacodynamic assay to determine doses which inhibit peripheral CGRP function and estimate potentially effective clinical doses in migraine (Hewitt et al, 2011; Li et al, 2014). Based on this model, doses of AGN-241689 of 10 mg QD, 30 mg QD, and 60 mg QD are potentially effective doses for migraine prevention. In addition, the PK characteristics of AGN-241689 suggest the possibility that a BID dosing regimen may provide better 24-hour CGRP inhibition than does a QD regimen. Based on these considerations, this study will investigate doses of AGN-241689 10 mg, 30 mg, and 60 mg QD and doses of 30 mg and 60 mg BID for 12 weeks.

Prior testing in the Phase 1 program suggests that the range of doses tested will be well-tolerated and safe in humans. Daily dosing of 170 mg per day was studied in healthy subjects for 28 days; this was well-tolerated with an unremarkable AE profile and no significant elevations of ALT or aspartate aminotransferase (AST) were observed. Results from the 28-day multiple dose study and other Phase 1 studies support the safety and tolerability of the dose range tested in this protocol.

2. Study Objectives and Clinical Hypotheses

2.1 Study Objectives

To evaluate the safety and tolerability of the following doses and dose regimens of AGN-241689 (10-mg QD, 30-mg QD, 30-mg BID, 60-mg QD, and 60-mg BID) for the prevention of episodic migraine.

To characterize the dose/response relationship across the following doses and dose regimens (10 mg QD, 30 mg QD, 30 mg BID, 60 mg QD, and 60 mg BID) for the prevention of episodic migraine.

To prospectively test for superiority of the following doses and dose regimens of AGN-241689 (10-mg QD, 30-mg QD, 30-mg BID, 60-mg QD, and 60-mg BID) versus placebo for the prevention of episodic migraine in this pivotal trial

2.2 Clinical Hypotheses

In individuals with episodic migraine, at least one active treatment arm, 60 mg QD or 60 mg BID is superior to placebo as measured by the change from baseline in mean monthly MPM days across the 12-week treatment period.

AGN-241689 has an acceptable safety profile and is well tolerated in patients with episodic migraine.

3. Study Design

3.1 Structure

This is a multi-center, randomized, double-blind, placebo-controlled, parallel group study conducted at approximately 75 sites in the United States. Approximately 810 patients will be randomized to one of six treatment arms (placebo, 10-mg QD, 30-mg QD, 30-mg twice daily, 60-mg QD, and 60-mg twice daily) in a 2:1:2:1:2:1 ratio as follows::

- Placebo (n = 180)
- AGN-241689 10-mg QD (n = 90)
- AGN-241689 30-mg QD (n = 180)
- AGN-241689 30-mg BID (n = 90)
- AGN-241689 60-mg QD (n = 180)
- AGN-241689 60-mg BID (n = 90)

More patients will be allocated to the 30-mg QD and 60-mg QD arms to maximize the power to detect a difference from placebo in the primary endpoint. Although fewer patients are allocated to the BID regimen arms and the 10-mg QD arm, these are still adequately powered to detect a clinically meaningful difference.

To maintain the blind, investigational product will be administered orally twice daily for 12 weeks to all patients. Patients, therefore, will receive either placebo twice daily, a morning dose of AGN-241689 with an evening dose of placebo, or AGN-241689 twice daily.

Patient participation will begin with a 4-week Screening/Baseline Period. Patients 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 Safety 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 (Safety Follow-up). For details, please see Table 1–1, Schedule of Visit and Procedures.

3.2 Efficacy Assessments

Efficacy assessments will be based on information recorded by the patient. 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, probable migraine, and headache days per the criteria listed in Sections 6.1.1.

[redacted]

3.5 Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will be established to review unblinded safety data and summary reports, identify any safety issues and trends, and make recommendations to the Sponsor, including modification or early termination of a 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.

3.6 Adjudication Committee

An Adjudication Charter will be established and will describe the process for the blinded surveillance, monitoring, and adjudication by the Clinical Adjudication Committee of events of post-treatment elevations of ALT and/or AST ≥ 3 x the upper limit of normal (ULN) in the AGN-241689 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 AGN-241689.

4. Study Population and Entry Criteria

4.1 Number of Patients

Approximately 810 patients will be randomized at approximately 75 sites in the US.

4.2 Inclusion Criteria

The following are requirements for entry into the study:

1. Written informed consent and patient privacy information (eg, Written Authorization for Use and Release of Health and Research Study Information) obtained from the patient prior to initiation of any study-specific procedures.

2. Male or female patients ages 18 to 75 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 International Classification of Headache Disorders, 3rd edition, beta version (ICHD-3 beta, 2013; Section 12.1.1)

4. Age of the patient at the time of migraine onset < 50 years

5. History of 4 to 14 migraine/probable migraine headache days per month (see Section 6.1.1 for definition) on average in the 3 months prior to Visit 1 in the Investigator's judgment

6. 4 to 14 migraine/probable migraine headache days in the 28-day baseline period per electronic diary (eDiary)

7. Completed at least 20 out of 28 days in the eDiary during baseline period and is able to read, understand, and complete the study questionnaires and eDiary per Investigator's judgment.

[redacted]

4.3 Exclusion Criteria

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

1. Difficulty distinguishing migraine headaches from tension-type or other headaches

2. Has a history of migraine with accompanied by diplopia or decreased level of consciousness or retinal migraine as defined by ICHD-3 beta version, 2013

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 beta version, 2013

[redacted]

8. Usage of opioids or barbiturates > 2 days/month**,** triptans or ergots ≥ 10 days/month, or simple analgesics (eg, aspirin, non-steroidal anti-inflammatory drugs [NSAIDs], acetaminophen) ≥ 15 days/month in the 3 months

prior to Visit 1 per investigator's judgment, or during the baseline period (barbiturates are excluded during the baseline period and for the duration of the study [see Section 12.2 Examples of Prohibited Medications])

9. Woman is pregnant, planning to become pregnant during the course of the study, or currently lactating. Women of childbearing potential must have a negative urine pregnancy test at Visit 1 and Visit 2

[redacted]

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

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

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

[redacted]

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

[redacted]

[redacted]

4.4 Permissible and Prohibited Medications/Treatments

4.4.1 Permissible Medications/Treatments

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

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

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

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

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

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

4.4.2 Prohibited Medications/Treatments

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

- Strong and moderate cytochrome P450 3A4 (CYP3A4) inhibitors, including but not limited to: systemic (oral/intravenous [IV]) itraconazole, ketoconazole, fluconazole; erythromycin, clarithromycin, telithromycin; diltiazem, verapamil; aprepitant, cyclosporine, nefazodone, cimetidine, quinine, and HIV protease inhibitors
- Strong and moderate CYP3A4 inducers, including but not limited to: barbiturates (eg, phenobarbital and primidone), systemic (oral/IV) glucocorticoids, nevirapine, efavirenz, pioglitazone, carbamazepine, phenytoin, rifampin, rifabutin, and St. John's wort
- Strong organic anion transporting polypeptide 1B1 (OATP1B1) inhibitors (eg, gemfibrozil)
- Drugs with narrow therapeutic margins with theoretical potential for CYP drug interactions (eg,warfarin)
- Medications with demonstrated efficacy for the prevention of migraine (eg, amitriptyline, topiramate, propranolol). Refer to Section 12.3.
- Botulinum toxin injections (eg, Botox®) into areas of the head, face, or neck within 6 months prior to Visit 1 and throughout the study period
- Acupuncture, TENS (transcutaneous electrical nerve stimulation), cranial traction, nociceptive trigeminal inhibition or occipital nerve block treatments, or dental splints for headache, within 4 weeks prior to entry into the baseline phase at week -4 or at any time during the study (including the week -4 to day 1 baseline phase)

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

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

For purposes of this study, females 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 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 reliable: hormonal contraceptives (ie, oral, patch, vaginal ring, injection, implant), male condom with intravaginal spermicide, diaphragm or cervical cap with spermicide, intrauterine device, vasectomized partner, or sexual abstinence.

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 patient will determine the appropriate method of contraception for the patient during the participation in the study.

If a female becomes pregnant during the study, the investigator will notify Allergan immediately after the pregnancy is confirmed and the patient will be exited from the study after appropriate safety follow-up. The investigator will (1) notify the patient's physician that the patient was being treated with an investigational drug AGN-241689 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

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

Alcohol intake should be limited to no more than 3 drinks per day throughout the study. A drink is defined as a 12-ounce can/bottle of beer, a 4-ounce glass of wine, or 1 ounce of liquor.

5. Study Treatments

5.1 Study Treatments and Formulations

Over-encapsulated tablets containing 10-mg [redacted], 30-mg [redacted] and 60-mg [redacted] of AGN-241689

5.2 Control Treatment(s)

Placebo [redacted] over-encapsulated tablets

5.3 Methods for Masking/Blinding

All study treatments will be provided in identical blister cards to maintain masking of the study.

Over-encapsulation will also be implemented to maintain study masking, and all patients will be instructed to take investigational product twice daily (one capsule in the morning and one capsule in the evening) at approximately the same times each day. Patients, therefore, will receive either placebo twice daily, a morning dose of AGN-241689 with an evening dose of placebo, or AGN-241689 twice daily.

5.4 Treatment Allocation Ratio and Stratification

Patients will be randomized to the following 6 arms in a 2:1:2:1:2:1 ratio:

- Placebo (n =180)
- AGN-241689 10-mg QD (n = 90)
- AGN-241689 30-mg QD (n = 180)
- AGN-241689 30-mg BID (n = 90)
- AGN-241689 60-mg QD (n = 180)
- AGN-241689 60-mg BID (n = 90)

No stratification will be performed.

5.5 Method for Assignment to Treatment Groups/Randomization

Prior to initiation of study treatment, each patient who provides informed consent will be assigned a patient number that will serve as the patient identification number on all study documents.

Central implementation of by-site randomization will be used for this study to assign patients into treatment groups.

At the time of randomization (i.e., Visit 2), eligible patients will be randomized by blocks in a 2:1:2:1:2:1 ratio into the following arms: placebo, 10-mg AGN-241689 QD, 30-mg AGN-241689 QD, 30-mg AGN-241689 twice daily, 60-mg AGN-241689 QD, and 60-mg AGN-241689 twice daily.

