abbvie

Protocol for Trial M22-061

Migraine: Atogepant versus Topiramate for Preventive Treatment of Migraine

VERSION:	5.0	DATE:	17 September 2024
SPONSOR:	AbbVie*	PLANNED NUMBER OF SITES:	85
ABBVIE INVESTIGATIONAL PRODUCT:	Atogepant	EU CT:	2022-501172-25-00

FULL TITLE: A Randomized, Double-blind, Parallel-group, Active Controlled Trial with Open-label Safety Extension to Evaluate the Tolerability, Safety, and Efficacy of Atogepant versus Topiramate in Subjects Requiring Preventive Treatment of Migraine (TEMPLE)

Incorporating Versions 1.0, 2.0, 3.0, 4.0, and 5.0

PRINCIPAL INVESTIGATORS: Investigator information on file at AbbVie.

SPONSOR/EMERGENCY MEDICAL CONTACT:*

[redacted], MD, MSc
AbbVie
Lechner Ödön fasor 7
H-1095 Budapest
Hungary

Mobile: [redacted]
Email: [redacted]

EMERGENCY 24-hour Number: +1 (973) 784-6402

*For European Union countries: the sponsor is AbbVie Deutschland GmbH & Co. KG. The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority. Additional trial contact information can be found in the Operations Manual (Appendix H).

abbvie

TABLE OF CONTENTS

1 SYNOPSIS 5

2 INTRODUCTION 8

2.1 Background and Rationale 8

2.2 Benefits and Risks to Subjects 9

3 OBJECTIVES AND ENDPOINTS 10

3.1 Objectives, Hypotheses, and Estimands 10

3.2 Primary Endpoint 11

3.3 Secondary Endpoints 11

3.4 Additional Efficacy Endpoints 12

3.5 Safety Endpoints 12

3.6 Pharmacokinetic Endpoints 12

3.7 Biomarker Research Endpoints 13

4 INVESTIGATIONAL PLAN 13

4.1 Overall Trial Design and Plan 13

4.2 Discussion of Trial Design 15

5 TRIAL ACTIVITIES 19

5.1 Eligibility Criteria 19

5.2 Contraception Recommendations 24

5.3 Prohibited Medications and Treatments 25

5.4 Prior and Concomitant Treatments 27

5.5 Discontinuation of Study Drug, Withdrawal of Subjects, and Discontinuation of Trial 28

5.6 Follow-Up After Subject Discontinuation of Study Drug or Trial 30

5.7 Study Drug 31

5.8 Randomization/Drug Assignment 32

5.9 Protocol Deviations 32

5.10 External Committees 33

5.11 Publication Policy 33

6 SAFETY CONSIDERATIONS 34

6.1 COMPLAINTS AND ADVERSE EVENTS 34

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE 38
7.1 STATISTICAL AND ANALYTICAL PLANS 38
7.2 DEFINITION FOR ANALYSIS POPULATIONS 38
7.3 HANDLING POTENTIAL INTERCURRENT EVENTS FOR THE PRIMARY AND KEY SECONDARY ENDPOINTS 39
7.4 STATISTICAL ANALYSES FOR EFFICACY 40
7.5 STATISTICAL ANALYSES FOR SAFETY 41
7.6 INTERIM ANALYSIS 41
7.7 OVERALL TYPE I ERROR CONTROL 42
7.8 SAMPLE SIZE DETERMINATION 42

8 ETHICS 43
8.1 INDEPENDENT ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD 43
8.2 ETHICAL CONDUCT OF THE TRIAL 43
8.3 SUBJECT CONFIDENTIALITY 43

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION 44

10 DATA QUALITY ASSURANCE 44

11 START AND COMPLETION OF THE TRIAL 44

12 REFERENCES 44

LIST OF TABLES

TABLE 1. SUMMARY OF RESULTS OF PHASE 3 TRIAL 3101-301-002 ("ADVANCE") 16

TABLE 2. SUMMARY OF RESULTS OF PHASE 3 TRIAL 3101-303-002 ("PROGRESS") 18

TABLE 3. IDENTITY OF STUDY DRUGS 31

LIST OF FIGURES

FIGURE 1. TRIAL SCHEMA 15

LIST OF APPENDICES

APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS 46

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR 49

APPENDIX C. LIST OF PROTOCOL SIGNATORIES 50

APPENDIX D. MIGRAINE PREVENTION MEDICATIONS 51

APPENDIX E. EXAMPLES OF PROHIBITED MEDICATIONS 53

APPENDIX F. ACTIVITIES SCHEDULES 56

APPENDIX G. PROTOCOL SUMMARY OF CHANGES 67

APPENDIX H. OPERATIONS MANUAL 70

1 SYNOPSIS

Title: A Randomized, Double-blind, Parallel-group, Active Controlled Trial with Open-label Safety Extension to Evaluate the Tolerability, Safety, and Efficacy of Atogepant versus Topiramate in Subjects Requiring Preventive Treatment of Migraine (TEMPLE)	
Background and Rationale:	Discontinuation rates for existing oral generic preventive treatments of migraine, including topiramate, are high due to poor tolerability or lack of efficacy. These limitations result in poor adherence and reluctance to initiate prophylactic treatment. Atogepant is a potent, selective oral calcitonin gene-related peptide receptor antagonist approved by the United States Food and Drug Administration for the preventive treatment of episodic migraine (EM) in adults. The purpose of this trial is to evaluate the tolerability, safety, and efficacy of atogepant compared to topiramate for the preventive treatment of migraine. **Benefit-Risk Analysis** There is a significant unmet need for additional effective and safe preventive treatments for migraine. In this study, all subjects will receive active treatment for the prevention of migraine, either topiramate or atogepant, and may use their usual medications for the acute treatments of migraine. Atogepant has been found efficacious, safe, and generally well tolerated in clinical trials, with the most commonly reported adverse drug reactions being nausea, constipation, fatigue/somnolence, decreased appetite, and decreased body weight. Subjects will undergo thorough safety monitoring during the study. An independent Data Safety Monitoring Board will review safety data throughout the study and make recommendations to the sponsor including modification or early termination of the study. An external hepatic event adjudication committee will also provide blinded surveillance, monitoring and adjudication of events of post-treatment elevations of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≥ 3 x the upper limit of normal (ULN) in this study. A newly identified risk of hypersensitivity, including anaphylaxis, dyspnea, rash, pruritus, urticaria, and facial edema, with the use of atogepant has been identified based on postmarketing safety reports. Overall, the benefit: risk assessment is favorable.
Objectives and Endpoints:	The primary objective of the trial is to evaluate the tolerability and safety of atogepant 60 mg once daily [QD] compared to the highest tolerated dose of topiramate (50, 75, or 100 mg/day) in subjects who require preventive treatment of migraine. The following primary endpoint will be evaluated: • Treatment discontinuation due to adverse events (AEs) during the 24-week double-blind (DB) treatment period.

	The following secondary endpoints will be evaluated: • Achievement of ≥ 50% improvement (reduction) in mean monthly migraine days (MMD) during Months 4 to 6 of the DB treatment period. • Change from baseline in mean MMD during Months 4 to 6 of the DB treatment period. • Change from baseline in Headache Impact Test (HIT-6) total score at Week 24. • Change from baseline in Migraine Specific Quality of Life Questionnaire (MSQ) Version 2.1 Role Function-Restrictive (RFR) domain score at Week 24. • Achievement of a rating of "much better" or "very much better" as assessed by Patient Global Impression of Change (PGIC) at Week 24. • Change from baseline in Patient-Reported Outcomes Measurement Information System (PROMIS) Cognitive Function – Abilities Subset – Short Form 6a Version 2.0 score at Week 6
Investigators:	Multicenter
Study Sites:	Approximately 85 sites
Study Population and Number of Subjects to be Enrolled:	A total of approximately 520 subjects with migraine.
Investigational Plan:	The trial is a multicenter, randomized, DB, double-dummy, parallel-group, active controlled trial with an open-label (OL) safety extension. The trial will consist of a screening/baseline period (4 to 5 weeks), a 24-week DB treatment period including a topiramate up-titration phase (6 weeks) and maintenance phase (18 weeks), an OL treatment period (52 weeks), and a safety follow-up period (4 weeks) for a total trial duration of up to 85 weeks. Subjects will collect daily headache data in a handheld electronic device and will attend regular study visits where clinical procedures will be performed. Procedures include self-administered questionnaires, safety assessments, and laboratory tests. Optional collection of samples for PK assessments and biomarker research will be collected at this time.
Key Eligibility Criteria:	Adult subjects with a history of ≥ 4 migraine days per month who require preventive treatment of migraine and are eligible for conventional migraine prophylaxis may be enrolled if they have not used topiramate or atogepant in the past and have no clinically significant cardiovascular, cerebrovascular, hematologic, endocrine, pulmonary, renal, hepatic, gastrointestinal, or neurologic disease.

Study Drug and Duration of Treatment:	Treatment duration will be approximately 76 weeks. During the DB treatment period, subjects will be randomized in a 1:1 ratio to one of 2 treatment groups: • Atogepant 60 mg QD • Topiramate at highest tolerated dose (50, 75, or 100 mg/day) During the OL treatment period, all subjects will receive atogepant 60 mg QD.
Date of Protocol Synopsis:	17 September 2024

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Trial Being Conducted?

Migraine is 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). Migraine affects 18% of women and 6% of men in the United States (US) and 17.6% of women and 8% of men in Europe.[1] Approximately one third of people with migraine have 3 or more migraines per month, and over half report severe impairment or the need for bed rest.[2] As of 2016, migraine is the second leading cause of disability worldwide.[3] Improving diagnosis and optimizing treatments for migraine have been recognized as critically important to overcoming current barriers to reduce the global burden of migraine.

Because there are no biological markers for migraine, diagnosis is based on clinical history, examination, and the exclusion of other headache disorders. Physicians apply clinical criteria to guide diagnoses and subsequent treatment. Episodic migraine (EM) is a syndrome diagnosis applied to patients with migraine with or without aura who have < 15 headache days per month. Chronic migraine (CM) is a specific International Classification of Headache Disorders, Third Edition (ICHD-3) diagnosis applied to a subset of patients with ≥ 15 headache days and ≥ 8 migraine days per month.[4-6] Patients can move bi-directionally from one category to the other over time.[7] Most patients with CM have evolved over time from EM. Conversely, patients with CM can revert to < 15 headache days and no longer meet criteria for the CM diagnosis. Episodic migraine and CM represent a continuum of patients, all diagnosed with migraine with or without aura.

The conventional medications used for migraine prevention were initially developed for other indications and include antiepileptic drugs (e.g., topiramate, valproate), antidepressants (e.g., amitriptyline), betablockers (e.g., propranolol, metoprolol), calcium channel antagonists (e.g., flunarizine), angiotensin converting enzyme inhibitors (e.g., lisinopril), angiotensin II receptor blockers (e.g., candesartan), and botulinum toxin.[8,9] Topiramate is one of the most widely used preventive medications and is recommended by several therapeutic guidelines as one of the initial choices for migraine prevention.[9] However, discontinuation rates for existing oral prophylactic medications, including topiramate, are high for both EM and CM.[10] Recent studies have indicated that approximately half of people with migraine discontinued their initial oral migraine prophylactic treatment within 60 days due to poor tolerability or lack of efficacy.[10,11] These limitations in currently available migraine prophylactic treatments result in poor adherence[11,12] and reluctance to initiate prophylactic treatment.[8]

Atogepant is a potent, selective oral calcitonin gene-related peptide (CGRP) receptor antagonist approved by the US Food and Drug Administration for the preventive treatment of EM in adults on 28 September 2021 (brand name QULIPTA™, recommended doses as per USPI: 10 mg, 30 mg, 60 mg once daily [QD]). A supplemental New Drug Application for CM in the US and a Marketing Authorization Application in Europe for the prophylaxis of migraine in adults with ≥ 4 migraine days were filed in June 2022 with a recommended dose as per the EU Summary of Product Characteristics (SmPC) of

60 mg QD. In clinical trials with subjects with EM or CM, atogepant was well tolerated and had an acceptable safety profile.

Considering the poor tolerability of and lack of adherence to conventional oral preventive treatments, this trial may provide important insights as to whether the novel treatment option provided by atogepant is associated with the additional benefits of better adherence and improved treatment outcomes compared to conventional prophylaxis, supporting clinicians to make appropriate treatment decisions to allow for the best outcomes for their patients. The trial was designed considering feedback received from clinical migraine experts and from the German Health Technology Assessment (HTA) body G-BA during the advice meeting. The trial will provide important data to support HTA Agencies' need for evidence for reimbursement purposes.

2.2 Benefits and Risks to Subjects

There is a significant unmet need for additional preventive treatments for migraine due to the poor tolerability and adherence of conventional oral preventive treatments. The efficacy, safety, and tolerability of atogepant have been demonstrated in adequate and well-controlled pivotal trials and long-term safety trials. Atogepant is generally well tolerated, with the most commonly reported adverse drug reactions in clinical trials being nausea, constipation, fatigue/somnolence, decreased appetite, and decreased body weight.

Asymptomatic aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevations above 3 × the upper limit of normal (ULN) were rarely observed during the clinical trials and there was a balance in the incidence of these elevations between atogepant treatment arms and placebo. No cases of severe liver injury or concurrent bilirubin elevations (≥ 2 × ULN) were observed during the clinical trials. Hepatotoxicity events are under close surveillance and monitoring during this study. In addition, an independent Data Safety Monitoring Board (DSMB) will review safety data throughout the study and make recommendations to the sponsor including modification or early termination (ET) of the study. An external hepatic event adjudication committee will also provide blinded surveillance, monitoring, and adjudication of events of post-treatment elevations of ALT and/or AST ≥ 3 × ULN in this study.

A newly identified risk of hypersensitivity, including anaphylaxis, dyspnea, rash, pruritus, urticaria, and facial edema, with the use of atogepant has been identified based on postmarketing safety reports. Serious hypersensitivity reactions, such as anaphylaxis, are rare, idiosyncratic in nature, and treatable with well-established treatment options as part of the standard of care.