An automated interactive web response system (IWRS) will be used to manage the randomization and treatment assignment based on a randomization scheme prepared by Allergan Biostatistics.

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

5.6 Treatment Regimen and Dosing

Treatments to be used in this trial are listed in (Table 5–1). Patients who meet all of the study entry criteria at Visit 2 will be randomized and provided with investigational product to be taken on an outpatient basis. Sites will subsequently dispense investigational product to patients at Visits 3, 4, 5, and 6. Patients will take their first dose of investigational product at the clinic at Visit 2 (Section 8.5) and will be instructed to take their investigational product twice daily (approximately 12 hours interval between doses) at approximately the same times each day. Investigational product will be administered orally for 12 weeks, and patients will be followed for 4 weeks following discontinuation of the investigational product.

Table 5–1 Study Treatments

Drug/Dose	Investigational Product Frequency	Investigational Product Administration (AM/PM)	Route of Administration
Placebo	Twice Daily	Placebo/ Placebo	Oral (capsule)
AGN-241689 10 mg QD	Twice Daily	AGN-241689 10 mg/ Placebo	Oral (capsule)
AGN-241689 30 mg QD	Twice Daily	AGN-241689 30 mg/ Placebo	Oral (capsule)
AGN-241689 30 mg BID	Twice Daily	AGN-241689 30 mg/ AGN-241689 30 mg	Oral (capsule)
AGN-241689 60 mg QD	Twice Daily	AGN-241689 60 mg/ Placebo	Oral (capsule)
AGN-241689 60 mg BID	Twice Daily	AGN-241689 60 mg/ AGN-241689 60 mg	Oral (capsule)

5.7 Storage of Investigational products/Treatments

The investigational product must be stored at room temperature in a securely locked cabinet. Further details regarding the storage of the investigational product 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 patient. 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, probable migraine, and headache days per the criteria listed in Sections 6.1.1. The HIT-6, ACM-I, EQ-5D-5L, PGIC, WPAI-SHP V2.0, and Patient Satisfaction with Study Medication will be administered in an electronic tablet (eTablet) at the clinic visits.

6.1.1 Efficacy Measures

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.3 Future Biomedical Research

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

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

6.4 Safety Measures

6.4.1 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 the investigational product, start and stop date, and seriousness of the event (eg, serious adverse event [SAE]), document all actions taken with regard to the investigational product, and detail any other treatment measures taken for the AE. For events noted as serious adverse events (SAEs), the Sponsor must be notified immediately to meet their reporting obligations to appropriate regulatory authorities.

6.4.2 Events of Clinical Interest

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

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

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

6.4.3 Clinical Laboratory Determinations

Blood and urine samples for clinical laboratory tests will be collected at the visits outlined in Table 1–1. Hematology, chemistry, and urinalysis will be conducted at these visits. Serology, coagulation parameters (INR), 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. Patients 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 patient from participation in the study.

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

Patients 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 exam including red blood cells/high-power field, white blood cells/high-power field, and casts/low-power field.
Coagulation	At Visit 1 only: international normalized ratio
Serology	At Visit 1 only: anti-hepatitis A IgM antibody, hepatitis B surface antigen, anti–hepatitis C 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. If positive, the urine drug screen may be repeated with permission from Allergan; a negative result or an explanation of a positive result because of 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.

6.4.4 Vital Signs

Vital sign measurements, including sitting and standing blood pressure (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 patient sits quietly for 5 minutes, followed by a second set of measurements taken after the patient stands for at least 3 minutes (but no longer than 10 minutes).

6.4.5 Physical Examination

A complete physical examination will be performed at the visits outlined in Table 1–1. A professionally trained physician or healthcare professional licensed to performed physical examinations will examine the patient 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.

6.4.6 Electrocardiograms

A 12-lead ECG will be performed at the visits outlined in Table 1–1. All ECGs should be performed after the patient has been supine for at least 5 minutes. A copy of the ECG 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 patient's eCRF.

6.4.7 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 patient's lifetime history of suicidal ideation and behavior. 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 patient should not be released from the study center until the results of C-SSRS are reviewed and it is confirmed that the patient is not considered to be at risk.

6.5 Other Study Supplies

The following will be provided by Allergan or a delegate of Allergan's:

- All supplies needed for blood and urine sampling (central laboratory analysis, urine culture/sensitivity), and urine dipstick reagent strips
- All supplies needed for PK sample collections
- Shipping materials for shipment of laboratory samples to central laboratory
- All supplies needed for ECG assessment including ECG machine
- Electronic diaries
- Electronic tablets

6.6 Summary of Methods of Data Collection

An IWRS will be used to randomize patients and manage investigational product inventory. All office visit data (ie, non-diary data) for this study will be collected by either the eTablet (eg, questionnaires for patient reported outcomes) or eCRFs via an electronic data capture system. Source documents will be used at the sites and may include a patient's medical record, hospital charts, clinic charts, the investigator's patient 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 Lab Procedure Manual.

Patients will use an eDiary daily to record the daily total duration of headache, headache characteristics, associated symptoms, the worst pain severity, and acute medication use both in the Screening/Baseline Period and double-blind treatment period until Visit 8. Training for the eDiary will be provided for qualified patients during the Screening/Baseline visit (Visit 1).

7. Statistical Procedures

7.1 Analysis Populations

All safety analyses will be performed using the safety population, consisting of all patients who received at least one dose of the study treatment. For safety data analyses, the patients will be analyzed according to actual treatment received (rather than as randomized). The Intent-to-Treat (ITT) Population will consist of all randomized patients. All efficacy analyses will be performed using the modified intent-to-treat (ITT) population, consisting of all

randomized patients who received at least 1 dose of study treatment, had an evaluable baseline period of diary data, and had at least 1 evaluable post-baseline 4-week (Weeks 1-4, 5-8, and 9-12) of diary data. For efficacy data analyses, the patients will be analyzed according to randomization assignment, regardless of actual treatment received.

7.2 Collection and Derivation of Primary and Secondary Efficacy Assessments

For analysis purposes, four weeks (28 days) will be considered as one month. On a daily basis during the 28-day baseline period and throughout the double-blind treatment period, patients 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. Patients will be able to report headache data, including absence of headache, for the day of the diary report and for the day immediately prior to the day of the diary report, as long as information reported is for a time subsequent to the patient'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 safety 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 1-4, 5-8 and 9-12, corresponding to days 1-28, 29-56 and 57-84). Therefore, for data analysis purposes, the number of migraine/probable migraine headache days during the first 28 days of the baseline phase, starting with the day of the screening visit, will serve as the "baseline", and change from baseline will be calculated for consecutive 28-day periods beginning with Day 1.

In order to be randomized, a patient should be in the baseline phase for at least 28 days and must report diary 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 diary window for a patient has at least 12 but less than 28 days of reported data, the prorated approach will be used. If a patient reports less than 12 days of headache data, the patient's observed counts in that particular 28-day dairy window will be set to missing for

that window. These prorating rules will be applied to all efficacy analyses of diary data unless otherwise stated.

7.2.1 Primary Efficacy Variable

The primary efficacy variable is the change from baseline in mean monthly MPM headache days across the 12-week treatment period. Baseline is defined as the number of MPM days during the first 28 days of the screening/baseline period, starting with the day of the screening visit.

7.2.2 Secondary Efficacy Variables

The 3 secondary efficacy variables include:

- Change from baseline in mean monthly headache days across the 12-week treatment period.
- Proportion of patients with at least a 50% reduction in mean monthly MPM headache days across the 12-week treatment period.
- Change from baseline in mean monthly acute medication use days across the 12-week treatment period

[redacted]

7.3 Hypothesis and Methods of Analysis

7.3.1 Primary Efficacy Analyses

The primary efficacy analysis is on the change from baseline in the mean monthly MPM headache days across the 12-week treatment period. The primary null hypothesis is that AGN-241689 treatment doses 10 mg QD, 30 mg QD, 60 mg QD, 30 mg BID and 60 mg BID are each equally effective to placebo in decreasing from baseline the number of headache days per 4 weeks. The alternative hypothesis is that at least one of those five doses of AGN-241689 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 and treatment group by visit interaction as categorical fixed effects. It will also include the baseline score and baseline-by-visit interaction as covariates. Pairwise contrasts in the MMRM model will be used to make the pairwise comparisons of each dose to placebo.

A sensitivity analysis 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. The sensitivity analysis will be done using a pattern-mixture model (PMM), under which data could be missing-not-at-random (MNAR), with repeated analyses combined via the reference-based multiple imputation (MI) procedure. An additional sensitivity, MI in conjunction with robust regression, will be performed in case of non-normality for the primary efficacy endpoint.

7.3.2 Secondary Efficacy Analyses

The secondary efficacy variables are identified in rank order in Section 7.2.2. The overall type I error rate for multiple comparisons across active treatment doses and the primary and secondary efficacy parameters will be controlled at the 0.05 level using a graphical approach by Bretz et al (2011). The weighting strategy of the multiple comparisons is designed to allocate initial alpha equally to the QD and BID dose regimens. Within each dosing regimen, individual AGN-241689 doses will be tested in a hierarchical order from high to low dose, i.e. for primary efficacy endpoint, low dose can be tested only if high dose comparison shows statistical significance. In addition, for a given dose comparison versus placebo, the strategy has the primary endpoint as gatekeeper to the secondary endpoints so that secondary endpoints can be tested only if primary hypothesis of the corresponding dose comparison reaches statistical significance. Weighted Bonferroni tests will be used for testing the hypotheses. A complete decision-flow graph and details of the graphical multiple comparison procedure will be presented in the statistical analysis plan of this study.

For continuous variables, pairwise comparisons will be analyzed using MMRM, with baseline covariate. For variables where data is binary, comparisons between treatment groups will be done by pairwise contrasts using logistic regressions for variables with only one postbaseline assessment or using generalized linear mixed model for variables with multiple postbaseline assessments.

[redacted]

7.6 Subgroup Analyses

There are no planned subgroup analyses.

7.7 Sample Size Calculation

The assumptions and corresponding power assessments for the primary efficacy endpoint are shown in the table below. The treatment difference assumption is based on results from other episodic migraine prevention studies: the placebo-adjusted reduction in monthly migraine days ranged from 1.1 to 2 days (topiramate [Silberstein et al, 2004 and Brandes et al, 2004], telcagepant [Ho et al, 2014], and CGRP monoclonal antibodies Ph2 studies [Dodick et al, 2014; Dodick et al, 2014; Bigal et al, 2015; Sun et al, 2016], and their Ph3 studies results reported from American Headache Society & American Academy of Neuroscience 2017). Common standard deviation is estimated based on blinded interim data assessments of this study. Power is calculated via 10,000 simulations based on multiplicity adjustment.

	60mg BID (n=90)	**30mg BID (n=90)**	**60mg QD (n=180)**	**30mg QD (n=180)**	**10mg QD (n=90)**
Assumed Treatment difference vs. placebo (placebo n = 180)	-1.6	-1.5	-1.5	-1.4	-1.2
Effect size (Common SD = 3.0)	0.53	0.5	0.5	0.47	0.4
Power	**97.0%**	**91.4%**	**99.3%**	**98.1%**	**80.3%**

QD = once daily; BID = twice daily; SD = standard deviation.

7.8 Interim Analyses

There is no interim analysis planned.

8. Study Visit Schedule and Procedures

Please see Table 1–1 for a schedule of visits and procedures and Figure 1 for a study visit flowchart.

8.1 Patient Entry Procedures

8.1.1 Overview of Entry Procedures

Prospective patients as defined by the criteria in Sections 4.3 and 4.4 (inclusion/exclusion criteria) will be considered for entry into this study.

8.1.2 Informed Consent and Patient Privacy

The study will be discussed with the patient and a patient wishing to participate must give informed consent prior to any study-related procedures or change in treatment. The patient 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 patient who provides informed consent and/or assent will be assigned a patient number that will be used on patient documentation throughout the study.

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

8.2 Washout Intervals

This study will not include a washout period.

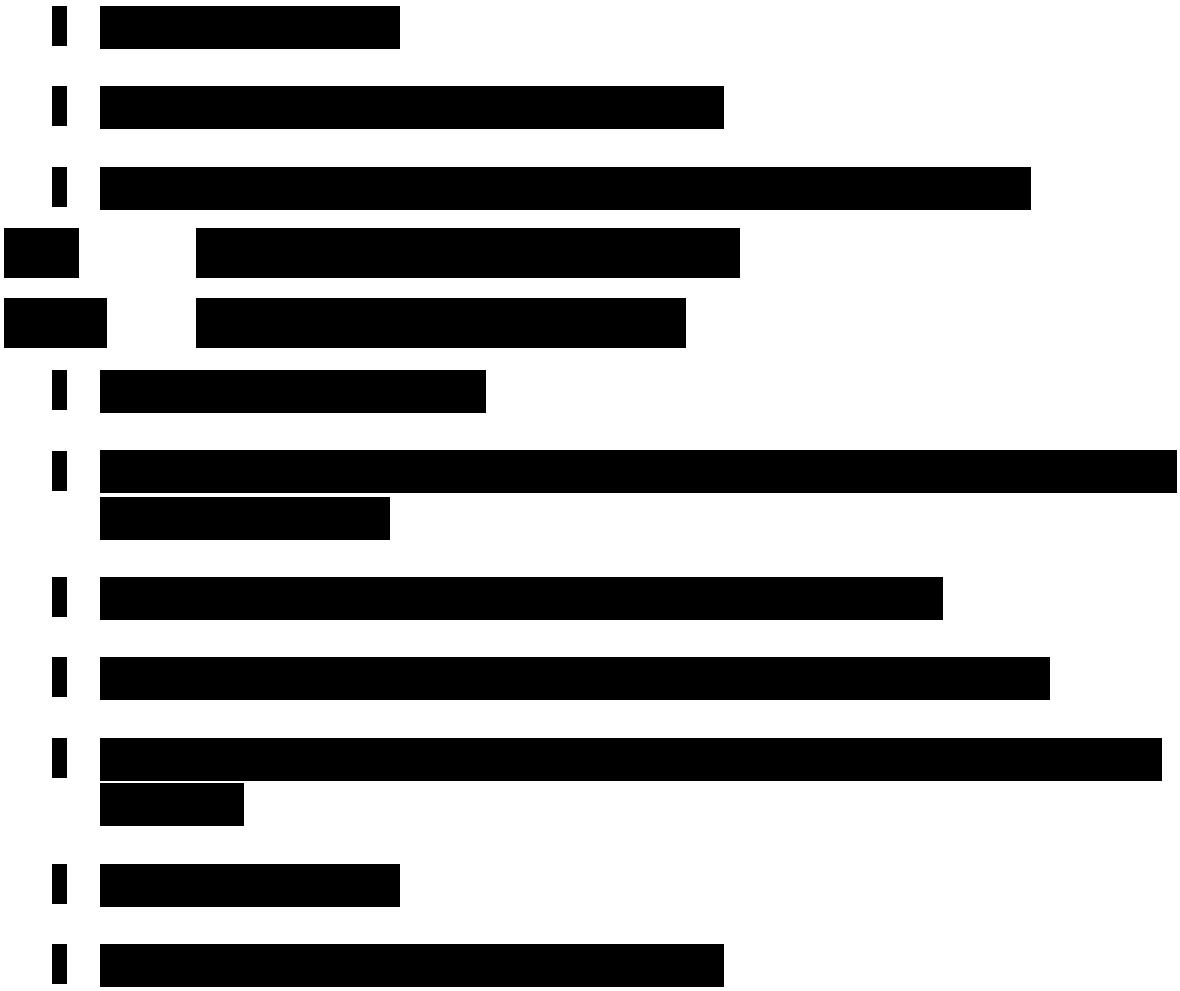
8.3 Procedures for Final Study Entry

At the Screening and Randomization visits (Visits 1 and 2), patients must meet all of the inclusion criteria and must not meet any of the exclusion criteria. Rescreening of patients may be considered with permission from Allergan. Also, all females 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 investigational product).

Prior to randomization, confirm that the patient had 4 to 14 migraine/probable migraine headache 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.

[redacted]



8.5 Instructions for the Patients

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

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

Patients should be instructed to take investigational product twice daily at approximately the same times each day (approximately 12 hours between doses). For dosing on Day 1 (Visit 2), the first dose is to be taken at the study site, and patients should be advised to take the second dose depending on the time of the site visit and the patient's usual routine.

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

8.6 Unscheduled Visits

Additional examinations and laboratory assessments may be performed as necessary to ensure the safety and well-being of the patients 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 1–1, and the timing of the visits should occur as close as possible to the day specified**.** At each visit, the patient will be asked if the patient 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.

Investigational product 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 investigational product.

8.8 Early Discontinuation of Patients

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

- Adverse event (AE)
- Lack of efficacy
- Withdrawal of consent (a clear reason must be documented)
- Lost to follow-up (Every effort must be made to contact the patient; a certified/traceable letter must be sent.)
- Pregnancy
- Protocol violation
- Non-compliance with study drug
- Study terminated by Sponsor
- Site terminated by Sponsor
- Other

Patients may voluntarily withdraw from the study at any time. Notification of early patient discontinuation from the study and the reason for discontinuation will be clearly documented on the appropriate case report form. All randomized patients 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/Early Termination and Visit 8 Safety Follow-up, 4 weeks post the last dose of IP.

8.9 Withdrawal Criteria

Women who become pregnant (Section 9.4) and patients who meet investigational product discontinuation criteria related to abnormal liver function tests (Section 9.5) and advised not to be re-challenged will be withdrawn from the study and should refrain from taking investigational product. The patient should return to the clinic for early termination procedures (Visit 7) and the Safety Follow-up Visit 8. Patients 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 Safety Follow-Up Visit 8.

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

8.10 Withdrawal from Future Biomedical Research

A patient 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 patient withdraws consent, their physical sample will be destroyed and no new health information identifying the patient 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 case report form. If AEs occur, the first concern will be the safety of the study participants.

9.1 Definitions

9.1.1 Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. In addition, during the screening period, AEs will be assessed regardless of the administration of a pharmaceutical product.

Note: AEs must be collected once informed consent has been obtained, regardless of whether or not the patient has been administered study drug.

Progression of treatment indication including new or worsening of anticipated clinical signs or symptoms, which are collected as clinical efficacy variables and assessed as unequivocally associated with the disease progression and /or lack of efficacy, should NOT be reported as AEs unless the disease progression is greater than anticipated in the natural course of the disease.

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 patient a general, non-directed question such as "How have you been feeling since the last visit?" Directed questioning and examination will then be done as appropriate. All reported AEs will be documented on the appropriate case report form.

9.1.2 Serious Adverse Event

An SAE is any AE occurring at any dose that results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (See Section 9.3 for procedures for reporting an SAE.)

Allergan considers all cancer adverse events as SAEs. In addition, Allergan considers any abortion (spontaneous or nonspontaneous) as an SAE.

Pre-planned surgeries or procedures for pre-existing, known medical conditions for which a patient 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 patient's entry into the study. If it has not been documented at the time of the patient's entry into the study, then it should be documented as a SAE and reported to Allergan.

9.1.3 Severity

A clinical determination will be made of the intensity of an AE. The severity assessment for a clinical AE must be completed using the following definitions as guidelines:

Mild	Awareness of sign or symptom, but easily tolerated.
Moderate	Discomfort enough to cause interference with usual activity.
Severe	Incapacitating with inability to work or do usual activity.

9.1.4 Relationship to Study Drug or Study Procedure

A determination will be made of the relationship (if any) between an AE and the study drug or study procedure, as applicable. A causal relationship is present if a determination is made that there is a reasonable possibility that the AE may have been caused by the drug or study procedure.

9.2 Procedures for Reporting Adverse Events

Any adverse event must be recorded on the appropriate case report form.

All SAEs that are drug-related and unexpected (not listed as treatment-related in the current Investigator's Brochure) must be reported to the governing Institutional Review Board/Independent Ethics Committee (IRB/IEC) as required by the IRB/IEC, local regulations, and the governing health authorities. Any adverse event 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) and for at least 30 days after the last dose of study drug must be immediately reported but no later than 24 hours after learning of an SAE. SAEs must be reported to Allergan (or Agent of Allergan)

as listed on the Allergan Study Contacts Page and recorded on the SAE form. All patients with an SAE must be followed up and the outcomes reported. The investigator must supply the sponsor and the IRB/IEC with any additional requested information (eg, autopsy reports and discharge summaries).