As such, considering atogepant's established efficacy and safety profile and the measures planned to minimize risk to subjects participating in this study, the benefits of treatment with atogepant outweigh the risks, including serious hypersensitivity reactions, such as anaphylaxis.

For further details regarding atogepant and topiramate, please see the current atogepant Investigator's Brochure and the topiramate SmPC or Product Monograph.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives, Hypotheses, and Estimands

Primary

The primary objective of the trial is to evaluate the tolerability and safety of atogepant 60 mg QD compared to the highest tolerated dose of topiramate (50, 75, or 100 mg/day) in subjects who require preventive treatment of migraine.

The hypothesis corresponding to the primary endpoint is that atogepant 60 mg QD will have superior tolerability and safety compared to topiramate at the highest tolerated dose (50, 75, or 100 mg/day) during the 24-week double-blind (DB) treatment period.

The estimand corresponding to the primary endpoint is defined as the relative risk in the proportion of subjects with adverse events (AEs) leading to treatment discontinuation during the DB treatment period between the atogepant group and the topiramate group in the Safety Population 1. Subjects who discontinue trial treatment due to any reasons other than AEs (e.g., lack of efficacy, withdrawal of consent, lost to follow-up) will be classified as subjects without AEs leading to treatment discontinuation.

Key Secondary

The key secondary objective is to demonstrate a higher rate of subjects treated with atogepant versus topiramate achieving ≥ 50% improvement (reduction) in mean monthly migraine days (MMDs) during Months 4 to 6 of the DB treatment period.

The estimand corresponding to the key secondary endpoint is defined as follows: the relative ratio (relative risk) in the proportion of subjects achieving ≥ 50% reduction in MMD across Months 4 to 6 of the DB treatment period between the atogepant group and the topiramate group in the modified intent-to-treat (mITT) population. Subjects who prematurely discontinue study treatment and use other prohibited migraine prophylactic treatment will have their off-treatment data after starting the new migraine prophylactic treatment excluded from the analysis; subjects who prematurely discontinue study treatment due to all reasons other than starting a new migraine prophylactic treatment will have their data collected after discontinuation of study treatment, and those off-treatment data will be included in the analysis. Subjects without an evaluable month of electronic diary (eDiary) data during the last 3 months of the DB treatment period (Months 4, 5, 6) will be treated as non-responders.

The estimands for additional key secondary endpoints include the following:

- The difference in the mean change from baseline in mean MMD across Months 4 to 6 of the DB treatment period between the atogepant group and the topiramate group in the mITT population regardless of premature discontinuation of study drug. Off-treatment data after starting a new migraine prophylaxis treatment will be excluded.
- The difference in the mean change from baseline in Headache Impact Test (HIT-6) total score at Week 24 between the atogepant group and the topiramate group in the mITT population

regardless of premature discontinuation of study drug. Off-treatment data after starting a new migraine prophylaxis treatment will be excluded.

- The difference in the mean change from baseline in Migraine Specific Quality of Life Questionnaire (MSQ) Version 2.1 Role Function-Restrictive (RFR) domain score at Week 24 between the atogepant group and the topiramate group in the mITT population regardless of premature discontinuation of study drug. Off-treatment data after starting a new migraine prophylaxis treatment will be excluded.
- The relative ratio in the proportion of subjects achieving a rating of "much better" or "very much better" at Week 24 assessed by Patient Global Impression of Change (PGIC) in the mITT population regardless of premature discontinuation of study drug. Off-treatment data after starting a new migraine prophylaxis treatment will be excluded. Subjects without a PGIC value at Week 24 will be treated as non-responders.
- The difference in the mean change from baseline in PROMIS Cognitive Function Abilities Subset Short Form 6a Version 2.0 score at Week 6 the DB treatment period between the atogepant group and the topiramate group in the mITT population regardless of premature discontinuation of study drug. Off-treatment data after starting a new migraine prophylaxis treatment will be excluded.

3.2 Primary Endpoint

The primary endpoint is treatment discontinuation due to AEs during the 24-week DB treatment period.

3.3 Secondary Endpoints

Key Secondary Endpoints

- Achievement of ≥ 50% improvement (reduction) in mean MMD during Months 4 to 6 of the DB treatment period.
- Change from baseline in mean MMD during Months 4 to 6 of the DB treatment period
- Change from baseline in HIT-6 total score at Week 24
- Change from baseline in MSQ Version 2.1 RFR domain score at Week 24
- Achievement of a rating of "much better" or "very much better" at Week 24 assessed by the PGIC
- Change from baseline in PROMIS Cognitive Function Abilities Subset Short Form 6a Version 2.0 score at Week 6

3.4 Additional Efficacy Endpoints

Additional efficacy endpoints include measurements assessed at visits as specified in the Activities Schedules (Appendix F).

- Change from baseline in MSQ Version 2.1 Role Function-Preventive domain score at Week 24
- Change from baseline in MSQ Version 2.1 Emotional Function domain score at Week 24
- Achievement of at least a 5-point improvement (decrease) from baseline in HIT-6 total score at Week 24
- Change from baseline in Short Form-36 (SF-36) Version 2 Physical Component Score (PCS) and Mental Component Score (MCS) at Week 24
- Achievement of at least a 5-point increase from baseline to Week 24 in SF-36 Version 2 PCS and MCS
- Change from baseline in Patient Global Impression of Severity (PGI-S) score at Week 24
- Changes from baseline in percent work time missed, percent impairment while working, percent overall impairment, and percent activity impairment due to migraine at Week 24 as assessed by the Work Productivity and Activity Impairment (WPAI): Migraine
- Achievement of a rating of satisfied or extremely satisfied at Week 24 assessed by the Patient Satisfaction with Study Medication (PSSM)
- Change from baseline in PROMIS Cognitive Function Abilities Subset Short Form 6a Version 2.0 score at Weeks, 1, 2, 3, 4, 5, 8, 12, 16, 20, and 24 (to be conducted in a subset of subjects, see Operations Manual [Appendix H], Section 3.7)

Additional endpoints may be defined in the Statistical Analysis Plan (SAP).

3.5 Safety Endpoints

Safety evaluations include AE monitoring, clinical laboratory testing (hematology, chemistry, and urinalysis), vital sign measurements, electrocardiogram (ECG) variables, Columbia Suicide Severity Rating Scale (C-SSRS) responses, and pregnancy tests as measures of safety and tolerability for the entire trial duration.

3.6 Pharmacokinetic Endpoints

Optional pharmacokinetic (PK) blood samples will be collected from consented subjects at visits as specified in the Activities Schedules (Appendix F) to determine atogepant and/or topiramate plasma concentrations. Population PK analyses will be conducted to predict individual atogepant and/or topiramate exposure (including but not limited to steady state area under the curve to the end of the dosing period and minimum observed concentration). Systemic exposure parameter data may be used to explore exposure response relationships.

3.7 Biomarker Research Endpoints

Optional biospecimens (blood, plasma, and saliva) will be collected at specified time points (Appendix F) throughout the trial to evaluate known and/or novel disease-related or drug-related biomarkers in circulation or at tissue sites. Assessments may include, but are not limited to, biomarkers related to the pathway(s) targeted by the study drug or those believed to be related to the disease being studied (e.g., pharmacogenomics analysis, analysis of neuropeptides such as CGRP). The information learned from analyzing these samples may be used to investigate factors influencing response to treatment, scientific questions related to the disease, and/or in the development of new therapies and diagnostic tests. The biomarker research results may not be included with the clinical study report (CSR). Further details regarding the biomarker research are located in the Operations Manual (Appendix H), Section 3.9.

4 INVESTIGATIONAL PLAN

4.1 Overall Trial Design and Plan

The trial is a multicenter, randomized, DB, double-dummy, parallel-group, active controlled, 24-week trial comparing the tolerability, safety, and efficacy of atogepant 60 mg QD and topiramate at the highest tolerated dose (50, 75, or 100 mg/day) in adult subjects with EM or CM who are eligible for conventional migraine prophylaxis, with a subsequent 52-week, open-label (OL) atogepant safety extension.

The trial will consist of a screening/baseline period (4 to 5 weeks), a 24-week DB treatment period including a topiramate up-titration phase (6 weeks) and maintenance phase (18 weeks), an OL treatment period (52 weeks), and a safety follow-up period (4 weeks) for a total trial duration of up to 85 weeks.

After completing the screening/baseline period, approximately 520 eligible subjects will be randomized in a 1:1 ratio into one of the following 2 treatment arms:

- Atogepant 60 mg QD
- Topiramate at highest tolerated dose (50, 75, or 100 mg/day)

During the DB treatment period, due to the DB, double-dummy design, blinded atogepant or matching placebo and blinded topiramate or matching placebo will be administered separately. The dose of topiramate (or matching placebo) will not be blinded and can be adjusted as allowed by the protocol. Rescue interventions for the acute treatment of migraine attacks are permitted throughout the trial. Use of any migraine prevention medication other than study drug is not permitted during the entire trial including the safety follow-up period. See Section 5.3 for information regarding prohibited medication and Section 5.4 for information regarding concomitant medication use.

Subjects who prematurely discontinue study drug during the DB treatment period but do not withdraw consent should remain in the trial and continue collecting eDiary and ePRO data and attend scheduled trial visits remotely or in-person as defined in the Simplified Schedule of Activities (SSA) for Subjects who

Discontinue Study Drug Early During the Double-blind Treatment Period (Appendix F) up until the end of the 24-week DB treatment period.

A subject will be considered to have completed the DB treatment period when the subject has completed eDiary data collection of 24 weeks and completed Visit 13/Week 24. Subjects who completed the DB treatment period may enter the 52-week OL treatment period provided that the following criteria are met:

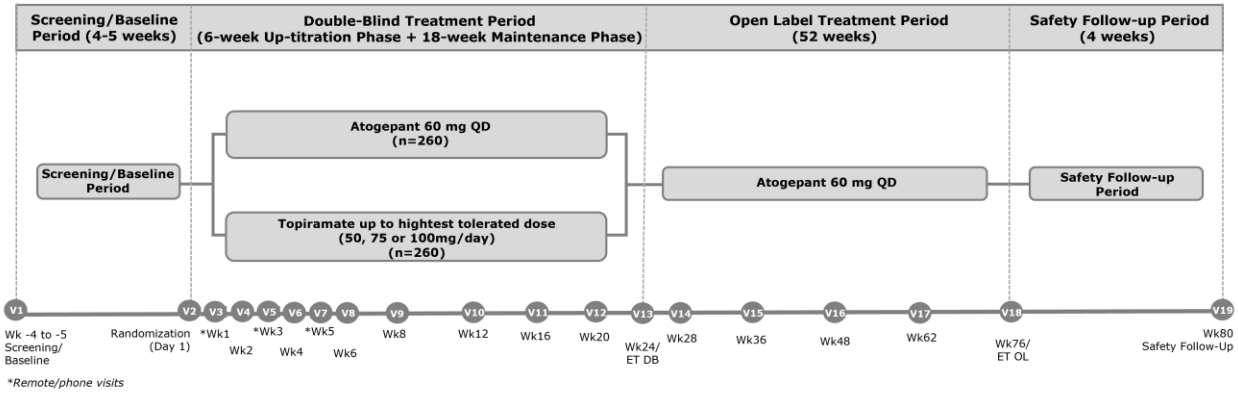
- Subject did not experience an AE that, in the investigator's opinion, may indicate an unacceptable safety risk
- Subject did not permanently discontinue study drug during the DB treatment period
- Subject did not start any new migraine preventive medication
- Subject will likely benefit from the OL atogepant treatment in the investigator's opinion

The schematic of the trial is shown in Figure 1. Clinical assessments, laboratory tests, collection of samples for optional PK assessments, and collection of optional biomarker samples will be performed at specified clinic visits or remotely as noted in the Study Activities Schedules (Appendix F). In the exceptional situations of a public health risk due to viral infection (e.g., COVID-19) to the subject or site staff or in situations of geopolitical conflict in Israel and surrounding impacted areas, additional remote study visits, conducted virtually or by phone, are permitted for selected visits, if agreed with the sponsor and permitted by site process and local regulations. During these remote study visits, the Study Activities for Remote Visits in Pandemic Situations or Geopolitical Conflict must be followed (Appendix F). Further details regarding trial procedures are located in the Operations Manual (Appendix H). See Section 5.1 for information regarding eligibility criteria.

An independent 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 ET of the trial, if emerging data show unexpected and clinically significant AEs related to study treatment. See Section 5.10 for information regarding the DSMB.

The primary analysis will be performed and a CSR prepared after the last subject completes the DB treatment period. Trial sites and subjects will remain blinded to DB treatment assignment throughout the entire study.

Figure 1. Trial Schema



DB = double-blind; ET = early termination; OL = open-label; QD = once daily; wk = week; V = visit

For subjects who complete the double-blind treatment period on blinded topiramate 75 mg/day or 100 mg/day, blinded topiramate may be down-titrated at investigator discretion during the first week of the open-label treatment period, in parallel with taking open-label atogepant. Details are provided in the Operations Manual (Appendix H).

4.2 Discussion of Trial Design

Choice of Control Group

Active treatment concurrent control has been selected as the appropriate control group to evaluate the primary endpoint of treatment discontinuation due to AEs during the 24-week DB treatment period. Topiramate was selected as the active comparator because it is an established conventional oral preventive treatment for migraine per its product labelling (SmPC or Product Monograph) and per therapeutic guidelines.

Appropriateness of Measurements

Standard statistical, clinical, patient-reported outcome (PRO), and laboratory procedures will be utilized in this trial. All efficacy assessments, safety-related measurements, and PROs in this trial are standard for assessing disease activity in subjects with migraine. All clinical and laboratory procedures in this trial are standard and generally accepted.

Suitability of Subject Population

This Phase 3b trial will provide tolerability, safety, and efficacy data for atogepant compared to topiramate in the prophylaxis of migraine in subjects eligible for conventional migraine prophylaxis; this population is of particular interest from national HTA and reimbursement perspectives.