In the event of an SAE, the investigator must:

1. Notify Allergan immediately by fax or email using the SAE form (contact details can be found on page 1 of the SAE form); phone numbers and relevant Allergan personnel contacts are also on the front page of protocol and Study Contacts Page.

2. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient.

3. Provide Allergan with a complete, written description of the adverse event(s) on the SAE form describing the event chronologically, including any treatment given (eg, medications administered, procedures performed) for the adverse event(s). Summarize relevant clinical information about the event: signs, symptoms, diagnosis, clinical course and relevant clinical laboratory tests, etc. Include any additional or alternative explanation(s) for the causality which includes a statement as to whether the event was or was not related to the use of the investigational drug.

4. Promptly inform the governing IRB/IEC of the SAE as required by the IRB/IEC, local regulations, and the governing health authorities.

9.4 Exposure to Investigational Product during Pregnancy

Study center personnel must report every pregnancy from the time he or she signs the ICF for the trial until 30 days after the last dose of investigational product on the Pregnancy Form as soon as possible (within 24 hours of learning of the pregnancy to **the SAE/pregnancy fax number,** [redacted]) even if no AE has occurred. Pregnancies in female partners of male patients must also be reported. The pregnancy must be followed to term and the outcome reported by completing a follow-up Pregnancy Form. If, however, the pregnancy is associated with a SAE (eg, if the mother is hospitalized for hemorrhage), 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 post treatment event of ALT or AST ≥ 3xULN is considered an Event of Clinical Interest. Any patient with this laboratory result after investigational product was taken must have repeat testing within 48 to 72 hours to confirm the abnormality. For this repeat testing, the following labs must be drawn: hematology and chemistry panels, international normalized ratio (INR), and a toxicology screen for acetaminophen. In addition, the investigator will perform a complete history and exam to evaluate for possible liver disease.

All Events of Clinical Interest must be reported to Allergan using the AE of Interest form and submitted within 24 hours of the time the Investigator becomes aware of the event. All new elements of history, physical exam, diagnostic testing results, and other relevant medical reports are to be reported for each event.

If an ALT or AST elevation ≥ 3 x ULN is confirmed and the patient meets any of the following criteria, close medical follow-up is required:

- Patients with ALT or AST ≥ 3 x ULN and ≤ 5 x ULN and who are asymptomatic with regard to possible liver disease (ie. No fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia (> 5%))
- Patients with ALT or AST ≥ 3 x ULN and ≤ 5 x ULN and (total bilirubin < 2 x ULN and INR < 1.5)

Patients who meet these criteria must be followed clinically and further medical evaluation will be done per the judgment of the investigator and in conjunction with medical personnel at Allergan. The Chemistry panel will be repeated 1 to 2 times per week to follow the course of ALT/AST elevation. An extra blood serology sample must be collected and sent to the central laboratory for further diagnostic testing at a later date if needed.

If an ALT or AST elevation ≥ 3 x ULN is confirmed and the patient meets any of the following criteria, close medical follow-up is also required:

- ALT or AST ≥ 3 x ULN and the patient is symptomatic with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (>5%)
- ALT or AST ≥ 3 x ULN **and (**total bilirubin > 2 x ULN or INR > 1.5)
- ALT or AST ≥ 5 x ULN

For these patients, possible etiologies for acute hepatic injury must be excluded. 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 PCR, anti-hepatitis E IgM. An extra serology blood sample will be collected and sent to the central laboratory for further diagnostic testing at a later date if needed. The patient must be followed clinically and further medical evaluation 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. For procedural details on the medical evaluation of liver disease, please see the Study Reference Manual.

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

Investigational product must be discontinued if any of the following criteria are met:

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

The patient may be re-challenged with investigational product only after consultation with the Allergan Medical Monitor. For patients who are not re-challenged with investigational product, the patient should be discontinued from the study and complete the Early Termination Visit 7 and Safety Follow-Up Visit 8. Patients should receive appropriate follow-up as per standard of care.

9.5.1 Potential Hy's Law Cases

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

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

A laboratory alert for potential Hy's laws cases will be in place, and the investigators and Allergan will be notified immediately when the above criteria have been met. Any potential Hy's laws case should be considered an SAE and also reported as an AE of Special Interest. Complete both an SAE and AE of Special Interest Form as soon as possible (within 24 hours of learning of the potential Hy's law) and fax it to the SAE fax number. The eCRF pages associated with potential Hy's law cases must be completed within 7 calendar days. Every effort to determine the cause of the liver abnormalities must be made, and close monitoring should be initiated in conjunction with the Allergan medical monitor and in accordance with the FDA "Guidance for Industry: Drug Induced Liver Injury - Pre-Marketing Clinical Evaluation" July 2009. For specific instructions, please refer to the Study Reference Manual.

9.6 Procedures for Unmasking of Investigational Product

When necessary for the safety and proper treatment of the patient, the investigator can unmask the patient's treatment assignment to determine which treatment has been assigned and institute appropriate follow-up care. When possible, the Allergan Medical Monitor should be notified prior to unmasking investigational product. The investigator must inform the Allergan Medical Monitor of the unmasking if there is no notification prior to the unmasking.

The treatment assignment for the patient can be determined by designated site personnel logging into the IWRS system via password protected access. The reason for breaking the code must be recorded in the patient's source documents.

10. Administrative Items

This protocol is to be conducted in accordance with the applicable Good Clinical Practice (GCP) regulations and guidelines, eg, the International Conference on Harmonisation (ICH) Guideline on GCP.

10.1 Protection of Human Patients

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 patient prior to any study-related activities or procedures in the study, and/or from the patient'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 21CFR Part 11)

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

10.2 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 patients, or when the changes involve only logistical or administrative aspects of the study (eg, change in monitors, change of telephone numbers).

10.3 Patient 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 drug may ultimately be marketed, but the patient's name will not be disclosed in these documents. The patient'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.

10.3.1 Patient Privacy

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

privacy requirements (eg, the Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information ("HIPAA").

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

10.4 Documentation

10.4.1 Source Documents

Source documents may include a patient's medical records, hospital charts, clinic charts, the investigator's patient study files, the eDiary, as well as the results of diagnostic tests such as , laboratory tests and electrocardiograms. The investigator's copy of the case report forms serves as part of the investigator's record of a patient's study-related data.

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

- Patient's name.
- Patient's contact information.
- The date that the patient entered the study, patient number, and patient randomization [or medication kit] number.
- The study title and/or the protocol number of the study and the name of Allergan.
- A statement that informed consent was obtained (including the date). A statement that written authorization or other local patient privacy required documentation for this study has been obtained (including the date).
- Dates of all patient visits.
- Patient's medical history
- Information regarding patient's diagnosis of migraine headache
- All concurrent medications (List all prescription and non-prescription medications being taken at the time of enrollment. At each subsequent visit, changes to the list of medications should be recorded.)
- Occurrence and status of any adverse events.

- The date the patient exited the study, and a notation as to whether the patient completed the study or reason for discontinuation.
- The results of laboratory tests performed by the site (eg, results of urine pregnancy tests)
- Key study variables

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

10.4.2 Case Report Form Completion

The investigator is responsible for ensuring that data are properly recorded on each patient'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.

10.4.3 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.

10.4.4 Retention of Documentation

All study related correspondence, patient records, consent forms, patient privacy documentation, records of the distribution and use of all investigational products, and copies of case report forms should be maintained on file.

For countries falling within the scope of the ICH guidelines, the sponsor-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 investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

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.

10.5 Labeling, Packaging, and Return or Disposal of Investigational Products/Treatments

10.5.1 Labeling/Packaging

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

10.5.2 Clinical Supply Inventory

The investigator must keep an accurate accounting of the number of investigational units received from Allergan, dispensed or administered to the patients, the number of units returned to the investigator by the patient (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 investigational product. The investigational product must be dispensed or administered only by an appropriately qualified person to patients in the study. The medication is to be used in accordance with the protocol.

10.5.3 Return or Disposal of Investigational Products/Treatments and/or Supplies

All clinical investigational products/treatments and/or supplies will be returned to Allergan or Allergan designee for destruction.

10.6 Monitoring by the Sponsor

A representative of the sponsor 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.

10.7 Handling of Biological Specimens

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

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

DBS samples obtained from patients in the PK substudy will be stored at the centralized clinical laboratory until ready for PK analyses by Allergan's Pharmacokinetics and Drug Distribution department using a validated method. This laboratory meets Good Laboratory Practice requirements.

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

10.8 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.

10.9 Coordinating Investigator

A signatory Coordinating Investigator will be designated prior to the writing of the Clinical Study Report.

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12. Attachments

12.1 Examination Procedures, Tests, Equipment, and Techniques

12.1.1 International Classification of Headache Disorders, 3rd Edition, Beta Version

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
    - 1.2.3.1.2 Familial hemiplegic migraine type 2
    - 1.2.3.1.3 Familial hemiplegic migraine type 3
    - 1.2.3.1.4 Familial hemiplegic migraine, other loci
  - 1.2.3.2 Sporadic hemiplegic migraine
- 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?

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. 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 episodic or chronic migraine diagnosis and the diagnosis 8.2 *Medication-overuse headache* should be given when medication overuse is present. When *pre-existing* migraine is made significantly worse (usually meaning a two-fold 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. Epidemiological studies have documented its high prevalence and high socio-economic and personal impacts. In the *Global Burden of Disease Survey 2010*, it was ranked as the third most prevalent disorder and seventh-highest specific cause of disability worldwide.

Migraine has two major subtypes. 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 premonitory phase, occurring hours or days before the headache, and a headache resolution phase. Premonitory and resolution 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 subtype of migraine, all subtypes 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*. Attacks of either type are included in the diagnostic criteria for 1.3 *Chronic 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.