Selection of Doses in the Trial

Atogepant

The selected atogepant dose is 60 mg QD for this trial. This dose is based on the results of Phase 3 trials of atogepant in subjects with migraine (EM and CM). The MAA is under review in the EU and the recommended dose of atogepant is 60 mg QD for the prophylaxis of migraine in adults.

The Phase 3 Trial 3101-301-002 ("ADVANCE") evaluated the efficacy, safety, and tolerability of atogepant 10, 30, and 60 mg QD compared to placebo in the prevention of migraine in subjects with EM. Results of the trial are summarized in Table 1.

Table 1. Summary of Results of Phase 3 Trial 3101-301-002 ("ADVANCE")

Efficacy Endpoint	Atogepant 10 mg QD N=214	Atogepant 30 mg QD N=223	Atogepant 60 mg QD N=222	Placebo N=214
MMD across 12 weeks				
Baseline	7.45	7.86	7.75	7.51
Mean change from baseline	-3.50	-3.89	-4.10	-2.34
Difference from placebo	-1.21	-1.38	-1.72	--
p-value	< 0.0001	< 0.0001	< 0.0001	--
Monthly Headache Days across 12 weeks				
Baseline	8.41	8.78	9.00	8.43
Mean change from baseline	-3.72	-4.02	-4.21	-2.33
Difference from placebo	-1.42	-1.53	-1.71	--
p-value	< 0.0001	< 0.0001	< 0.0001	--
Monthly Acute Medication Use Days across 12 weeks				
Baseline	6.57	6.69	6.89	6.48
Mean change from baseline	-3.50	-3.59	-3.86	-2.14
Difference from placebo	-1.31	-1.33	-1.50	--
p-value	< 0.0001	< 0.0001	< 0.0001	--
≥ 50% MMD Responders across 12 weeks				
% Responders	55.6	58.7	60.8	29.0
Odds ratio versus placebo	3.06	3.53	3.82	--
p-value	< 0.0001	< 0.0001	< 0.0001	--
MSQ Version 2.1 RFR domain score at Week 12				
Baseline	44.79	44.24	47.48	46.78
Mean change from baseline	30.84	31.13	30.52	19.49
Difference from placebo	9.90	10.08	10.80	--
p-value	< 0.0001	< 0.0001	< 0.0001	--

CSR = clinical study report; MMD = monthly migraine days; MSQ = Migraine Specific Quality of Life Questionnaire; QD = once daily; RFR = Role Function-Restrictive

Cross-reference: Study 3101-301-002 CSR, Table 11-2, Table 11-7, Table 11-8, Table 11-9, and Table 11-10

All atogepant doses demonstrated clinically meaningful and statistically significant improvement over placebo for the primary endpoint of change from baseline in mean MMD across the 12-week treatment period, and the secondary endpoints of change from baseline in mean monthly headache days and mean monthly acute medication use days across the 12-week treatment period, and MSQ Version 2.1 RFR domain score at Week 12. Treatment with all doses of atogepant also resulted in a significantly higher proportion of subjects who reached ≥ 50% reduction in the 3-month average of MMD across the treatment period compared to the subjects on placebo. A clear dose-response relationship was evident, with the atogepant 60 mg dose consistently providing greater numerical improvement across all primary and secondary efficacy endpoints compared with the 30 mg and 10 mg doses, and the 30 mg dose providing greater numerical improvement compared with the 10 mg dose.

Subgroup analyses in subjects who had been previously failed one or more oral preventive treatments suggested that least-squares mean difference for atogepant versus placebo was numerically higher in each atogepant arm but especially in the 60 mg QD arm compared to the overall trial population (-1.50, -1.49, and -2.24 days for atogepant 10, 30, and 60 mg QD, respectively; atogepant New Drug Submission, Module 2.7.3, Figure 3-13). All atogepant doses were well tolerated and no significant difference was detected in the AE profile of the 3 atogepant doses.

Additionally, the 52-week Phase 3 Trial 3101-302-002 evaluated the long-term safety, tolerability, and efficacy of atogepant 60 mg QD compared to standard of care in the prevention of EM. Consistent with the 12-week studies, atogepant 60 mg QD was safe and well-tolerated (Study 3101-302-002 CSR). A clinically relevant reduction in mean MMD, mean monthly headache days, mean monthly acute medication use days, and mean monthly triptan use days was achieved within the first month and was sustained over the 1-year treatment period. The least square mean change from baseline in the MMD was -3.84 days at Weeks 1 through 4 and -5.19 days at Weeks 49 through 52 (Study 3101-302-002 CSR, Table 11-1).

The efficacy, safety, and tolerability of atogepant 30 mg twice a day (BID) and 60 mg QD compared to placebo in CM was evaluated in the Phase 3 Trial 3101-303-002 ("PROGRESS"). Results of the trial are summarized in Table 2.

Table 2. Summary of Results of Phase 3 Trial 3101-303-002 ("PROGRESS")

Efficacy Endpoint	Atogepant 30 mg BID N=253	Atogepant 60 mg QD N=256	Placebo N=246
MMD across 12 weeks			
Baseline	18.56	19.16	18.95
Mean change from baseline	-7.50	-7.13	-5.19
Difference from placebo	-2.41	-1.82	--
p-value	< 0.0001	0.0009	--
Monthly Headache Days across 12 weeks			
Baseline	21.14	21.52	21.40
Mean change from baseline	-7.53	-7.14	-5.23
Difference from placebo	-2.32	-1.87	--
p-value	< 0.0001	0.0005	--
Monthly Acute Medication Use Days across 12 weeks			
Baseline	14.47	15.46	15.42
Mean change from baseline	-6.60	-6.45	-4.23
Difference from placebo	-2.63	-2.13	--
p-value	< 0.0001	< 0.0001	--
≥ 50% MMD Responders across 12 weeks			
% Responders	42.7	41.0	26.0
Odds ratio versus placebo (%)	2.13	2.04	--
p-value	0.0001	0.0003	--
MSQ v2.1 RFR Domain score at Week 12			
Baseline	44.00	43.56	43.55
Mean change from baseline	26.00	24.24	17.69
Difference from placebo	7.96	6.15	--
p-value	< 0.0001	0.0009	--

BID = twice daily; MMD = monthly migraine days; CSR = clinical study report; MSQ = Migraine Specific Quality of Life Questionnaire; QD = once daily; RFR = Role Function-Restrictive

Cross-reference: Study 3101-303-002 CSR, Table 17, Table 19, Table 21, Table 23, and Table 25

Both atogepant doses demonstrated clinically meaningful and statistically significant improvement over placebo for the primary endpoint of change from baseline in mean MMD across the 12-week treatment period and the secondary endpoints of change from baseline in mean monthly headache days and mean monthly acute medication use days across the 12-week treatment period, and MSQ Version 2.1 RFR domain score at Week 12. Treatment with both doses of atogepant also resulted in a significantly higher

proportion of subjects who reached ≥ 50% reduction in the 3-month average of MMD across the treatment period compared to the subjects on placebo. Atogepant 30 mg BID and atogepant 60 mg QD both had an acceptable safety and tolerability profile in subjects with CM which was consistent with the known safety profile of atogepant in subjects with EM.

Topiramate

Topiramate is to be dosed at the highest tolerated dose determined during the 6-week DB up-titration phase. During the DB up-titration phase, topiramate (or matching placebo) is titrated up starting with 25 mg/day and increased by 25 mg/day in weekly increments with the aim to reach the target dose of 100 mg/day that is the recommended daily dose of topiramate per SmPC and Product Monograph. Subjects need to reach the dose of at least 50 mg/day by the end of the up-titration phase (Week 6/Visit 8) to be allowed to continue taking study medication during the DB maintenance phase. The doses of blinded topiramate to be administered during the DB maintenance phase are 50, 75, or 100 mg/day (highest tolerated dose).

Refer to Section 5.7 for details regarding study drugs. Refer to the Operations Manual (Appendix H), Section 6 for complete dosing instructions. Refer to the topiramate SmPC or Product Monograph for additional information.

5 TRIAL ACTIVITIES

5.1 Eligibility Criteria

Inclusion Criteria

Subjects must meet all of the following criteria in order to be included in the trial.

Consent

- 1. Subjects must voluntarily sign and date an informed consent approved by an independent ethics committee (IEC)/institutional review board (IRB) prior to the initiation of any screening or trial-specific procedures.
- 2. Subject is **willing and able to comply** with procedures required in this protocol, including able to read, understand, and complete the study questionnaires and eDiary per investigator's judgment.

Demographics

- 3. Adult **individuals**, ages 18 to 80 years old (inclusive) at screening (Visit 1).

Disease/Condition Activity

- 4. **Documented history of migraine** (with or without aura) for ≥ 12 months prior to screening (Visit 1) according to the ICHD-3.[6]
- 5. **Age** of the subject at the **time of migraine onset** < 50 years.

- 6. History of **≥ 4 migraine days per month** on average across the **3 months prior to screening** (Visit 1) as per investigator judgement and subject interview.
- 7. **Completed at least 20 out of the last 28 days prior to randomization (Visit 2) in the eDiary** during the screening/baseline period.
- 8. Total of **≥ 4 migraine days per month** during the last **28 days of the screening/baseline period** as confirmed by eDiary.
- 9. Subject must be **eligible for conventional migraine prophylaxis**, i.e., eligible for treatment with at least one of the following: propranolol/metoprolol, amitriptyline, flunarizine, topiramate or onabotulinum toxin A, per investigator judgment.
- 10. Subjects must be **suitable for treatment with topiramate** according to topiramate label (SmPC and Product Monograph), especially considering contraindications, warnings, and precautions (e.g., risk of/history of nephrolithiasis, decreased renal function, eye diseases, metabolic acidosis), based on investigator judgment.

Contraception

- 11. Female subject is **not pregnant, not planning to become pregnant or donate eggs during the course of the trial, and is not currently lactating.**
- 12. Female subjects of childbearing potential must have a **negative serum pregnancy test** at screening/Visit 1 and negative **urine pregnancy test at** randomization/Visit 2.
- 13. Female subjects of childbearing potential must be using at least 1 protocol-specified highly effective **method of birth control** from at least 30 days before randomization/Visit 2 until 30 days after the last dose of the study drug (see Section 5.2).
- 14. Male subjects with **sexually active female partner(s) of childbearing potential** must use protocol-specified contraception from randomization/Visit 2 until 30 days after the last dose of double-blind study drug and refrain from donating sperm during this period (see Section 5.2).

Exclusion Criteria

Subjects will not be eligible for trial participation if they meet any of the following criteria.

Disease Condition/Activity

- 1. Difficulty **in distinguishing migraine from tension-type** or other headaches per investigator's judgement.
- 2. History of **migraine accompanied by diplopia or decreased level of consciousness**, or **retinal migraine** as defined by ICHD-3.[6]
- 3. Current diagnosis of new **persistent daily headache, trigeminal autonomic cephalgia** (e.g., cluster headache), or **painful cranial neuropathy** as defined by ICHD-3.[6]

Subject History

- 4. **Concurrent pain condition** that, in the opinion of the investigator, may significantly impact the current headache disorder (e.g., fibromyalgia, facial pain).
- 5. Confounding **psychiatric conditions**, **dementia, epilepsy, or significant neurological diseases other than migraine**, per investigator judgment.
- 6. Clinically significant **hematologic, endocrine, pulmonary, renal, hepatic, gastrointestinal, or neurologic disease**.
  - If there is a history of such a disease, but the condition has been stable for more than 1 year prior to screening (Visit 1) and is judged by the investigator as not likely to interfere with participation in the trial, the subject may be included.
  - Subjects on dialysis for renal failure and subjects who are currently being treated for epilepsy are excluded.
- 7. Clinically significant **cardiovascular or cerebrovascular disease** per the investigator's opinion including, but not limited to:
  - Clinically significant ischemic heart disease (e.g., unstable angina pectoris)
  - Clinically significant cardiac rhythm or conduction abnormalities (e.g., atrial fibrillation, second- or third-degree heart block) or risk factors for Torsade de Pointes (e.g., heart failure, hypokalemia, bradycardia)
  - Myocardial infarction, transient ischemic attack, or stroke within 6 months prior to screening (Visit 1)
  - Heart failure defined as New York Heart Association functional classification system, Class III or IV
- 8. History of **malignancy** in the 5 years prior to screening (Visit 1), except for adequately treated basal cell or squamous cell skin cancer, or in situ cervical cancer.
- 9. History of **any prior gastrointestinal procedures or gastrointestinal conditions** that may affect the absorption or metabolism of study drug (e.g., diarrhea syndromes, inflammatory bowel disease); subjects with prior gastric bariatric interventions (e.g., Lap Band) which have been reversed are not excluded.
- 10. History of **acute hepatitis** within 6 months of screening (Visit 1); or history of any **chronic liver disease** (including nonalcoholic fatty liver disease, viral chronic hepatitis, or cirrhosis).
- 11. Significant **risk of self-harm based** on clinical interview or responses on the C-SSRS, or of harm to others in the opinion of the investigator. Subjects must be excluded if they report suicidal ideation with intent, with or without a plan, (i.e., Type 4 or 5 on the C-SSRS) in the past 6 months or report suicidal behavior in the 6 months prior to screening/Visit 1 or randomization/Visit 2.
- 12. History of **hypersensitivity or clinically significant adverse reaction to a CGRP-receptor antagonist** or hypersensitivity to any component of the study drugs.
- 13. History of drug or alcohol abuse or dependence within the past year prior to screening (Visit 1).

- 14. Known active severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. If a subject has signs/symptoms suggestive of SARS-CoV-2 infection, the subject must have a negative molecular test (e.g., PCR) or 2 negative antigen test results at least 24 hours apart. Note: SARS-CoV-2 diagnostic tests should be applied following local requirements/recommendations.
  - Subjects who do not meet SARS-CoV-2 infection eligibility criteria must be screen failed and may only rescreen for the study after they meet the following SARS-CoV-2 infection viral clearance criteria:
    - At least 10 days since first positive test result have passed in asymptomatic patients or at least 10 days since recovery, defined as resolution of fever without use of antipyretics and improvement in symptoms.
- 15. Unremitting symptoms of "long COVID" due to prior SARS-CoV-2 infection or any other lasting symptoms that, in the investigator's opinion, may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study.