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Diagnostic criteria:

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

Notes:

1. One or a few migraine attacks may be difficult to distinguish from symptomatic migraine-like attacks. Furthermore, the nature of a single or a few attacks may be difficult to understand. Therefore, at least five attacks are required. Individuals who otherwise meet criteria for 1.1 *Migraine without aura* but have had fewer than five attacks, should be coded 1.5.1 *Probable migraine without aura.*
2. When the patient falls asleep during a migraine attack and wakes up without it, duration of the attack is reckoned until the time of awakening.
3. In children and adolescents (aged under 18 years), attacks may last 2-72 hours (the evidence for untreated durations of less than 2 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. In young children, photophobia and phonophobia may be inferred from their behaviour. Migraine attacks can be associated with cranial autonomic symptoms and symptoms of cutaneous allodynia.

Migraine without aura often has a menstrual relationship. ICHD-3 beta offers criteria for A1.1.1 *Pure menstrual migraine* and A1.1.2 *Menstrually related migraine*, but in the Appendix because of uncertainty over whether they should be regarded as separate entities.

Very frequent migraine attacks are now distinguished as 1.3 *Chronic migraine*. When there is associated medication overuse, both 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 migraine without aura, although blood flow changes may occur in the brainstem, as may cortical changes secondary to pain activation. This contrasts with the pathognomonic spreading oligaemia of migraine with aura. Although the bulk of the literature suggests that CSD does not occur in migraine without aura, some recent studies disagree. Furthermore, it has been suggested that glial waves or other cortical phenomena may be involved in migraine without aura. The messenger molecules nitric oxide (NO), 5-hydroxytryptamine (5-HT) and calcitonin gene-related peptide (CGRP) are involved. Although 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 recent 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, the central mesencephalic grey and the thalamus, have been recognized. New highly receptor-specific acute medications such as the triptans, which are $5HT_{1B/D}$ receptor agonists, $5\text{-}HT_{1F}$ receptor agonists and CGRP receptor antagonists have demonstrated efficacy in the acute treatment of attacks. Because of their high receptor-specificity, their mechanism of action provides new insight into migraine mechanisms. It is now clear that migraine without aura is a neurobiological disorder; clinical as well as basic neuroscience has advanced our knowledge of migraine mechanisms, and continues to do so.

1.2 Migraine with aura

Previously used terms:

Classic or classical migraine; ophthalmic, hemiparaesthetic, hemiplegic or aphasic migraine; migraine accompagnée; complicated migraine.

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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 two of the following four characteristics:
   1. at least one aura symptom spreads gradually over ≥5 minutes, and/or two or more symptoms occur in succession
   2. each individual aura symptom lasts 5-60 minutes[1]
   3. at least one aura symptom is unilateral[2]
   4. the aura is accompanied, or followed within 60 minutes, by headache
D. Not better accounted for by another ICHD-3 diagnosis, and transient ischaemic attack has been excluded.

Notes:

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

Comments:
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 pain 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.

When the aura includes motor weakness, the disorder should be coded as 1.2.3 *Hemiplegic migraine* or one of its subforms.

Aura symptoms of these different types 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 1 hour, but motor symptoms are often longer lasting.

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.

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*.

Premonitory symptoms may begin hours or a day or two before the other symptoms of a migraine attack (with or 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. The terms 'prodrome' and 'warning symptoms' are best avoided, because they are often mistakenly used to include aura.

Migraine aura is sometimes associated with a headache that does not fulfil 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 1 to

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several hours, gradual transition into hyperaemia occurs in the same region. Cortical spreading depression of Leão is the likely underlying mechanism.

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 is not recognized in this classification. They are all coded as 1.2.1 *Migraine with typical aura*. 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. Patients with 1.2.3 *Hemiplegic migraine* have motor weakness, and this is classified as a separate subform because of genetic and pathophysiological differences from migraine with typical aura. Such patients often have brainstem symptoms in addition.

The previously defined syndromes, *migraine with prolonged aura* and *migraine with acute-onset aura*, have been abandoned. The great majority of patients with such attacks have other attacks that fulfil criteria for one of the recognized subforms of 1.2 *Migraine with aura*, and should be coded to that diagnosis. The rest 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.

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 1 hour, a mix of positive and negative features and complete reversibility.

Diagnostic criteria:

A. At least two attacks fulfilling criteria B and C
B. Aura consisting of visual, sensory and/or speech/language symptoms, each fully reversible, but no motor, brainstem or retinal symptoms
C. At least two of the following four characteristics:
   1. at least one aura symptom spreads gradually over ≥5 minutes, and/or two or more symptoms occur in succession
   2. each individual aura symptom lasts 5-60 minutes[1]
   3. at least one aura symptom is unilateral[2]
   4. the aura is accompanied, or followed within 60 minutes, by headache
D. Not better accounted for by another ICHD-3 diagnosis, and transient ischaemic attack has been excluded.

Notes:

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

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. Fulfils criteria for 1.2.1 *Migraine with typical aura*
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. Fulfils criteria for 1.2.1 *Migraine with typical aura*
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

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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. At least two attacks fulfilling criteria B-D
B. Aura consisting of visual, sensory and/or speech/language symptoms, each fully reversible, but no motor[1] or retinal symptoms
C. At least two of the following brainstem symptoms:
   1. dysarthria
   2. vertigo
   3. tinnitus
   4. hypacusis
   5. diplopia
   6. ataxia
   7. decreased level of consciousness
D. At least two of the following four characteristics:
   1. at least one aura symptom spreads gradually over ≥5 minutes, and/or two or more symptoms occur in succession
   2. each individual aura symptom lasts 5-60 minutes[2]
   3. at least one aura symptom is unilateral[3]
   4. the aura is accompanied, or followed within 60 minutes, by headache
E. Not better accounted for by another ICHD-3 diagnosis, and transient ischaemic attack has been excluded.

Notes:

1. When motor symptoms are present, code as 1.2.3 *Hemiplegic migraine*.
2. When for example three symptoms occur during an aura, the acceptable maximal duration is 3×60 minutes.
3. Aphasia is always regarded as a unilateral symptom; dysarthria may or may not be.

Comments:
Originally the terms *basilar artery migraine* or *basilar migraine* were used but, as 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 C may occur with anxiety and hyperventilation, and therefore are subject to misinterpretation.

1.2.3 Hemiplegic[1] migraine

Description:
Migraine with aura including motor weakness.

Diagnostic criteria:

A. At least two attacks fulfilling criteria B and C
B. Aura consisting of both of the following:
   1. fully reversible motor weakness
   2. fully reversible visual, sensory and/or speech/language symptoms
C. At least two of the following four characteristics:
   1. at least one aura symptom spreads gradually over ≥5 minutes, and/or two or more symptoms occur in succession
   2. each individual non-motor aura symptom lasts 5 60 minutes, and motor symptoms last <72 hours[2]
   3. at least one aura symptom is unilateral[3]
   4. the aura is accompanied, or followed within 60 minutes, by headache
D. Not better accounted for by another ICHD-3 diagnosis, and transient ischaemic attack and stroke have been excluded.

Notes:

1. The term *plegic* means paralysis in most languages, but most attacks are characterized by motor weakness.
2. In some patients, motor weakness may last weeks.
3. Aphasia is always regarded as a unilateral symptom; dysarthria may or may not be.

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

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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. Fulfils 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 (FHM)* than was possible previously. Specific genetic subtypes 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 subtype (if discovered) should be specified at the fifth digit.

It has been shown that 1.2.3.1 *Familial hemiplegic migraine (FHM)* 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 CSF pleocytosis can occur.

1.2.3.1 *Familial hemiplegic migraine (FHM)* may be mistaken for epilepsy and (unsuccessfully) treated 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. Fulfils criteria for 1.2.3.1 *Familial hemiplegic migraine*
B. A causative mutation on the CACNA1A gene has been demonstrated.

1.2.3.1.2 Familial hemiplegic migraine type 2 (FHM2)

Diagnostic criteria:

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

1.2.3.1.3 Familial hemiplegic migraine type 3 (FHM3)

Diagnostic criteria:

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

1.2.3.1.4 Familial hemiplegic migraine, other loci

Diagnostic criteria:

A. Fulfils 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

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

Diagnostic criteria:

A. Fulfils 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.

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Sporadic cases usually require neuroimaging and other tests to rule out other causes. A lumbar puncture may be necessary to rule out 7.3.5 *Syndrome of transient Headache and Neurological Deficits with cerebrospinal fluid Lymphocytosis (HaNDL)*.

1.2.4 Retinal migraine

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

Diagnostic criteria:

A. At least two attacks fulfilling criteria B and C
B. Aura consisting of 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:
   1. clinical visual field examination
   2. the patient's drawing (made after clear instruction) of a monocular field defect
C. At least two of the following three characteristics
   1. the aura spreads gradually over ≥5 minutes
   2. aura symptoms last 5-60 minutes
   3. the aura is accompanied, or followed within 60 minutes, by headache
D. 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 cannot be ascertained as the underlying aetiology.

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[1,2]

Description:
Headache occurring on 15 or more days per month for more than 3 months, which has the features of migraine headache on at least 8 days per month.

Diagnostic criteria:

A. Headache (tension-type-like and/or migraine-like) on ≥15 days per month for >3 months[2] and fulfilling criteria B and C
B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for 1.1 *Migraine without aura* and/or criteria B and C for 1.2 *Migraine with aura*
C. On ≥8 days per month for >3 months, fulfilling any of the following[3]:
   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.

Notes:

1. The diagnosis of 1.3 *Chronic migraine* excludes the diagnosis of 2. *Tension-type headache* or its subtypes because tension-type-like headache is within the diagnostic criteria for 1.3 *Chronic migraine*.
2. The reason for singling out chronic from 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. It is extremely difficult to keep such patients medication-free in order to observe the natural history of the headache. In this situation, attacks with or without aura are both counted, as well as tension-type-like headaches. 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 subtype 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, and the diagnosis of 8.2 *Medication-overuse headache* may in a sense be inappropriate (assuming that chronicity induced by drug overuse is always reversible). For these reasons, and because of the general rule, patients meeting criteria for 1.3 *Chronic migraine* and for 8.2 *Medication-overuse headache* should be given both diagnoses. After drug withdrawal, migraine will either revert to the episodic subtype or remain chronic, and be re-diagnosed accordingly; in the latter case, the diagnosis of 8.2 *Medication-overuse*

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headache may be rescinded. In some countries, it is usual practice to diagnose 8.2 *Medication-overuse headache* only on discharge.
3. Characterization of frequently recurring headache generally requires a headache diary to record information on pain and associated symptoms day-by-day for at least 1 month. Sample diaries are available at http://www.i-h-s.org.