Laboratory and Other Assessments

- 16. Clinically significant **laboratory values** or laboratory values meeting any of the following criteria at screening/Visit 1:
  - Serum ALT > 1 × ULN
  - Serum AST > 1 × ULN
  - Total bilirubin > 1 × ULN (except for subjects with a diagnosis of Gilbert's disease)
  - Serum albumin < 2.8 g/dL
- 17. **Clinically significant ECG abnormalities** at screening (Visit 1) as determined by the investigator.
- 18. QT interval corrected for heart rate using Fridericia's formula (QTcF) > 450 msec for males or QTcF > 470 msec for females at screening (Visit 1) on the central vendor ECG report.
- 19. **Hypertension** as defined by sitting systolic blood pressure (BP) > 160 mm Hg or sitting diastolic BP > 100 mm Hg at screening/Visit 1 or randomization/Visit 2. Vital sign measurements that exceed these limits may be repeated only once.
- 20. Positive result on **hepatitis B surface antigen** or **anti-hepatitis C antibody** testing at screening (Visit 1).
- 21. Positive result on the **urine drug screen** at screening (Visit 1) unless explained by disclosed concomitant medication use (e.g., opioids prescribed for migraine pain, use of benzodiazepines for insomnia).

Prior and Concomitant Medications

- 22. Use of **recreational or illicit drugs** (including cannabis/cannabidiol (CBD) oil, regardless of legality) at screening (Visit 1).

- 23. History of an **inadequate response** to compounds from > 4 classes of prior migraine preventive medications with demonstrated efficacy for the prevention of migraine (see Appendix D for list of medications with demonstrated efficacy for the prevention of migraine and classification of inadequate response to migraine preventive medications).
- 24. Requirement for any medication, diet (i.e., grapefruit juice), or non-pharmacological treatment that is on the list of **prohibited concomitant medications** or treatments during the 30 days (unless otherwise specified in Section 5.3) prior to screening (Visit 1) and throughout the trial.
- 25. Use of any medications with demonstrated efficacy for the **prevention of migraine** 30 days prior to screening (Visit 1) or throughout the trial period irrespective of the medical indication for which it is used (see Section 5.3 and Appendix D).
- 26. Use of any medications for the **prevention of migraine** 30 days prior to screening (Visit 1) or throughout the trial.
- 27. **Prior exposure to topiramate or atogepant**.
- 28. Previous use of a **prophylactic migraine medication targeting the CGRP pathway** (e.g., erenumab, fremanezumab, galcanezumab, eptinezumab) as part of the general health-care provision. (Note: not exclusionary if administered as an Investigational Medicinal Product [IMP] in a clinical trial ≥ 6 months prior to screening [Visit 1]).
- 29. Usage of **opioids and/or barbiturates** ≥ 4 days/month in the 3 months prior to screening (Visit 1) per investigator's judgment, or during the screening/baseline period (barbiturates are excluded 30 days prior to screening (Visit 1) and for the entire duration of the trial).
- 30. Usage of **therapeutic or cosmetic botulinum toxin injections** (e.g., Dysport®, BOTOX®, Xeomin®, Myobloc®, Jeuveau™) into areas of the head, face, or neck within 6 months prior to screening (Visit 1) or throughout the trial.
- 31. Subject is currently enrolled in another clinical trial or has been treated with **any investigational drug or device** within 30 days or 5 half-lives of the drug (whichever is longer) prior to the first dose of study drug (including studies using marketed compounds or devices).

Other

- 32. Subject is employed by or is an immediate family member (parents, spouses or in a spouse-like relationship, siblings, or children) of one of the investigators, trial staff, or sponsor.
- 33. Subject has a condition or is in a situation which, in the investigator's opinion, may put the subject at significant risk, may confound the trial results, or may interfere significantly with the subject's participation in the trial.
- 34. Medical or other reasons (e.g., unlikely to adhere to the trial procedures, keep appointments, or is planning to relocate during the trial) that, in the investigator's opinion, might indicate that the subject is unsuitable for the trial.

5.2 Contraception Recommendations

Contraception Requirements for Female Subjects

Subjects must follow the following contraceptive guidelines as specified:

- Female Subjects, Nonchildbearing Potential

  Female subjects do not need to use birth control during or following study drug treatment if considered of non-childbearing potential due to meeting any of the following criteria:

  1. Premenopausal female subject with permanent sterility or permanent infertility due to one of the following:
     - Permanent sterility due to a hysterectomy, bilateral salpingectomy, bilateral oophorectomy.
     - Non-surgical permanent infertility due to Mullerian agenesis, androgen insensitivity, or gonadal dysgenesis; investigator discretion should be applied to determining trial entry for these individuals.
  2. Postmenopausal female subject
     - Age > 55 years with no menses for 12 or more months without an alternative medical cause.
     - Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone (FSH) level ≥ 30 IU/L.

- Female Subjects, of Childbearing Potential
  - Review and document pregnancy avoidance recommendations with female subjects of childbearing potential.
  - Female subjects of childbearing potential must avoid pregnancy while taking study drugs and for at least 30 days after the last dose of study drug.
  - Female subjects must commit to one of the following methods of birth control:
    - Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation-initiated at least 30 days before randomization/Visit 2.
    - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 30 days before randomization/Visit 2.
    - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
    - Intrauterine device.
    - Intrauterine hormone-releasing system.
    - Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject).

- Practice true abstinence, defined as: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

If a hormonal contraception method is used during the DB period, a barrier method described below (preferably male condom) must be used in addition to the hormonal contraception method until 30 days after the last dose of DB study drug:

- Male condom with or without spermicide, OR
- Female condom with or without spermicide, OR
- Cap, diaphragm, or sponge with spermicide

An additional barrier method of contraception is not required from 30 days after the last dose of DB study drug up until the end of the OL period.

If required per local practices, 1 barrier method described above should be used in addition to one of the birth control methods listed above (excluding true abstinence).

Contraception recommendations related to use of concomitant therapies prescribed should be based on the local label.

Contraception Requirements for Male Subjects (through at least 30 days after the last dose of double blind study drug)

Male subjects who are sexually active with a female partner of childbearing potential must agree to use male condoms, even if the male subject has undergone a successful vasectomy, from randomization/Visit 2 through at least 30 days after the last dose of double-blind study drug. Male subjects must also refrain from donating sperm during this period.

5.3 Prohibited Medications and Treatments

Potential interactions of each concomitant medication with topiramate use, as outlined in the SmPC or Product Monograph, must be individually assessed by the investigator. Additional clinical monitoring may be necessary as per investigator judgement (e.g., to ensure stable control of diabetes).

The following medications are prohibited 30 days prior to screening (Visit 1) (unless otherwise specified below) for all subjects and throughout the trial (see also Appendix E):

- Strong CYP3A4 inhibitors, including but not limited to: systemic (oral/intravenous [IV]) itraconazole, ketoconazole, clarithromycin, telithromycin, nefazodone, and human immunodeficiency virus protease inhibitors
- Strong and moderate CYP3A4 inducers, including but not limited to: barbiturates (e.g., phenobarbital and primidone), systemic dexamethasone, efavirenz, carbamazepine, phenytoin, rifampin, rifabutin, and St John's wort

- Strong OATP1B1/OATP1B3 inhibitors (e.g., atorvastatin, pitavastatin, telmisartan, cyclosporine, teriflunomide)
- Drugs with narrow therapeutic margins with theoretical potential for cytochrome P450 (CYP) drug interactions (e.g., warfarin)
- Oral medications with demonstrated efficacy for the prevention of migraine, irrespective of the indication of treatment (i.e., propranolol, metoprolol, atenolol, bisoprolol, timolol, nadolol, flunarizine, valproate, divalproex, amitriptyline, nortriptyline, venlafaxine, desvenlafaxine, lisinopril, candesartan, products with local approval for the prevention of migraine [e.g., oxetorone, pizotifen, cinnarizine, iprazochrome, cyproheptadine]). See also Appendix D.
- Herbal medications with efficacy for the prevention of migraine (e.g., feverfew)
- Any medication if administered for the prevention of migraine
- Cannabis, CBD oil
- Therapeutic or cosmetic botulinum toxin injections (e.g., Dysport®, Botox®, Xeomin®, Myobloc®, Jeuveau™) into areas of the head, face, or neck within 6 months prior to screening (Visit 1) and throughout the trial period
- Injectable medications blocking the CGRP pathway (e.g., eptinezumab, erenumab, galcanezumab, fremanezumab) within 6 months prior to screening (Visit 1) and throughout the trial period.
- Any gepant, including ubrogepant, rimegepant, zavegepant, atogepant (other than the study drug).
- Cranial traction, nociceptive trigeminal inhibition, occipital nerve block treatments, or dental splints for headache, within 30 days prior to screening (Visit 1) or at any time during the trial (including the screening/baseline period).
- Use of acupuncture, non-invasive neuromodulation devices (e.g., transcutaneous supraorbital neurostimulator, single-pulse transcranial magnetic stimulator, vagus nerve stimulator, etc.) for the prophylaxis of migraine within 30 days prior to screening (Visit 1) or at any time during the trial (including the screening/baseline period).

The following dietary restrictions apply for the study:

- Subjects should refrain from consuming grapefruit or grapefruit juice from the time the consent form is signed until completion of the study.
- Subjects should refrain from making significant changes to their diet or caffeine intake during the study.
- Subjects should avoid alcohol intake while taking double-blind study medication, including any blinded topiramate taper-off. During the open-label period, alcohol intake should be limited to no more than 1 drink/day. A drink is defined as approximately a 12-ounce (approximately 355 mL) can/bottle of beer, a 4-ounce (approximately 120 mL) glass of wine, or 1 ounce (approximately 30 mL) of liquor.

5.4 Prior and Concomitant Treatments

Any concomitant medication, vaccine, or treatment that is not prohibited in Section 5.3 is allowed, with the following clarifications and restrictions:

- Potential interactions of each concomitant medication with topiramate must be individually assessed by the investigator. Additional clinical monitoring may be necessary per investigator judgement (e.g., to ensure stable control of diabetes).
- Aspirin up to 325 mg/day is allowed for cardiac and cerebrovascular prophylaxis.
- Selective serotonin reuptake inhibitors (SSRIs) or selective norepinephrine reuptake inhibitors (SNRIs), with the exception of venlafaxine and desvenlafaxine, are permitted provided that treatment is stable for at least 60 days prior to screening (Visit 1), continues without change in dose throughout the trial, and is not used for the treatment of migraine or headaches.
- Subjects may use rescue interventions for the acute treatment of migraine attacks throughout the trial as needed. This includes both pharmacological interventions and non-pharmacological interventions as follows:
  - Any triptan
  - Any ergot derivative
  - Any ditan
  - Any opioid (Note: opioid use on ≥ 4 days/month is prohibited throughout the trial.)
  - Any nonsteroidal anti-inflammatory drug
  - Any other analgesic (e.g., acetaminophen, metamizole)
  - Any antiemetic agent
  - Nonpharmacological treatment (e.g., biofeedback, psychotherapy, acupuncture, vagus nerve stimulation, transcutaneous supraorbital nerve stimulation, single-pulse transcranial magnetic stimulator or other locally accepted and endorsed non-invasive interventions) for the **acute** treatment of migraine

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the trial must be recorded from 6 months prior to screening/Visit 1 through the safety follow-up period.

All prior and concomitant headache/migraine medications including migraine prevention medications must be recorded.

Any questions regarding concomitant or prior treatment should be raised to the AbbVie Therapeutic Area Medical Director. For information regarding potential drug interactions with atogepant or topiramate, refer to the atogepant Investigator's Brochure and topiramate SmPC or Product Monograph.

COVID 19 Pandemic Related Vaccination Guidance

Given the ongoing COVID-19 pandemic, selected non-live vaccines (e.g., mRNA, non-replicating viral vector, protein subunit, etc.) to prevent SARS-CoV-2 infection may be administered during screening, the treatment period, or follow-up, as long as components of the vaccine are not contraindicated.

The decision to receive a locally available vaccine should be based on local guidance and an individual discussion between the treating physician and the subject.

The potential impact of atogepant and topiramate on SARS-CoV-2 vaccination is unknown. Therefore, study drug should be administered as follows:

- The first doses of study drugs, when possible, are preferred to be given at least ± 7 days from the SARS-CoV-2 vaccine administration.

Note: The above guidance applies to all SARS-CoV-2 vaccine doses given as part of the complete vaccination course.

These recommendations may be subject to change based on the evolving knowledge around the use of SARS-CoV-2 vaccines in patients with migraine and as more data are collected in real-world scenarios and clinical trials.

Any SARS-CoV-2 vaccine information must be documented on the COVID-19 vaccine electronic case report form (eCRF). Refer to the Operations Manual (Appendix H) for instructions on reporting any AEs associated with the COVID-19 vaccine.

5.5 Discontinuation of Study Drug, Withdrawal of Subjects, and Discontinuation of Trial

Premature Discontinuation of Study Drug During the Double blind Treatment Period

Discontinuation of study drug during the DB treatment period occurs when the study drug is stopped earlier than Visit 13/Week24.

Discontinuation of study drug may occur due to the reasons including, but not limited to, the following:

- Clinically significant AEs as determined by the investigator.
- Introduction of prohibited medications or change in dose of current medications which would place the subject at risk if study drug is continued.
- The investigator believes it is in the best interest of the subject. The investigator must discontinue study drug for the subject if, as per the investigator's judgement, the continuation of study drug would negatively impact the risk/benefit of trial participation for the subject.
- Subjects who do not reach the minimum dose of blinded topiramate 50 mg/day by the end of the DB up-titration period due to AEs preventing dose escalation.
- Meeting any of the mandatory study drug discontinuation criteria (see below).

Subjects who discontinue study drug during the DB period for reasons other than withdrawal of consent or lost to follow-up and do not meet mandatory trial withdrawal criteria should remain in the trial, continue collecting data in the daily eDiary, and attend scheduled trial visits remotely or in-person as per the SSA for Subjects who Discontinue Study Drug Early During the DB Period (Appendix F) until Week 24 and attend the Visit 13/Week 24 visit in-person per the general Study Activities Schedule for the Double-blind Treatment, Open-label Treatment, and Safety Follow-up Periods. During this time, subjects may continue using rescue treatments for the acute treatment of migraine attacks.

Mandatory Study Drug Discontinuation

Subjects meeting any of the following criteria at any time during the study must discontinue study drug:

- Subjects who become pregnant while on study drug must permanently discontinue study drug.
- Subjects who reply with "Yes" to Questions 4 or 5 in the suicidal ideation section indicating having suicidal ideation with intent (with or without plan), or "Yes" to any question in the suicidal behavior section of the C-SSRS at any study visit must permanently discontinue study drug.
- Subjects who experience any serious AE of hypersensitivity or anaphylactic reaction must permanently discontinue study drug.
- Subjects who experience a nonserious AE of hypersensitivity must permanently discontinue study drug, unless there is clear alternative etiology.
- Subjects meeting any of the following mandatory study drug discontinuation criteria related to abnormal liver function tests:
    - ALT or AST ≥ 3 × ULN and the subject is symptomatic with the appearance of fatigue nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> 5%)
    - ALT or AST ≥ 3 × ULN and total bilirubin > 2 × ULN
    - ALT or AST ≥ 3 × ULN and International Normalized Ratio > 1.5
    - ALT or AST ≥ 5 × ULN for more than 2 weeks
    - ALT or AST ≥ 8 × ULN

Subjects who discontinue study drug due to abnormal liver function tests may be rechallenged with study drug only after careful evaluation of the case including thorough evaluation of potential alternative etiologies and after consultation with and approval of the sponsor's Therapeutic Area Medical Director.

Withdrawal of Subjects from the Trial

A subject may voluntarily withdraw or be withdrawn from the trial at any time for reasons including, but not limited to, the following:

- The investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the trial.
- The investigator determines the subject is significantly noncompliant with trial procedures.

The following conditions require subjects to be withdrawn from the trial:

- The subject does not continue into the OL treatment period at Visit 13/Week 24.
- The subject starts any migraine preventive medication other than study drug at any time during the trial (Therapeutic Area Medical Director should be notified).
- The subject permanently discontinues study drug during the OL treatment period.

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the subject's final status. At a minimum, 2 telephone calls must be made and 1 certified letter must be sent and documented in the subject's source documentation.

Discontinuation of Trial

AbbVie may terminate this trial prematurely, either in its entirety or at any site. The investigator may also stop the trial at their site if they have safety concerns. If AbbVie terminates the trial for safety reasons, AbbVie will promptly notify the investigator.

5.6 Follow-Up After Subject Discontinuation of Study Drug or Trial

Discontinuation of Study Drug and Continuation of Trial Participation

To minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment during the DB treatment period should remain in the trial. All subjects who discontinue study drug during the DB treatment period but remain in the trial must follow the SSA for Subjects who Discontinue Study Drug Early During the DB Treatment Period (Appendix F). Subjects must attend the Early DB Treatment Discontinuation Visit in-person as soon as possible but not later than approximately 2 weeks following treatment discontinuation. Subsequent visits may be conducted remotely per investigator discretion. Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug.

Premature Discontinuation of Trial

All randomized subjects who are withdrawn from the trial, regardless of cause, should be seen for final trial assessments. The final assessments will be defined as completion of the evaluations scheduled for:

- Visit 13/DB ET (for subjects who were withdrawn during the DB treatment period), or
- Visit 18/OL ET (for subjects who were withdrawn during the OL treatment period)

Every effort should be made for all subjects who are withdrawn from the trial to attend the Safety Follow-up Visit (Visit 19/SFU) 4 weeks after the last dose of study drug.

In the event a subject withdraws consent from the clinical trial, biomarker research will continue unless the subject explicitly requests analysis to be stopped. When AbbVie is informed the subject has withdrawn biomarker consent and no longer wishes biomarker samples research to continue, samples will not be analyzed and no new biomarker analysis data will be collected for the withdrawn subject or added to the existing data or database(s). A subject may withdraw consent for optional biomarker

research at any time and remain in the clinical trial. Data generated from clinical trial and/or optional biomarker research before subject withdrawal of consent will remain part of the trial results.

5.7 Study Drug

Atogepant

Atogepant (or matching placebo during the DB period) will be taken orally QD beginning on the day of randomization/Visit 2 and should be taken at approximately the same time each day. Atogepant and matching placebo can be taken with or without food. If subjects forget to take their atogepant or matching placebo dose at their regularly scheduled dosing time, they should take the forgotten dose as soon as they remember and then take the next dose at the next scheduled dosing time.

Topiramate

Topiramate (or matching placebo) during the DB period will be taken orally QD in the evening for the first week, beginning on the evening of randomization/Visit 2 and should be taken at approximately the same time each day. After the blinded topiramate dose is escalated, topiramate or matching placebo will be taken twice daily and should be taken at approximately the same times each day. Topiramate can be taken with or without food. If subjects forget to take their topiramate or matching placebo dose at their regularly scheduled dosing time, they should take the forgotten dose as soon as they remember and then take the next dose at the next scheduled dosing time.

AbbVie will provide atogepant, topiramate, and each matching placebo (Table 3). AbbVie-provided study drug should not be substituted or alternately sourced unless otherwise directed by AbbVie. If a subject is unable to come to the trial site to pick up their study drug due exceptional situations related to a pandemic (e.g., COVID-19) or in situations of geopolitical conflict in Israel and surrounding impacted areas, then upon agreement with the sponsor, a direct to patient (DTP) study drug shipment can be made from the trial site to the subject if allowed by site process and local regulations. AbbVie will submit any required notifications to the regulatory authority as applicable. Refer to the Operations Manual, Section 3.14 (Appendix H) for details on DTP shipment of study drug.

Table 3. Identity of Study Drugs

	Investigational Product		Comparator	
	Atogepant	**Placebo**	**Topiramate**	**Placebo**
Dosage form	Tablet	Tablet	Capsule	Capsule
Strength	60 mg	N/A	25, 50 mg	N/A
Dosage	60 mg QD	N/A	25, 50, 75, 100 mg/day	N/A
Route of administration	Oral	Oral	Oral	Oral

N/A = not applicable; QD = once daily

Atogepant, topiramate, and each matching placebo will be packaged in blister cards or bottles with quantities sufficient to accommodate trial design. Each kit will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the

label and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding trial visit. Site staff will complete all blank spaces on the label before dispensing to subjects. Study drug will only be used for the conduct of this trial.

Upon completion of or discontinuation from study treatment, all original study drug units (empty or containing unused study drugs) will be returned to the sponsor (or designee) or destroyed on site if permitted by local regulations as agreed with AbbVie. All return or destruction procedures will be according to instructions from the sponsor and according to local regulations following completion of drug/device accountability procedures.

5.8 Randomization/Drug Assignment

All subjects will be assigned a unique identification number (subject number) by the IRT at screening/Visit 1. For subjects who rescreen, the subject number assigned by the IRT at initial screening/Visit 1 should be used.

Randomization will be stratified by country and based on whether the subject can be classified as having CM ("Yes" if ≥ 15 headache days and ≥ 8 migraine days during the 28-day screening/baseline period, "No" otherwise). The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule (i.e., atogepant or topiramate).

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team) will remain blinded to each subject's DB treatment assignment until the primary analysis is complete. The investigator, trial site personnel, and the subject will remain blinded throughout the entire study. To maintain the blind, the matching placebo tablets and capsules provided for the trial will be identical in appearance to atogepant or topiramate, respectively.

The IRT system will provide direct access to the investigator(s) to unblinded subject treatment information in the case of a medical emergency. The IRT system can be used by the investigator(s) 24 hours a day, 7 days per week, without any prior contact with AbbVie.

5.9 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to trial subjects. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic or in situations of geopolitical conflict in Israel and surrounding impacted areas), the investigator is responsible for notifying IEC/ IRB, regulatory authorities, and AbbVie, as applicable.

5.10 External Committees

Data Safety Monitoring Board

An external DSMB composed of clinicians and statisticians independent of AbbVie and with relevant expertise in their field will review unblinded data from the ongoing trial. The DSMB is responsible for safeguarding the interests of trial subjects, assessing the safety of the study drug during the trial, as well as for monitoring the integrity and interpretability of the trial. The DSMB will provide recommendations to the sponsor, including modification or ET of the trial, if emerging data show unexpected and clinically significant AEs related to study treatment.

A separate DSMB charter will be prepared outside of the protocol and will further describe the roles and responsibilities of the DSMB members, frequency and scope of the data reviews, and expectations for blinded communications.

External Hepatic Event 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 × ULN in the atogepant program. The purpose of this charter will be to provide a standardized process for the adjudication of data associated with these events to determine whether an elevation was related to atogepant.

5.11 Publication Policy

AbbVie as the sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and sponsor 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 clinical study report of the multicenter study except as agreed with the sponsor.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data.

Investigators are NOT employed by the organization sponsoring the study. There is an agreement between investigators and the sponsor (or its agents) that restricts the investigator's rights to discuss or publish study results after the study is completed.

AbbVie requests that any investigator or institution that plans on presenting/publishing results, provide written notification of their request 60 days prior to their presentation/publication. AbbVie requests that no presentation/publication will be instituted until 12 months after a study is completed or after the first presentation/publication, whichever occurs first. A delay may be proposed for a presentation/publication if AbbVie needs to secure patent or proprietary protection.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device. Complaints associated with any component of this investigational product must be reported to AbbVie.

Product Complaint

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (e.g., printing illegible), missing components/product, device damage or not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 24 hours of the trial site's knowledge of the event.

Reporting will be done via electronic data capture (EDC). The date the product complaint details are entered into EDC and the form is saved represents the date reported to AbbVie. A back-up paper form will be provided for reporting complaints related to unassigned product or in the event of an EDC system issue. If a back-up paper form is used, the date the form is emailed to RD_PQC_QA@abbvie.com represents the date reported to AbbVie.

All follow-up information is to be reported to the sponsor (or an authorized representative) and documented in source as required by the sponsor. Product complaints associated with AEs will be reported in the trial summary. All other complaints will be monitored on an ongoing basis. Product complaints occurring during the trial will be followed up to a satisfactory conclusion.

Medical Complaints/Adverse Events and Serious Adverse Events

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which 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 the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from "special situations" such as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, or drug withdrawal, all which must be reported whether associated with an AE or not. Any worsening of a pre-existing condition or illness is

considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the trial, necessitate therapeutic medical intervention, meets protocol-specific criteria, and/or if the investigator considers them to be clinically significant.

The investigators will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the trial. All AEs will be followed to a satisfactory conclusion.

An elective surgery/procedure scheduled to occur during a trial will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and/or the surgery/procedure has been pre-planned prior to trial entry. However, if the pre-existing condition deteriorates unexpectedly during the trial (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

If any of the following events are reported, then the following supplemental report must be completed.

Event	Supplemental Report
Cardiac events **Arrythmias** **Myocardial infarction or unstable angina** **Heart failure** **Cerebral vascular accident and transient ischemic attack** **Cardiovascular procedures (SAE Supplemental Procedure eCRF)**	MACE eCRF
Discontinuation or interruption of study drug due to a hepatic-related AE **A hepatic-related SAE** **ALT/AST ≥ 3 × ULN**	Hepatic AE eCRF Hepatic Supplemental Lab eCRF Hepatic Supplemental Procedures eCRF

If an AE, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance as a serious AE (SAE) within 24 hours of the site being made aware of the SAE (refer to Section 4.2 of the Operations Manual (Appendix H) for reporting details and contact information):

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.

Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a trial subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All AEs will be collected from the time of study drug administration until 30 days after the last dose of study drug, whether solicited or spontaneously reported by the subject. After 30 days following the last dose of study drug or completion of study treatment only spontaneously reported SAEs will be collected (nonserious AEs will not be collected). In addition, trial procedure-related serious and nonserious AEs will be collected from the time the subject signs the trial-specific informed consent.

The following definitions will be used for Serious Adverse Reactions (SAR) and Suspected Unexpected Serious Adverse Reaction (SUSAR):

SAR	Defined as all noxious and unintended responses to an IMP related to any dose administered that result in an SAE as defined above.
SUSAR	Refers to individual SAE case reports from clinical trials where a causal relationship between the SAE and the IMP was suspected by either the sponsor or the investigator, is unexpected (not listed in the applicable Reference Safety Information), and meets one of the above serious criteria.

AbbVie will be responsible for SUSAR reporting for the Investigational Medicinal Product (IMP) in accordance with global and local requirements, including reporting to EudraVigilance database in accordance with EU Clinical Trial Regulation.

Adverse Events of Special Interest

Adverse events will be monitored throughout the trial to identify any of special interest that may indicate a trend or risk to subjects. All AEs of special interest (AESIs) must be reported to the sponsor within 24 hours of the site being made aware of the AESI. All new elements of history, physical

examination, diagnostic testing results, and other relevant medical reports are to be reported for each AESIs.

The following AESIs will be monitored during the trial:

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

Any subject with elevated ALT or AST laboratory value ≥ 3 × ULN after receiving study drug must have repeat testing within 48 to 72 hours to confirm the abnormality. If an ALT or AST ≥ 3 × ULN is confirmed, close medical follow-up is required, including additional laboratory testing as specified in the Operations Manual (Appendix H), Section 3.15 (Table 2). The investigator must contact the sponsor's Therapeutic Area Medical Director to discuss all cases of confirmed ALT/AST elevation ≥ 3 × ULN. All ALT/AST elevations must be followed until ALT and AST return to < 1.5 × ULN and there is full clinical resolution.