1.4 Complications of migraine

Comment:
Code separately for both the migraine subtype and for the complication.

1.4.1 Status migrainosus

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

Diagnostic criteria:

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

Notes:

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

Comments:
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 1.3 *Chronic migraine* and 8.2 *Medication-overuse headache* but not for 1.4.1 *Status migrainosus*. When overuse of medication is of shorter duration than 3 months, code for the appropriate migraine subtype(s) only.

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1.4.2 Persistent aura without infarction

Description:
Aura symptoms persisting for 1 week or more without evidence of infarction on neuroimaging.

Diagnostic criteria:

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

Comments:
Persistent aura symptoms are rare but well documented. They are often bilateral and may last for months or years. The 1-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 as a result of cerebral infarction of other causes. Attacks lasting more than 1 hour and less than 1 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 associated with an ischaemic brain lesion in the appropriate territory demonstrated by neuroimaging.

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
C. Neuroimaging demonstrates ischaemic infarction in a relevant area
D. Not better accounted for by another diagnosis.

Comments:
Ischaemic stroke in a migraine sufferer may be categorized as cerebral infarction of other cause coexisting with migraine, cerebral infarction of other cause presenting

with symptoms resembling migraine with aura, or cerebral infarction occurring during the course of a typical migraine with aura attack. 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 two-fold increased risk of ischaemic stroke in patients with migraine with aura patients 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 frequency of aura and the nature of aura symptoms denoting the increase in risk is unknown. Most studies have shown a lack of association between 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 1 hour after, an attack of migraine with aura
C. Not better accounted for by another diagnosis.

Comment:
Migraine and epilepsy are prototypical examples of paroxysmal brain disorders. Although migraine-like headaches are quite frequently seen in the epileptic postictal period, sometimes a seizure occurs during or following a migraine attack. This phenomenon, sometimes referred to as *migralepsy*, is a rare event, originally described in patients with 1.2 *Migraine with aura*. Evidence for association with 1.1 *Migraine without aura* is still 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 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 subforms
B. Not fulfilling ICHD-3 criteria for any other headache disorder
C. Not better accounted for by another ICHD-3 diagnosis.

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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 ≥1 hour and up to 10 days
   3. attacks occur ≥1 week apart
D. Complete freedom from symptoms between attacks
E. Not attributed to another disorder.[1]

Note:

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

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

This disorder was not included as a childhood periodic syndrome in ICHD-I, but it was 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 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. During attacks, at least two of the following:
   1. anorexia
   2. nausea
   3. vomiting
   4. pallor

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D. Attacks last 2-72 hours when untreated or unsuccessfully treated
E. Complete freedom from symptoms between attacks
F. Not attributed to another disorder.[1]

Note:

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

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

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

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

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

1.6.2 Benign paroxysmal vertigo

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

Diagnostic criteria:

A. At least five attacks fulfilling criteria B and C
B. Vertigo[1] occurring without warning, maximal at onset and resolving spontaneously after minutes to hours without loss of consciousness
C. At least one of the following 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.

Note:

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.

Comments:
Posterior fossa tumours, seizures and vestibular disorders must be excluded.

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

1.6.3 Benign paroxysmal torticollis

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

Diagnostic criteria:

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

Notes:

1. Attacks tend to recur monthly.
2. Ataxia is more likely in older children within the affected age group.

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

The differential diagnosis includes gastro-oesophageal reflux, idiopathic torsional dystonia and complex partial seizure, but particular attention must be paid to

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the posterior fossa and craniocervical junction where congenital or acquired lesions may produce torticollis. These observations need further validation by patient diaries, structured interviews and longitudinal data collection.

1.6.3 *Benign paroxysmal torticollis* may evolve into 1.6.2 *Benign paroxysmal vertigo* or 1.2 *Migraine with aura* (particularly 1.2.2 *Migraine with brainstem aura*), or cease without further symptoms.

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12.2 Examples of Prohibited Medications

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

- Strong OATP1B1 inhibitors e.g, Gemfibrozil (Lopid™)

	Strong/moderate CYP3A4 inducers	**Strong/moderate CYP3A4 inhibitors**
Anti-Depressants/ **Anti-Anxiety**	Barbiturates • Amobarbital (Amytal™) • Aprobarbital (Alurate™) • Butalbital (Fiorinal™, Fioricet™) • Butabarbital (Busodium™ Butisol™) • Mephobarbital (Mebaral™) • Pentobarbital (Nembutal™) • Phenobarbital (Luminal™ Solfoton™) • Secobarbital (Seconal™)	Nefazodone (Serzone™)
Anti-Seizure	Carbamazepine (Atretol™, Carbatrol™, Epitol™, Equetro™, Tegretol™) Oxcarbazepine (Trileptal™) Phenytoin (Dilantin™, Phenytek™) Primidone (Myidone™, Mysoline™)	
Diabetes	Pioglitazone (Actos™) Troglitazone (Rezulin™, Resulin™)	
Antiemetic		Aprepitant (Emend™)
Anti-Hypertension		Diltiazem (Cardizem™) Verapamil (Calan™, Calan SR™)
Glucocorticoid (Systemic)	Betamethasone (Celestone™) Dexamethasone (Baycadron™, DexPak™) Hydrocortisone (Cortef™) Methylprednisolone (Medrol™) Prednisolone (Prelone™) Prednisone (Deltasone™) Triamcinolone (Kenalog™)	

Antibiotics	Rifabutin (Mycobutin™) Rifampicin/ Rifampin (Rifadin™, Rifater™, Rimactane™)	Erythromycin (Benzamycin™, EryTab™) Clarithromycin (Biaxin™) Telithromycin (Ketek™)
Anti-Fungal		Fluconazole (Diflucan™, Trican™) Itraconazole (Sporanox™) Ketoconazole (Nizoral™)
Anti-HIV	Efavirenz (Stocrin™,Sustiva™) Nevirapine (Viramune™)	Indinavir (Crixivan™) Nelfinavir (Viracept™) Ritonavir (Norvir™) Saquinavir (Fortovase™, Invirase™)
Immune Suppressant		Cyclosporine - Oral/IV only (Neoral™,Sandimmune™)
Others	St. John's Wort Enzalutamide (Xtandi™) Modafinil (Provigil™) Armodafinil (Nuvigil™)	Buprenorphine (Cizol™, Subutex™, Suboxone™) Quinine

Drugs with narrow therapeutic margins with potential for CYP drug interactions	Warfarin(Coumadin™) Digoxin (Digitek™, Lanoxin™, Digox™) Cisapride (Prepulsid™, Propulsid™) Pimozide (Orap™)
Drugs with demonstrated efficacy for the prevention of migraine	Topiramate (Topamax™) Valproic acid, sodium valproate, divalproex (Depakote™) Amitriptyline (Elavil™) Nortriptyline (Pamelor™) Metoprolol (Lopressor™, Toprol™) Atenolol (Tenormin™) Nadolol (Corgard™) Propranolol (Inderal™) Timolol (Apo-Timol™) Venlafaxine (Effexor™)
Non-pharmacologic headache interventions:	Acupuncture TENS (transcutaneous electrical nerve stimulation) Cranial traction Nociceptive trigeminal inhibition Occipital nerve block treatments Dental splints for headache

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

- BOTOX injections into areas of the head, face, or neck

12.3 Classification of Migraine Preventive Medications

Below is a list of migraine preventive medications considered effective or probably effective sorted by mechanism of action. Of note, topiramate and valproic acid derivatives are considered separate categories. A history of inadequate response to 3 or more of these medications (2 of which have different mechanisms of action) will exclude the patient from the study.

Pharmacologic Category	**Drug Name**
Anticonvulsant	Topiramate
Anticonvulsant	Valproic acid, sodium valproate, divalproex
Tricyclic Antidepressant	Amitriptyline
	Nortriptyline
Beta-blockers	Metoprolol
	Atenolol
	Nadolol
	Propranolol
	Timolol
SNRI (serotonin norepinephrine reuptake inhibitor)	Venlafaxine

12.4 Glossary of Abbreviations

Term/Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BID	twice daily
BP	blood pressure
CGRP	calcitonin gene-related peptide
CIDV	capsaicin-induced dermal vasodilatation
CRF	case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP3A4	cytochrome P450 3A4
DBS	dry blood spot
ECG	electrocardiogram
eCRF	electronic case report form
eTablet	electronic tablet
EQ-5D-5L	European Quality of Life – 5-Dimensional – 5-Level
GCP	Good Clinical Practices
HIPAA	Health Insurance Portability and Accountability Act
HIT-6	Headache Impact Test
ICH	International Conference on Harmonisation
ICHD-3 beta	International Classification of Headache Disorders criteria, 3rd edition (beta version, 2013)
IEC	Independent Ethics Committee
IgM	immunoglobulin M
INR	coagulation parameters
IRB	Institutional Review Board
IV	intravenous
IWRS	interactive web response system
MI	multiple imputation
MMRM	mixed-effects model for repeated measures
NSAID	nonsteroidal anti-inflammatory drug
PGIC	Patient Global Impression of Change
PR	pain relief
QD	once daily

QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$)
PK	pharmacokinetic
SAE	serious adverse event
SAP	statistical analysis plan
ULN	upper limit of normal
WPAI-SHP	Work Productivity and Activities Impairment-Specific Health Problem

12.5 Protocol Amendment 1 Summary

Title: A Phase 2/3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study To Evaluate The Efficacy, Safety, And Tolerability Of Multiple Dosing Regimens Of Oral AGN-241689 In Episodic Migraine Prevention

Protocol CGP-MD-01

Date of Amendment: 11 Nov 2016

Amendment Summary

This amendment includes changes made to Protocol CGP-MD-01 (09 May 2016*)*. The protocol was amended to: 1) update contact information; 2) correct or rephrase inaccurate text; 3) update the Schedule of visits and procedures; 4) exclude patients who have used injectable monoclonal antibodies for CGRP; 5) modify exclusion criteria #21 and #24; 6) clarify use of SSRIs and SNRIs; 7) clarify childbearing potential, acceptable contraception, and male participation requirements; 8) clarify the timing of the PK sampling; 9) exclude patients who use benzodiazepines; 10) reorder the secondary efficacy variables for the EU; 11) resort all the additional efficacy variables and the Health Outcomes Variables into 2 new sections; 12) make instructions for the management of patients with ALT or AST elevations obligatory; and 13) clarify various study activities.

Following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
Protocol Title Page	Revised the name of the US Agent from Allergan (~~North America~~) to Allergan Sales, LLC Added the emergency contact number: +1-866-438-8820 [redacted] Removed the contact information for the Medical Monitor, and inserted: Refer to the Study Contacts Page Added the "Protocol Amendment 1 Date" to the title page	The name of Allergan in the US has changed To remove need to consult the study contacts page for this information The number has changed To preclude the need for amendment should the contact info change To reflect the approval date of Amendment 1
Protocol Summary, Response Measures	Replaced ~~acute medication use~~ with triptan use. Corrected the text relating to the name of the measure: Patient Satisfaction with Study Medication ~~for Migraine Prevention.~~ (in this section and throughout the protocol)	For accuracy To use the correct name of the measure
Protocol Summary, General Statistical Methods	Corrected the name of the MMRM: mixed-effects model for ~~reported~~ repeated measures (in this section and elsewhere in the protocol). Reordered the secondary efficacy variables for the European Union	To use the correct name of the model For accuracy
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Section	Revision	Rationale
[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]

Section	Revision	Rationale
Section 1.2, Overview of AGN-241689	[redacted] AGN-241689	For accuracy
Section 3.2 Efficacy Assessments	Deleted the full list of primary, secondary, and additional efficacy parameters (for the US and EU), and added text regarding how assessments will be collected: Efficacy assessments will be based on information recorded by the patient. 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, probable migraine, and headache days per the criteria listed in Sections [redacted]	To eliminate repetition of information already stated elsewhere (Section 7.2), and to describe the mode of data collection
[redacted]	[redacted]	[redacted]
Section 3.5 ~~Drug~~ Data Safety Monitoring Board	Changed the name of the ~~Drug~~ Safety Monitoring Board to Data Safety Monitoring Board	For accuracy
Section 4.3 Exclusion Criteria	Added text to criterion #8: (barbiturates are excluded during the baseline period and for the duration of the study [see Section 12.2 Examples of Prohibited Medications]). [redacted] #24	For clarity To allow patients with reversions to be included To exclude patients who have used injectable monoclonal antibodies for the CGRP pathway
Section 4.4.1 Permissible Medications/Treatments	Inserted text regarding use of SSRIs and SNRIs: Selective serotonin reuptake inhibitors (SSRI) or serotonin norepinephrine reuptake inhibitors (SNRI) will be permitted provided that treatment	To allow for patient use of stable-dose (at least 60 days prior to screening) SSRIs and

Section	Revision	Rationale
	is stable for at least 60 days prior to screening (Visit 1) and continues without change in dose throughout the study.	SNRIs.
Section 4.4.3 Definition of Females of (Non-) Childbearing Potential and/or Acceptable Contraceptive Methods	Adjusted text that defines childbearing potential, acceptable contraception, and male participant requirements: For purposes of this study, females 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 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 reliable: hormonal contraceptives (ie, oral, patch, vaginal ring, injection, implant), male condom with intravaginal spermicide, diaphragm or cervical cap with spermicide, ~~vaginal contraceptive ring,~~ intrauterine device, ~~surgical sterilization (bilateral tubal ligation, bilateral salpingectomy),~~ vasectomized partner, or sexual abstinence. Male participants must also refrain from donating sperm during the course of the study.	For clarity regarding acceptable means of contraception , and to forbid sperm donation during the study.
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Section	Revision	Rationale
	[redacted].	
[redacted]	[redacted]	[redacted]
6.3 Future Biomedical Research	Revised text to clarify possible uses of samples and to clarify destruction of by-products of the samples from patients who withdraw consent.	For clarity
Table 6–1 Clinical Laboratory Parameters	Added benzodiazepines to the list of urine drug screen parameters	To accurately reflect the urine drug screens being conducted
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Section 8.9 Withdrawal Criteria	The withdrawal criteria have been restated: Women who become pregnant (Section 9.4) and patients who meet investigational product discontinuation criteria ~~experience treatment-emergent AEs~~ related to abnormal liver function tests (Section 9.5) and advised not to be re-challenged will be withdrawn from the study and should refrain from taking investigational product. The patient should return to the clinic for early termination procedures (Visit 7) and the Safety Follow-up Visit 8.	For clarity
Section 8.10 Withdrawal from Future Biomedical Research	Text regarding destruction of patient's samples has been replaced with: A patient 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 patient withdraws consent, their physical	For accuracy

Section	Revision	Rationale
	sample will be destroyed and no new health information identifying the patient 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.	
Section 9.5 ALT or AST Elevations	Throughout this section, the instructions for patients with ALT or AST $\geq$ 3xULN, have been made obligatory. All previous instructions that indicated "~~should~~" have been replaced with "must" or "will" , and additional instructions have been added to paragraphs 4, 6, and 9: An extra blood serology sample ~~should~~ must be collected and sent to the central laboratory for further diagnostic testing at a later date if needed. An extra serology blood sample ~~should~~ will be collected and sent to the central laboratory for further diagnostic testing at a later date if needed. For patients that are not re-challenged with investigational product the patient should be discontinued from the study and complete the Early Termination Visit 7 and Safety Follow-Up Visit 8. Patients should receive appropriate follow-up as per standard of care.	For patient safety
Section 9.6 Procedures for Unmasking of Investigational Product	Text has been revised to make notification of the sponsor obligatory when there was no prior notification of unmasking	For clarity
Section 12.2 Examples of Prohibited Medications	Armodafinil (Nuvigil™) has been added to the "Others" row	For accuracy
Section 12.3 Classification of Migraine Preventive Medications	Text has been added to Paragraph 1 to clarify that the list refers to medications that are effective or probably effective for prevention of migraine. Explanatory footnotes have been deleted.	For accuracy

12.6 Protocol Amendment 2 Summary

Title: A Phase 2/3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study To Evaluate The Efficacy, Safety, And Tolerability Of Multiple Dosing Regimens Of Oral AGN-241689 In Episodic Migraine Prevention

Protocol CGP-MD-01

Date of Amendment 2: 11 Sep 2017

Amendment Summary

This amendment includes changes made to original Protocol CGP-MD-01 (09 May 2016*)* as amended with Amendment 1 (11 Nov 2016). The protocol was amended to: 1) allow participation of patients with history of hemiplegic migraine; 2) revise the primary and secondary efficacy endpoints for the US and EU; 3) revise the multiple comparisons procedure; 4) update the sample size calculation; 5) define "one month" for the efficacy analysis; 6) revise the additional efficacy variables for the US and EU; and 7) clarify the section on early discontinuation of patients.

Following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. In this summary, added text is shown underlined, and deleted text is shown as strikethrough. Minor editorial and document formatting revisions have not been summarized.

Section	**Revision**	**Rationale**
Protocol Summary, Clinical Hypotheses, and Section 2.2 Clinical Hypotheses	Rewrite the Clinical Hypotheses**:** In individuals with episodic migraine, at least one ~~of the following doses (10 mg QD, 30 mg QD, 30 mg BID, 60 mg QD, and 60 mg BID) dose~~ active treatment arm, 60 mg QD or 60 mg BID is superior to placebo as measured by the change from baseline in mean monthly ~~number of~~ migraine/probable migraine (MPM) headache days across the 12-week treatment period ~~in the last 28 days of the treatment period ending with week 12~~.	Per discussion with regulatory authority
Protocol Summary, Study Population Characteristics, Key Exclusion Criteria, Section 4.3 (criterion #2)	Remove the exclusion of participants with history of ~~hemiplegic migraine~~: Has a history of migraine with accompanied by diplopia or decreased level of consciousness or~~, hemiplegic migraine, and~~ retinal migraine as defined by ICHD-3 beta version, 2013	Per discussion with regulatory authority
Protocol Summary, Response Measures	Revise the efficacy measure for triptan use: Frequency of migraine or probable migraine headache days, headache days, and ~~triptan use~~ acute medication use days	Per discussion with regulatory authority
Protocol Summary, General Statistical Methods, and Section	Revise the primary efficacy endpoint: The primary efficacy endpoint is the change from baseline in mean monthly MPM headache days across the 12-week treatment period ~~the frequency~~	Per discussion with regulatory authority

Section	Revision	Rationale
7.3.1 Primary Efficacy Analyses	~~of migraine/probable migraine headache days per 4 weeks, the primary measurement time is the 28 days ending with diary week 12, and the primary analysis is on the change from baseline~~. Comparisons between each dose group and placebo 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 and treatment group by visit interaction as categorical fixed effects. It will also include the baseline score and baseline-by-visit interaction as covariates. Pairwise contrasts in the MMRM model will be used to make the pairwise comparisons of dose to placebo. A sensitivity analysis 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. The sensitivity analysis will be done using a pattern-mixture model (PMM), under which data could be missing-not-at-random (MNAR), with repeated analyses combined via the multiple imputation procedure (MI). An additional sensitivity, multiple imputation in conjunction with robust regression, will be performed in case of non-normality for the primary efficacy endpoint.	
Protocol Summary, General Statistical Methods	Revise the secondary efficacy endpoints: Secondary efficacy endpoints ~~will be analyzed separately for the United States (US) and Europe (EU) submissions. Secondary efficacy endpoints for the US~~ include: (1) Change from baseline in mean monthly headache days across the 12-week treatment period ~~Change from baseline in number of headache days to the last 28 days of the treatment period ending with week 12~~; (2) Proportion of patients with at least a 50% reduction in mean monthly MPM days across the 12-week treatment period ~~migraine/probable migraine headache days in the last 28 days of the treatment period ending with week 12~~; (3) Change from baseline in mean monthly acute medication use days across the 12-week treatment period ~~Change from baseline in the activities of daily living (ADL) domain score of the ACM-I (Assessment of Chronic Migraine Impact) at week 12; (4) Proportion of patients "satisfied" or "extremely satisfied" with study medication for migraine prevention at week 12. Secondary efficacy endpoints for the EU include: (1) Change from baseline in number of headache days to the last 28~~	Per discussion with regulatory authority