Adverse Event Severity and Relationship to Study Drug

The investigator will rate the severity of each AE as mild, moderate, or severe.

The investigator will use the following definitions to rate the severity of each AE:

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

The investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship.

Pregnancy

While not an AE, pregnancy in a trial subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Subjects who become pregnant during the trial must discontinue study drug (Section 5.5). If a pregnancy occurs in a trial subject during the entire study period, or in the partner of a trial subject during the DB treatment period or within 30 days after the last dose of double-blind study drug, information regarding the pregnancy and the outcome will be collected.

In the event of pregnancy occurring in a subject's partner during the DB treatment period or within 30 days after the last dose of double-blind study drug, written informed consent from the partner must be obtained prior to collection of any such information. AbbVie will provide a separate consent form for this purpose. Pregnancy in a subject's partners will be collected from the date of the first dose through 30 days following the last dose of double-blind study drug.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth, or congenital anomaly is considered an SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The statistical methods provided in this protocol will be focused on primary and key secondary analyses. Complete and specific details of the statistical analysis will be described in the SAP.

The primary analysis will be conducted by the study team after all subjects have completed the last visit for the DB Period or withdrawn from the trial (i.e., Visit 13/Week 24/DB ET). Trial sites and subjects will remain blinded to DB treatment assignment throughout the entire study.

7.2 Definition for Analysis Populations

The mITT population includes all randomized subjects who received at least 1 dose of study treatment, had an evaluable baseline period of eDiary data and had at least 1 evaluable post-baseline 4-week (1 month) period of eDiary data within 24 weeks after the first dose of study medication (Month 1 to Month 6), regardless of whether on study treatment or off study treatment.

The Safety Population 1 consists of all subjects who received at least 1 dose of study treatment during the DB treatment period. Subjects will be summarized according to the study treatment received for the majority of the treatment period.

The Safety Population 2 consists of all subjects who received at least 1 dose of study treatment during the OL treatment period.

7.3 Handling Potential Intercurrent Events for the Primary and Key Secondary Endpoints

The primary endpoint (defined in Section 3.2) will be analyzed in the Safety Population 1 and the following methods will be used to address potential intercurrent events:

- Subjects who discontinue study treatment due to any reasons other than AEs (e.g., lack of efficacy, withdrawal of consent, lost to follow-up, etc) will be classified as subjects without AEs leading to treatment discontinuation.

The secondary endpoints (defined in Section 3.3) will be analyzed based on the mITT population, and the following methods will be used to address the potential intercurrent events:

- A 50% responder is defined as a subject achieving at least a 50% reduction from baseline in mean MMD during Months 4 to 6 of the DB treatment period.
    - Regardless of whether or not allowed rescue medications are taken, data are included in the analysis. Use of acute migraine medications as rescue medications is considered in the definition of migraine/headache day as described in Section 3.7 of the Operations Manual.
    - Subjects who discontinue study treatment due to all reasons other than starting a new migraine prophylactic treatment will have their data collected after discontinuation of study treatment, and those off-treatment data will be included in the analysis.
    - Subjects who prematurely discontinue study treatment and use other prohibited migraine prophylactic treatment will have their off-treatment data after starting the new migraine prophylactic treatment excluded from the analysis.
    - Subjects without an evaluable month of eDiary data during the last three months of the DB treatment period (Months 4, 5, 6) will be treated as non-responders.
- For the endpoint of achieving a rating of "much better" or "very much better" at Week 24 assessed by the PGIC, off-treatment data after starting a new migraine prophylaxis treatment will be excluded. Subjects without a PGIC value at Week 24 will be treated as non-responders.

Potential intercurrent events for other continuous key secondary endpoints will be handled using the following methods:

- Regardless of whether or not allowed rescue medications are taken, data are included in the analysis. Use of acute migraine medications as rescue medications is considered in the definition of migraine/headache day as described in Section 3.7 of the Operations Manual.
- Subjects who discontinue study treatment due to all reasons other than starting a new migraine prophylactic treatment will have their data collected after discontinuation of study treatment, and those off-treatment data will be included in the analysis.
- Subjects who prematurely discontinue study treatment and use other prohibited migraine prophylactic treatment will have their off-treatment data after starting the new migraine prophylactic treatment excluded from the analysis.

7.4 Statistical Analyses for Efficacy

All analyses on efficacy variables will be performed in the mITT population, unless otherwise specified. Baseline for efficacy is defined as the last non-missing efficacy assessment before the first dose of DB study drug.

Summary and Analysis of the Primary Endpoint

The Primary endpoint is treatment discontinuation due to AEs during the 24-week DB treatment period. Analysis of the primary endpoint will be conducted on the Safety Population 1 (see Section 7.5).

Summary and Analysis of Secondary Endpoint

Summary and Analysis of Key Secondary Endpoints

For key secondary endpoint of achieving ≥ 50% improvement (reduction) in mean MMD during Months 4 to 6 of the DB treatment period, the number and proportion (n, %) of subjects achieving ≥ 50% improvement (reduction) in mean MMD during Months 4 to 6 of the DB treatment period will be summarized based on mITT population. The relative ratio as the primary measure in response rates of atogepant versus topiramate will be provided. Comparison of the 50% responders (i.e., adjusted relative ratio [relative risk], 95% confidence interval [CI], p-value) will be made between the atogepant group and the topiramate group using the MN method,[13] adjusting for CM status at baseline (Yes or No).

Odds ratio and between groups difference in 50% response rates of atogepant versus topiramate will also be provided. The odds ratio between atogepant group and topiramate will be estimated and tested from logistic regression model, which assumes a binary distribution for the response and uses a logit link, with model terms including treatment group and baseline MMDs.

A mixed model for repeated measures will be used to analyze continuous secondary endpoints. The model will include treatment group, visit (derived as month), CM status at baseline (Yes or No), and treatment group by visit interaction as categorical fixed effects. It will also include the baseline score and baseline-by-visit interaction as covariates. Model parameters were estimated using restricted maximum likelihood method incorporating all observed cases during the DB period assuming data missing at random. An unstructured covariance matrix will be used to model the covariance of within-subject repeated measurements. The Kenward-Roger approximation[14] will be used to estimate the denominator degrees of freedom. In the event of non-convergence of the model using unstructured covariance matrix, a structured covariance matrix will be used in combination with empirical variance estimate (i.e., sandwich estimator) to address the potential mis-specified situation. Pairwise contrasts in the mixed-effect repeated measures model will be used to make the pairwise comparisons of atogepant to topiramate.

For the endpoint of achieving a rating of "much better" or "very much better" at Week 24 assessed by the PGIC, relative risk, odds ratio, and risk difference between the atogepant group and the topiramate group will be derived. These methods are in line with those utilized for achieving ≥ 50% improvement (reduction) in mean MMD during Months 4 to 6 of the DB treatment period. However, the CM status at baseline (Yes or No) will be included in the logistic model, replacing the baseline MMDs.

Summary and Analysis of Additional Efficacy Endpoints

Additional endpoints, as described in Section 3.4, will also be analyzed. Analysis details will be provided in the SAP.

Subgroup Analysis for Efficacy

To evaluate the treatment effect across subgroup categories, the estimate of the between-group treatment effect (with a 95% CI) for atogepant versus topiramate for key secondary endpoints will be provided within each category of the following classification variables unless specified otherwise:

- Chronic migraine (i.e., ≥ 15 headache days and ≥ 8 migraine days during the 28-day screening/baseline period): Yes or No

7.5 Statistical Analyses for Safety

All safety analyses will be performed on the Safety Population 1 or Safety Population 2. Subjects will be assigned to a treatment group based on the treatment actually received, regardless of the treatment randomized. The safety endpoints include AEs, clinical laboratory evaluations, vital sign measurements, ECG parameters, the C-SSRS, and pregnancy tests. For each of the clinical laboratory, vital sign, and ECG parameters, the last non-missing safety assessment before the first dose of study drug will be used as the baseline for all analyses of that safety parameter.

Continuous variables will be summarized by the number of subjects, mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of subjects. Additional details for the safety analysis will be provided in the SAP.

Summary and Analysis of the Primary Endpoint

The primary endpoint is treatment discontinuation due to AEs during the 24-week DB treatment period. Analysis of the primary endpoint will be conducted on the Safety Population 1.

Number and proportion (n, %) of subjects with treatment discontinuation during the DB treatment period will be summarized. The relative risk of AE-related treatment discontinuation rate for atogepant versus topiramate as the primary measure will be provided. Comparison of the primary endpoint (i.e., adjusted relative ratio [relative risk], 95% CI, *P* value) will be made between atogepant group and the topiramate group using the MN method,[13] adjusting for CM status at baseline (Yes or No).

Odds ratio and between groups difference in AE-related treatment discontinuation rate for atogepant versus topiramate will be provided. The odds ratio between atogepant group and topiramate will be estimated and tested from logistic regression model, which assumes a binary distribution for the response and uses a logit link, with model terms including treatment group and baseline MMDs.

7.6 Interim Analysis

An independent DSMB will review safety data throughout the trial and make recommendations to the sponsor, including modification or ET of the trial.

Refer to Section 5.10 for information regarding external committees.

7.7 Overall Type I Error Control

The overall type I error rate for multiple comparisons of the primary and secondary efficacy endpoints will be controlled at a 2-sided 0.05 significant level as follows:

A fixed-sequence procedure is used for multiple comparisons of primary and key secondary endpoints. The primary endpoint is tested first at a 0.05 significance level; if significant, then the key secondary endpoints will be tested sequentially according to the prespecified order listed below unless specified otherwise at level 0.05. Once 1 hypothesis is tested not significantly, all subsequent hypotheses cannot be formally rejected.

- Achievement of ≥ 50% improvement (reduction) in mean MMD during Months 4 to 6 of the DB treatment period.
- Change from baseline in mean MMD during Months 4 to 6 of the DB treatment period.
- Change from baseline in HIT-6 total score at Week 24.
- Change from baseline in MSQ Version 2.1 RFR domain score at Week 24.
- Achievement of a rating of "much better" or "very much better" at Week 24 assessed by the PGIC.
- Change from baseline in PROMIS Cognitive Function Abilities Subset Short Form 6a Version 2.0 score at Week 6.

7.8 Sample Size Determination

The planned total sample size of 520 randomized subjects (260 subjects per arm) will have at least 95% power to detect a 15% treatment difference in the primary endpoint, assuming 20% treatment discontinuation rate due to AEs with atogepant, and 35% with topiramate at a 0.025 one-sided significant level. The assumed rate of AEs leading to treatment discontinuation is based on atogepant long-term episodic Study 3101-302-002 and HER-MES study,[15] adjusted to use more conservative rates for sample size calculation.

The sample size of 260 subjects per arm will have approximately 99% power to detect a 20% treatment difference in the key secondary endpoint, achieving ≥ 50% reduction in monthly migraine days across last 3 months, assuming 51% response rate with atogepant and 31% response rate with topiramate at a 0.025 one-sided significant level. The assumed response rates are based on Study HER-MES[15] and are adjusted to a more conservative rate in the atogepant arm for sample size calculation.

The assumptions for sample size calculation were monitored and updated based on blinded data review using a cutoff date of 01 August 2024. The pooled rate in TEAE leading to treatment discontinuation was 16.9%; the pooled rate for 50% responder rate was 48.9%.

The sample size of 260 subjects per arm will have at least 98.9% power to detect a 13.8% treatment difference in the primary endpoint, assuming 10% treatment discontinuation rate due to AEs with

atogepant, and 23.8% with topiramate at a 0.05 significance level. The assumed rate of AEs leading to treatment discontinuation in atogepant is based on Study M23-072 adjusted to use more conservative rate for sample size calculation.

The sample size of 260 subjects per arm will have approximately 93% power to detect a 15% treatment difference in the key secondary endpoint, achieving ≥ 50% reduction in monthly migraine days across last 3 months, assuming 56.4% response rate with atogepant and 41.4% response rate with topiramate at a 0.05 significant level. The assumed response rates are calculated using the blinded pooled responder rate is approximately 48.9% and assuming the treatment difference is 15%.

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the informed consent form(s) must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the trial. In addition, all changes to the consent form(s) will be IEC/IRB approved.

8.2 Ethical Conduct of the Trial

The trial will be conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation (ICH) guidelines, EU Clinical Trial Regulation, applicable regulations, and guidelines governing clinical trial conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the investigator are specified in Appendix B. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

8.3 Subject Confidentiality

Before a subject's data is shared with AbbVie, the study investigator and staff will replace the subject's name, address, and contact information with a generic code which AbbVie cannot link to that subject's identify to protect the confidentiality of the data.

For the personal data that Deutschland GmbH & Co KG acting as sponsor of the submitted study ("AbbVie Deutschland ") controls and maintains, AbbVie Deutschland has developed a robust security program focused on due diligence in design, managed change, and information security governance. Information Security policies govern the Information Security functions including identity and access management, operations, infrastructure, application, and third-party security requirements. The risk-based AbbVie Data Classification Tool dictates the level of scrutiny and control required for the relevant activities per AbbVie's Information Security policies taking into account the sensitivity of the data.

AbbVie Deutschland has a data protection impact assessment program to ensure and document the appropriate controls and safeguards stated above are in place for clinical trial data that it controls and maintains and these processing activities respect privacy of clinical trial subjects. AbbVie Deutschland

also maintains robust security incident response policies and procedures, including requirements for the containment of any data related incidents, the mitigation measures where needed, and notification to authorities or affected individuals where required.

AbbVie Deutschland as the sponsor shall document any personal data breaches for which it is a controller and notify where required the competent national supervisory authority without undue delay and at the latest within 72 hours after becoming aware of such an incident. AbbVie Deutschland shall create and maintain appropriate records of such an incident.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s), including EU Clinical Trial Regulation. During the COVID-19 pandemic or in situations of geopolitical conflict in Israel and surrounding impacted areas, remote data review/verification may be employed if allowed by the local regulatory authority, IRB/IEC, and the trial site.

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of trial results. Data will be generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements, including EU Clinical Trial Regulation.

11 START AND COMPLETION OF THE TRIAL

The start-of-trial is defined as the date of the first site activated.

The end-of-trial is defined as the date of end of trial participation (i.e., the last visit) by the last subject in the last country where the trial was conducted.

12 REFERENCES

1. Stovner LJ, Andree C. Prevalence of headache in Europe: a review for the Eurolight project. J Headache Pain. 2010;11(4):289-99.

2. Lipton RB, Bigal ME, Diamond M, et al. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology. 2007;68(5):343-9.

3. GBD. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1211-59.

4. Katsarava Z, Buse DC, Manack AN, Lipton RB. Defining the differences between episodic migraine and chronic migraine. Curr Pain Headache Rep. 2012;16(1):86-92.

5. Olesen J, Diener HC, Husstedt IW, et al. Calcitonin gene-related peptide receptor antagonist BIBN 4096 BS for the acute treatment of migraine. N Engl J Med. 2004;350(11):1104-10.

6. ICHD-3. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013;33(9):629-808.

7. Serrano D, Lipton RB, Scher AI, et al. Fluctuations in episodic and chronic migraine status over the course of 1 year: implications for diagnosis, treatment and clinical trial design. J Headache Pain. 2017;18(1):101.

8. Silberstein SD. Preventive Migraine Treatment. Continuum (Minneap Minn). 2015;21(4 Headache):973-89.

9. Diener HC, Tassorelli C, Dodick DW, et al. Guidelines of the International Headache Society for controlled trials of acute treatment of migraine attacks in adults: Fourth edition. Cephalalgia. 2019;39(6):687-710.

10. Blumenfeld AM, Bloudek LM, Becker WJ, et al. Patterns of use and reasons for discontinuation of prophylactic medications for episodic migraine and chronic migraine: results from the second international burden of migraine study (IBMS-II). Headache. 2013;53(4):644-55.

11. Hepp Z, Dodick DW, Varon SF, et al. Persistence and switching patterns of oral migraine prophylactic medications among patients with chronic migraine: A retrospective claims analysis. Cephalalgia. 2017;37(5):470-85.

12. Berger A, Bloudek LM, Varon SF, Oster G. Adherence with migraine prophylaxis in clinical practice. Pain Pract. 2012;12(7):541-9.

13. Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med. 1985;4(2):213-26.

14. Kenward MG aR, J. H. Small Sample Inference for Fixed Effects from Restricted Maximum Likelihood. Biometrics. 1997:53:983 97.

15. Reuter U, Ehrlich M, Gendolla A, et al. Erenumab versus topiramate for the prevention of migraine - a randomised, double-blind, active-controlled phase 4 trial. Cephalalgia. 2022;42(2):108-18.

APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
ACE	angiotensin converting enzyme
AE	adverse event
AESIs	AEs of special interest
Ag	antigen
ALT	alanine aminotransferase
ANA	antinuclear antibody
ARB	angiotensin receptor blocker
AST	aspartate aminotransferase
BID	twice a day
BP	blood pressure
BUN	blood urea nitrogen
CBD	cannabidiol
CGRP	calcitonin gene-related peptide
CI	confidence interval
CM	chronic migraine
COVID-19	coronavirus disease – 2019
CP	conditional power
CRP	C-reactive protein
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome P450
DB	double-blind
DNA	deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
DTP	direct-to-patient
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
ePRO	electronic Patient Reported Outcomes
EM	episodic migraine

ET	early termination
EU	European Union
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GLP	glucagon-like peptide
HDL	high density lipoprotein
HIT-6	Headache Impact Test
HTA	Health Technology Assessment
ICH	International Council for Harmonisation
IEC	independent ethics committee
IgG	immunoglobulin G
IMP	Investigational Medicinal Product
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
IV	Intravenous
LDH	lactate dehydrogenase
LDL	low density lipoprotein
MACE	major adverse cardiac event
MCS	Mental Component Score
mITT	modified intent-to-treat
MMDs	monthly migraine days
mRNA	messenger ribonucleic acid
MSQ	Migraine Specific Quality of Life Questionnaire
OL	open-label
PBO	placebo
PCR	polymerase chain reaction
PCS	Physical Component Score
PGIC	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PRO	patient-reported outcome

PROMIS	Patient-Reported Outcomes Measurement Information System
PSSM	Patient Satisfaction with Study Medication
QD	once daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
RFR	Role Function-Restrictive
RNA	ribonucleic acid
RSI	Reference Safety Information
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SDAC	Statistical Data Analysis Center
SF-36	Short Form-36
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SmPC	Summary of Product Characteristics
SNRIs	selective norepinephrine reuptake inhibitors
SSA	Simplified Schedule of Activities
SSRIs	selective serotonin reuptake inhibitors
SUSAR	suspected unexpected serious adverse reactions
ULN	upper limit of normal
US	United States
USPI	United States Package Insert
VLDL	very LDL
WBC	white blood cell
WPAI	Work Productivity and Activity Impairment

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M22-061: A Randomized, Double-blind, Parallel-group, Active Controlled Trial with Open-label Safety Extension to Evaluate the Tolerability, Safety, and Efficacy of Atogepant versus Topiramate in Subjects Requiring Preventive Treatment of Migraine (TEMPLE)

Protocol Date: 17 September 2024

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP) and local laws and regulations and guidelines governing the trial at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the trial in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the trial about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the trial, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all trial-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. Reporting promptly (within one [1] calendar day) to AbbVie, the ethics committees/institutional review boards (as required) and other appropriate individuals (e.g., coordinating investigator, institution director):
    - All changes in the research activity and all unanticipated problems involving risks to human subjects or others
    - Any departure from relevant clinical trial law or regulation, GCP, or the trial protocol that has the potential to affect the following:
        - Rights, safety, physical or mental integrity of the subjects in the clinical trial
        - Scientific value of the clinical trial, reliability or robustness of data generated
10. Providing direct access to source data documents for trial-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)	

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]		Neuroscience Clinical Development Statistics

APPENDIX D. MIGRAINE PREVENTION MEDICATIONS

Below is a list of migraine-preventive medications considered effective or probably effective sorted by therapeutic class based on mechanism of action. Of note, topiramate and valproic acid derivatives are considered separate classes. A history of inadequate response to > 4 of these medication classes will exclude the subject from the trial (see Section 5.1).

Pharmacologic Class	**Drug Name**
Class 1: Beta-blockers	Metoprolol Bisoprolol Atenolol Nadolol Propranolol Timolol
Class 2: Anti-epileptic I	Topiramate
Class 3: Anti-epileptic II	Valproic acid Sodium valproate Divalproex
Class 4: Tricyclic antidepressant	Amitriptyline Nortriptyline
Class 5: Calcium channel blocker	Flunarizine
Class 6: Serotonin-norepinephrine reuptake inhibitor (SNRI)	Desvenlafaxine Venlafaxine
Class 7: Angiotensin converting enzyme (ACE) inhibitor	Lisinopril
Class 8: Angiotensin receptor blocker (ARB)	Candesartan
Class 9: Botulinum toxin	OnabotulinumtoxinA (Botox®)
Class 10: Other	Locally approved products for migraine prevention, for example: Oxetorone Pizotifen Cinnarizine Iprazochrome Cyproheptadine

Classification of Inadequate Response to Migraine preventive Medications

Failure of a prophylactic medication can be based on tolerability or efficacy and is determined by investigator judgement.

- For **efficacy**, failure is defined as no meaningful reduction in frequency of migraine days (after an adequate trial of at least 2 months at generally accepted therapeutic doses) during the past 7 years prior to screening (Visit 1) per investigator judgement and subject interview.

- For **tolerability**, failure is defined as discontinuation of a drug treatment due to adverse effects at any previous time. In assessing failure of a migraine preventive drug based on inadequate tolerability, the entire medical history can be considered. For example, a subject who tried and discontinued propranolol 10 years ago due to hypotension or light-headedness should be considered to have failed this treatment.

APPENDIX E. EXAMPLES OF PROHIBITED MEDICATIONS

Potential interactions of each concomitant medication with topiramate use, especially per SmPC or Product Monograph, must be individually assessed by the investigator. Additional clinical monitoring may be necessary as per investigator judgement (e.g., to ensure stable control of diabetes).

The following medications are prohibited 30 days prior to screening (Visit 1) and throughout the trial period:

- Strong OATP1B1 and OATP1B3 inhibitors e.g., atorvastatin, pitavastatin, telmisartan, cyclosporine, teriflunomide
- Cannabis, CBD oil
- Any medication if administered for the preventive treatment of migraine

Medication Class	**Strong/moderate CYP3A4 inducers**	**Strong CYP3A4 inhibitors**
Anti-depressants/Anti-anxiety	Barbiturates: Amobarbital Aprobarbital Butalbital Butabarbital Mephobarbital Pentobarbital Phenobarbital Secobarbital	Nefazodone
Anti-seizure	Carbamazepine Oxcarbazepine Phenytoin Primidone	
Glucocorticoid (Systemic)	Systemic Dexamethasone	
Antibiotics (systemic)	Rifabutin Rifampicin/Rifampin	Clarithromycin Telithromycin
Anti-fungal (systemic)		Itraconazole Ketoconazole
Anti-HIV	Efavirenz	Indinavir Nelfinavir Ritonavir Saquinavir
Medication Class	**Strong/moderate CYP3A4 inducers**	**Strong CYP3A4 inhibitors**
Others	John's Wort Enzalutamide Modafinil Armodafinil	

Drugs with narrow therapeutic margins with potential for CYP drug interactions
Warfarin Digoxin Cisapride Pimozide
Drugs with demonstrated efficacy for the prevention of migraine
Topiramate Valproic acid, sodium valproate, divalproex sodium Amitriptyline Nortriptyline Metoprolol Bisoprolol Atenolol Nadolol Propranolol Timolol Flunarizine Candesartan Lisinopril Desvenlafaxine Venlafaxine
Products with local approval for the prevention of migraine
Oxetorone Pizotifen Cinnarizine Iprazochrome Cyproheptadine
Herbal medications with efficacy for the prevention of migraine
Feverfew
Gepants (oral or intranasal medications blocking the CGRP pathway)
Ubrogepant Rimegepant Zavegepant Atogepant (other than the study drug)
Non-pharmacologic headache interventions for the prevention of migraine
Acupuncture Non-invasive neuromodulation devices (e.g., transcutaneous supraorbital neurostimulator, single pulse transcranial magnetic stimulator, vagus nerve stimulator). Cranial traction Nociceptive trigeminal inhibition Occipital nerve block treatments Dental splints for headache

CYP = cytochrome P450; HIV = human immunodeficiency virus

The following treatments are prohibited 6 months prior to screening (Visit 1) and throughout the trial period:

- Therapeutic or cosmetic botulinum toxin injections into areas of the head, face, or neck.
- Injectable monoclonal antibodies blocking the CGRP pathway.

APPENDIX F. ACTIVITIES SCHEDULES

Study Activities – Double blind Treatment, Open label Treatment, and Safety Follow up Periods

The following table shows the required activities across the 19 subject encounters. Remote study visits may be conducted in-person at the investigator's discretion. The individual activities are described in detail in the **Operations Manual** (Appendix H).

Study Activities – Double blind Treatment, Open label Treatment, and Safety Follow up Periods

	Screening/ Baseline	DB Treatment Period												OL Treatment Period					Safety Follow-up
		Up Titration Phase							Maintenance Phase										
	V1 – Screening	V2 – Randomization	V3 – Week 1 (Remote)	V4 – Week 2	V5 – Week 3 (Remote)	V6 – Week 4	V7 – Week 5 (Remote)	V8 – Week 6	V9 – Week 8	V10 – Week 12	V11 – Week 16	V12 – Week 20	V13 – Week 24/DB ET	V14 – Week 28	V15 – Week 36	V16 – Week 48	V17 – Week 62	V18 – Week 76/OL ET	V19 – Week 80/Follow-up Visit
	Day –35 to Day –28	Day 1	Day 8 (±1)	Day 15 (±1)	Day 22 (±1)	Day 29 (±1)	Day 36 (±1)	Day 43 (±1)	Day 57 (±3)	Day 85 (±3)	Day 113 (±3)	Day 141 (±3)	Day 169 (+3)	Day 197 (±3)	Day 253 (±3)	Day 337 (±3)	Day 435 (±3)	Day 533 (±3)	Day 561 (±3)
INTERVIEWS & QUESTIONNAIRES																			
Informed consent	✓																		
Eligibility criteria	✓	✓						✓					✓						
Demographics	✓																		
Medical/surgical history	✓																		
Migraine history	✓																		
AE assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant treatment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Provide handheld electronic diary (eDiary), instructions, and training	✓																		
Review eDiary data and eDiary compliance		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓						
Collect eDiary instrument		✓											✓						
C SSRS	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

	Screening/ Baseline	DB Treatment Period												OL Treatment Period					Safety Follow-up
		Up Titration Phase							Maintenance Phase										
	V1 – Screening	V2 – Randomization	V3 – Week 1 (Remote)	V4 – Week 2	V5 – Week 3 (Remote)	V6 – Week 4	V7 – Week 5 (Remote)	V8 – Week 6	V9 – Week 8	V10 – Week 12	V11 – Week 16	V12 – Week 20	V13 – Week 24/DB ET	V14 – Week 28	V15 – Week 36	V16 – Week 48	V17 – Week 62	V18 – Week 76/OL ET	V19 – Week 80/Follow-up Visit
	Day –35 to Day –28	Day 1	Day 8 (±1)	Day 15 (±1)	Day 22 (±1)	Day 29 (±1)	Day 36 (±1)	Day 43 (±1)	Day 57 (±3)	Day 85 (±3)	Day 113 (±3)	Day 141 (±3)	Day 169 (+3)	Day 197 (±3)	Day 253 (±3)	Day 337 (±3)	Day 435 (±3)	Day 533 (±3)	Day 561 (±3)
MSQ v2.1		✓				✓			✓	✓	✓	✓	✓						
HIT 6		✓				✓			✓	✓	✓	✓	✓						
SF 36 v2		✓				✓			✓	✓	✓	✓	✓						
PGI S		✓				✓			✓	✓	✓	✓	✓						
PGIC						✓			✓	✓	✓	✓	✓						
WPAI: Migraine		✓				✓			✓	✓	✓	✓	✓						
PSSM						✓			✓	✓	✓	✓	✓						
PROMIS Cognitive Function (subset of subjects)		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓						
LOCAL LABS & EXAMS																			
12 lead ECG	✓									✓			✓		✓	✓	✓	✓	
Height (screening only) and weight	✓	✓		✓		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Vital signs	✓	✓		✓		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Physical examination	✓												✓					✓	✓
Urine pregnancy test		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