Section	Revision	Rationale
	~~days of the treatment period ending with week 12; (2) Proportion of patients with at least a 50% reduction in migraine/probable migraine headache days per 28 day period at the end of the 12 week treatment period; (3) Change from baseline in number of triptan use days to the last 28 days of the treatment period ending with week 12; (4) Change from baseline in the HIT-6 total score (Headache Impact Test) at week 12.~~	
Protocol Summary, General Statistical Methods	Revise the multiple comparisons procedure: The overall type I error rate for multiple comparisons across active treatment doses and the primary and ~~four~~ secondary efficacy parameters will be controlled at the 0.05 level using a graphical approach by Bretz et al (2011~~2009~~). The weighting strategy of the multiple comparisons is designed to allocate initial alpha equally to the QD and BID dose regimens. Within each dosing regimen, individual AGN-241689 doses will be tested in a hierarchical order from high to low dose, i.e. for primary efficacy endpoint, low dose can be tested only if high dose comparison shows statistical significance. In addition, for a given dose comparison versus placebo, the strategy has the primary endpoint as gatekeeper to the secondary endpoints so that secondary endpoints can be tested only if primary hypothesis of the corresponding dose comparison reaches statistical significance. ~~allocates ¼ weight to each of 30 mg QD, 30 mg BID, 60 mg QD and 60 mg BID comparisons versus placebo for the primary hypothesis. If any of those comparisons is rejected, 20% of the corresponding weight will be propagated to test 10 mg QD versus placebo for the primary hypothesis and 80% of the weight will be propagated to test the first secondary hypotheses in the corresponding dose versus placebo. Then for the comparison of each dose versus placebo, 100% of the weight will be propagated sequentially for the remaining secondary endpoints. Finally, if for one of the doses efficacy can be shown for primary and all the secondary endpoints, the associated weight is passed on to other doses. This weighting strategy implies that the 10 mg QD versus placebo comparison can only be tested if at least one of the 30 mg QD, 30 mg BID, 60 mg QD and 60 mg BID versus placebo comparisons for the primary hypothesis is rejected and a small amount of weight is to be allocated to the 10 mg QD versus placebo comparison, since it is~~	Per discussion with regulatory authority

Section	Revision	Rationale
	~~selected as a likely suboptimal dose. Similarly, under this strategy, no secondary hypothesis can be rejected until a primary hypothesis of the corresponding dose comparison is rejected. The primary endpoint will serve as the gatekeeper for the secondary endpoints.~~ Weighted ~~Simes~~ Bonferroni tests will be used for testing the hypotheses. ~~within each endpoint as the associated test statistics are positively correlated, and a Bonferroni mixture will be used to combine test results across different endpoints.~~ A complete decision-flow graph and details of the graphical multiple comparison procedure will be presented in the statistical analysis plan of this study.	
Protocol Summary, General Statistical Methods, Sample Size Calculation; and Section 7.7	Revise the Sample Size Calculation: The assumptions and corresponding power assessments for the primary efficacy endpoint are shown in the table below (*Note: the revised table is not included here).* The treatment difference assumption is based on results from other episodic migraine prevention studies: the placebo-adjusted reduction in monthly migraine days ranged from 1.1 to 2 days (topiramate [Silberstein et al. 2004 and Brandes et al. 2004], telcagepant [Ho et al., 2014], and CGRP monoclonal antibodies Ph2 studies [Dodick et al., 2014; Dodick et al., 2014; Bigal et al., 2015; Sun et al 2016], and their Ph3 studies results reported from American Headache Society & American Academy of Neuroscience 2017). Common standard deviation is estimated based on blinded interim data assessments of this study. Power is calculated via 10,000 simulations based on multiplicity adjustment. ~~The following table displays the power calculations for treatment comparisons of 30 mg or 60 mg QD versus placebo and 30 mg or 60 mg BID versus placebo, respectively. The differences between treatment groups in the mean number of migraine/probable migraine headache days change from baseline at the primary timepoint (Week 12) is assumed to be 1.5 for the comparison of 30 mg or 60 mg QD versus placebo (assumed equally effective for 30 mg QD and 60 mg QD), and be 1.75 for the comparison of 30 mg or 60 mg BID versus placebo (assumed equally effective for 30 mg BID and 60 mg BID). With the allocated ¼ weight, each of the hypotheses will be tested at alpha level of~~	Updated to reflect revised primary endpoint and multiplicity strategy

Section	Revision	Rationale
	~~0.0125 using the Bonferroni approach for power calculation. This is a more conservative power assessment compared to the weighted Simes test used in the final analysis. The statistical power calculations are focused on doses of 30 mg QD, 30 mg BID, 60 mg QD and 60 mg BID, because the 10 mg QD is considered to likely be a suboptimal dose and is only tested if at least one of the 4 doses comparison is significant. For critical alpha level 0.0125, the powers are displayed based on a standard deviation estimate of 4.0.~~	
Section 6.1.1.4 Acute Medication Use Day and Triptan Use Day	Describe the allowed medications for headache pain: The allowed medications include the following categories of drugs: triptans, ergots, opioids, analgesics (including acetaminophen), NSAIDs (including aspirin), and antiemetics.	For clarity
[redacted]	[redacted]	[redacted]
Section 7.2 Collection and Derivation of Primary and Secondary Efficacy Assessments	Revise section to define "one month". For analysis purposes, four weeks (28 days) will be considered as one month.	For clarity
Section 7.2.1 Primary Efficacy Variable	Revise the primary efficacy variable: The primary efficacy variable is the change from baseline in mean monthly MPM headache days across the 12-week treatment period. ~~the frequency of migraine/probable migraine headache days to the 28-day period ending with Week 12 (ie, Day 57 to Day 84 inclusive, relative to the day 1 treatment start).~~	Per discussion with regulatory authority

Section	Revision	Rationale
Section 7.2.2 Secondary Efficacy Variables ~~for the United States~~	Revise the secondary efficacy variables: The 3~~4~~ secondary efficacy variables ~~for the US~~ include: • Change from baseline in mean monthly ~~number of~~ headache days across the 12-week treatment period ~~to the last 28 days of the treatment period ending with week 12~~. • Proportion of patients with at least a 50% reduction in mean monthly migraine/probable migraine headache days across the 12-week treatment period ~~in the last 28 days of the treatment period ending with week 12~~. • Change from baseline in mean monthly acute medication use days ~~the activities of daily living (ADL) domain score of the ACM-I (Assessment of Chronic Migraine Impact) at week 12~~ • ~~Proportion of patients "satisfied" or "extremely satisfied" with study medication for migraine prevention at week 12.~~	Per discussion with regulatory authority
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Section	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Section	Revision	Rationale
		[redacted]
Section 7.3.2 Secondary Efficacy Analyses	Revise this section: The secondary efficacy variables are identified in rank order ~~for the US and EU, respectively,~~ in Sections~~s~~ 7.2.2~~ and 7.2.3~~. ~~To control the type 1 error rate for multiple secondary endpoints, a gatekeeping approach will be used for these secondary variables at the primary visit (week 12) according to the rank order specified.~~ ~~Specifically, t~~ The overall type I error rate for multiple comparisons across active treatment doses and the primary and secondary efficacy parameters will be controlled at the 0.05 level using a graphical approach by Bretz et al. (2011). The weighting strategy of the multiple comparisons is designed to allocate initial alpha equally to the QD and BID dose regimen. Within QD or BID dose regimen, AGN-241689 doses will be tested in a hierarchical order from high to low dose, i.e. for primary efficacy endpoint, low dose can be tested only if high dose comparison shows statistical significance. In addition, for a given dose comparing versus placebo, the strategy has the primary endpoint as gatekeeper to the secondary endpoints so that secondary endpoints can be tested only if primary hypothesis of the corresponding dose comparison reaches statistical significance.~~allocates ¼ weight to each of 30 mg QD, 30 mg BID, 60 mg QD and 60 mg BID comparisons versus placebo for the primary hypothesis. If any of those comparisons is rejected, 20% of the corresponding weight will be propagated to test 10 mg QD versus placebo for the primary hypothesis and 80% of the weight will be propagated to test the first secondary hypotheses in the corresponding dose versus placebo. Then for the comparison of each dose versus placebo, 100% of the weight will be propagated sequentially for the remaining secondary endpoints. Finally, if for one of the doses efficacy can be shown for primary and all the secondary endpoints, the associated weight is passed on to other doses. This weighting strategy implies that the 10 mg QD versus placebo comparison can only be tested if at least one of the 30 mg QD, 30 mg BID, 60 mg QD and 60 mg BID	

Section	Revision	Rationale
	~~versus placebo comparisons for the primary hypothesis is rejected and a small amount of weight is to be allocated to the 10 mg QD versus placebo comparison, since it is selected as a likely suboptimal dose. Similarly, under this strategy, no secondary hypothesis can be rejected until a primary hypothesis of the corresponding dose comparison is rejected. The primary endpoint will serve as the gatekeeper for the secondary endpoints.~~ Weighted ~~Simes~~ Bonferroni tests will be used for testing the hypotheses~~ within each endpoint as the associated test statistics are positively correlated, and a Bonferroni mixture will be used to combine test results across different endpoints~~. A complete decision-flow graph and details of the graphical multiple comparison procedure will be presented in the statistical analysis plan of this study.	
[redacted]	[redacted]	[redacted]
Section 8.8 Early Discontinuation of Patients	Revise the last paragraph of this section: Patients may voluntarily withdraw from the study at any time. Notification of early patient discontinuation from the study and the reason for discontinuation will be clearly documented on the appropriate case report form. All randomized patients who prematurely discontinue from the study, regardless of cause, should be seen for ~~a~~ final study assessments. The final assessments will be defined as completion of the evaluations scheduled for Visit 7/Early Termination and Visit 8 Safety Follow-up, 4 weeks post the last dose of IP.	For clarity
Section 11. References	Additional references added.	To support revised sample size calculation