	Screening/ Baseline	DB Treatment Period												OL Treatment Period					Safety Follow-up
		Up Titration Phase							Maintenance Phase										
	V1 – Screening	V2 – Randomization	V3 – Week 1 (Remote)	V4 – Week 2	V5 – Week 3 (Remote)	V6 – Week 4	V7 – Week 5 (Remote)	V8 – Week 6	V9 – Week 8	V10 – Week 12	V11 – Week 16	V12 – Week 20	V13 – Week 24/DB ET	V14 – Week 28	V15 – Week 36	V16 – Week 48	V17 – Week 62	V18 – Week 76/OL ET	V19 – Week 80/Follow-up Visit
	Day –35 to Day –28	Day 1	Day 8 (±1)	Day 15 (±1)	Day 22 (±1)	Day 29 (±1)	Day 36 (±1)	Day 43 (±1)	Day 57 (±3)	Day 85 (±3)	Day 113 (±3)	Day 141 (±3)	Day 169 (+3)	Day 197 (±3)	Day 253 (±3)	Day 337 (±3)	Day 435 (±3)	Day 533 (±3)	Day 561 (±3)
CENTRAL LABS																			
Serum pregnancy test	✓																		
Clinical laboratory tests	✓	✓		✓		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Urine drug screen	✓																		
Optional PK sample		✓		✓		✓		✓	✓	✓	✓	✓	✓						
Optional biomarker sample: whole blood DNA		✓																	
Optional biomarker sample: plasma and saliva		✓						✓					✓						
TREATMENT																			
Randomization/ drug assignment		✓																	
Access IRT	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Dispense study drug		✓		✓		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		

	Screening/ Baseline	DB Treatment Period												OL Treatment Period					Safety Follow-up
		Up Titration Phase							Maintenance Phase										
	V1 – Screening	V2 – Randomization	V3 – Week 1 (Remote)	V4 – Week 2	V5 – Week 3 (Remote)	V6 – Week 4	V7 – Week 5 (Remote)	V8 – Week 6	V9 – Week 8	V10 – Week 12	V11 – Week 16	V12 – Week 20	V13 – Week 24/DB ET	V14 – Week 28	V15 – Week 36	V16 – Week 48	V17 – Week 62	V18 – Week 76/OL ET	V19 – Week 80/Follow-up Visit
	Day –35 to Day –28	Day 1	Day 8 (±1)	Day 15 (±1)	Day 22 (±1)	Day 29 (±1)	Day 36 (±1)	Day 43 (±1)	Day 57 (±3)	Day 85 (±3)	Day 113 (±3)	Day 141 (±3)	Day 169 (+3)	Day 197 (±3)	Day 253 (±3)	Day 337 (±3)	Day 435 (±3)	Day 533 (±3)	Day 561 (±3)
Blinded topiramate up titration (Visits 3 8, if no AE prevents dose escalation)			✓	✓	✓	✓	✓	✓											
Study drug reconciliation				✓		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓ (if need)

AE = adverse event; C-SSRS = Columbia Suicide Severity Rating Scale; DB = double-blind; ECG = electrocardiogram; ET = early termination; HIT = Headache Impact Test; IRT = interactive response technology; MSQ = Migraine Specific Quality of Life Questionnaire; OL = open-label; PGI-S = Patient Global Impression of Severity; PGIC = Patient Global Impression of Change; PK = pharmacokinetic; PROMIS = Patient-Reported Outcomes Measurement Information System; PSSM = Patient Satisfaction with Study Medication; SF-36 = Short Form Health Survey; V = Visit; WPAI = Work Productivity and Activity Impairment

Study Activities – Simplified Schedule of Activities (SSA) for Subjects who Discontinue Study Drug Early During the Double blind Treatment Period

All subjects who discontinue study drug early during the DB treatment period but remain in the trial must follow the SSA for Subjects who Discontinue Study Drug Early During the Double-blind Treatment Period until Week 24. Subjects must attend the Early DB Treatment Discontinuation Visit in-person as soon as possible but not later than 2 weeks following treatment discontinuation. Further visits of the SSA until Visit 12-SSA/Week 20, as applicable, may be conducted remotely per investigator discretion (see Operations Manual, Section 2.2). The Early DB Treatment Discontinuation Visit may be conducted simultaneously with the next scheduled SSA visit (if it is not later than approximately 2 weeks following treatment discontinuation). Visit 13/Week 24 should be conducted in-person per the general Schedule of Activities for the Double-blind Treatment, Open-label Treatment, and Safety Follow-up Periods (above).

The following table shows the required visit activities for subjects who discontinue study drug early during the DB treatment period. The individual activities are described in detail in the **Operations Manual** (Appendix H).

Simplified Schedule of Activities for Subjects Who Discontinue Study Drug Early During the Double blind Period

Activity	DB Treatment Period					
	Early DB Treatment Discontinuation Visit	V6 – SSA Week 4	V9 – SSA Week 8	V10 – SSA Week 12	V11 – SSA Week 16	V12 – SSA Week 20
		Day 29 (±1)	Day 57 (±3)	Day 85 (±3)	Day 113 (±3)	Day 141 (±3)
INTERVIEWS & QUESTIONNAIRES						
AE assessment	✓	✓	✓	✓	✓	✓
Prior/concomitant treatment	✓	✓	✓	✓	✓	✓
Review eDiary data and eDiary compliance	✓	✓	✓	✓	✓	✓
C SSRS	✓	✓	✓	✓	✓	✓
MSQ v2.1		✓	✓	✓	✓	✓
HIT 6		✓	✓	✓	✓	✓
SF 36 v2		✓	✓	✓	✓	✓
PGI S		✓	✓	✓	✓	✓
PGIC		✓	✓	✓	✓	✓
WPAI: Migraine		✓	✓	✓	✓	✓
PROMIS Cognitive Function (subset of subjects)		✓	✓	✓	✓	✓
LOCAL LABS & EXAMS						
Body weight	✓					
Vital signs	✓					
Urine pregnancy test	✓					
12 lead ECG	✓					

Activity	DB Treatment Period					
	Early DB Treatment Discontinuation Visit	V6 – SSA Week 4	V9 – SSA Week 8	V10 – SSA Week 12	V11 – SSA Week 16	V12 – SSA Week 20
		Day 29 (±1)	Day 57 (±3)	Day 85 (±3)	Day 113 (±3)	Day 141 (±3)
CENTRAL LABS						
Clinical laboratory tests	✓					
Optional PK sample	✓					
Optional biomarker sample: whole blood DNA	✓					
Optional biomarker sample: plasma and saliva	✓					
TREATMENT						
Access IRT	✓					
Dispense study drug (blinded topiramate down titration, if needed)	✓					
Study drug reconciliation	✓					

AE = adverse event; C-SSRS = Columbia Suicide Severity Rating Scale; DB = double-blind; ECG = electrocardiogram; HIT = Headache Impact Test; IRT = interactive response technology; MSQ = Migraine Specific Quality of Life Questionnaire; PGI-S = Patient Global Impression of Severity; PGIC = Patient Global Impression of Change; PK = pharmacokinetics; PROMIS = Patient-Reported Outcomes Measurement Information System; SF-36 = Short Form Health Survey; SSA = simplified schedule of activities; WPAI = Work Productivity and Activity Impairment

Study Activities for Remote Visits due to Pandemic Situations or Geopolitical Conflict During the DB Treatment Period

Remote study visits, conducted virtually or by phone if permitted by local regulations, are permitted for selected visits during the DB treatment period, in exceptional situations of a public health risk due to viral infection (e.g., COVID-19) to the subject or site staff or in situations of geopolitical conflict in Israel and surrounding impacted areas if agreed with the sponsor and permitted by site process and local regulations. During remote study visits, the below Study Activities Schedule should be followed. The individual activities are described in detail in the **Operations Manual** (Appendix H).

Study Activities – Remote Visits due to Pandemic Situations or Geopolitical Conflict During the Double blind Treatment Period

	DB Treatment Period									
	Up Titration Phase						Maintenance Phase			
	V3 – Week 1	V4 – Week 2	V5 – Week 3	V6 – Week 4	V7 – Week 5	V8 – Week 6	V9 – Week 8	V10 – Week 12	V11 – Week 16	V12 – Week 20
	Day 8 (±1)	Day 15 (±1)	Day 22 (±1)	Day 29 (±1)	Day 36 (±1)	Day 43 (±1)	Day 57 (±3)	Day 85 (±3)	Day 113 (±3)	Day 141 (±3)
INTERVIEWS & QUESTIONNAIRES										
Eligibility criteria						✓				
AE assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant treatment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Review eDiary data and eDiary compliance	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
C SSRS	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
MSQ v2.1				✓			✓	✓	✓	✓
HIT 6				✓			✓	✓	✓	✓
SF 36 v2				✓			✓	✓	✓	✓
PGI S				✓			✓	✓	✓	✓
PGIC				✓			✓	✓	✓	✓
WPAI: Migraine				✓			✓	✓	✓	✓
PSSM				✓			✓	✓	✓	✓
PROMIS Cognitive Function (subset of subjects)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

	DB Treatment Period									
	Up Titration Phase						Maintenance Phase			
	V3 – Week 1	V4 – Week 2	V5 – Week 3	V6 – Week 4	V7 – Week 5	V8 – Week 6	V9 – Week 8	V10 – Week 12	V11 – Week 16	V12 – Week 20
	Day 8 (±1)	Day 15 (±1)	Day 22 (±1)	Day 29 (±1)	Day 36 (±1)	Day 43 (±1)	Day 57 (±3)	Day 85 (±3)	Day 113 (±3)	Day 141 (±3)
LOCAL LABS & EXAMS										
Urine pregnancy test		✓		✓		✓	✓	✓	✓	✓
TREATMENT										
Access IRT	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Dispense and ship study drug		✓		✓		✓	✓	✓	✓	✓
Blinded topiramate up titration (Visits 3 8, as applicable, if no AE prevents dose escalation)	✓	✓	✓	✓	✓	✓				

AE = adverse event; C-SSRS = Columbia Suicide Severity Rating Scale; HIT = Headache Impact Test; IRT = interactive response technology; MSQ = Migraine Specific Quality of Life Questionnaire; PGI-S = Patient Global Impression of Severity; PGIC = Patient Global Impression of Change; PROMIS = Patient-Reported Outcomes Measurement Information System; SF-36 = Short Form Health Survey; WPAI = Work Productivity and Activity Impairment

APPENDIX G. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	19 August 2022
Version 2.0	27 October 2022
Version 3.0	31 March 2023
Version 4.0	28 August 2023

The purpose of this version is to correct minor clerical errors for consistency throughout the protocol and to update the following:

- **Information on a newly identified risk of hypersensitivity and anaphylactic reactions with the use of atogepant was added**:
  - Section 1 and Section 2.2 Added description of hypersensitivity reactions and anaphylaxis to the discussion of benefits and risks to subjects.
  - Section 5.5 Added discontinuation criteria for nonserious hypersensitivity and serious hypersensitivity or anaphylactic reactions.
- **Updates were made to the planned statistical analyses**:
  - Section 1, Section 3.1, Section 3.3, and Section 3.4 1) Clarified the key secondary endpoints with respect to off-treatment data; 2) added the endpoint, change from baseline in PROMIS Cognitive Function Abilities Subset Short Form 6a Version 2.0 score at Week 6, to the list of key secondary endpoints; 3) consolidated the list of key secondary endpoints to one common list for all countries.
  - Section 1, Section 7.1, and Section 7.6 Removed the planned unblinded interim analysis for futility and SSR due to following reasons: 1) due to fast enrollment, the enrollment will be completed by the time of the interim analysis would start so that futility analysis is infeasible; 2) the study has sufficient power for testing the primary endpoint. The planned interim analysis can be removed to avoid unnecessary unblinding of the ongoing study and protect data integrity.
  - Section 7.3 Clarified handling of potential intercurrent events to align with updates made to the key secondary endpoints.
  - Section 7.4 Clarified the summary and analysis of key secondary endpoints and subgroup analysis for efficacy to align with updates made to the key secondary endpoints.
  - Section 7.7 Updated the Type 1 error control strategy as the planned unblinded interim analysis is removed.
  - Section 7.8 The assumptions for sample size calculation were monitored and updated based on blinded data review. This revision supports that the study has sufficient > 90% power for testing the primary endpoint and key secondary endpoint (50% responders).

- **Accommodations for remote visits (previously specified for the COVID-19 pandemic) were extended to situations of geopolitical conflict in Israel and surrounding impacted areas:**
  - Section 4.1, Section 5.7, Section 5.9, Section 9, and Appendix F Added the potential for remote study visits (for selected visits, if agreed with the sponsor and permitted by site process and local regulations).
- **The requirement for male contraception was limited to the DB treatment period and for at least 30 days after the last dose of double-blind study drug because male contraception is no longer required for atogepant**
  - Section 5.1 Inclusion Criterion 14 and Section 5.2 Clarified that male contraception requirements are limited to the DB treatment period and through at least 30 days after last dose of double-blind study drug.
  - Section 6.1 Clarified that the reporting requirements for pregnancy in the partner of a male subject are limited to the DB treatment period and through at least 30 days after the last dose of double-blind study drug.
  - Section 6.1 was updated to add the Hepatic Supplemental Procedures eCRF and for minor clarifications to the AE definition, AE collection period, and SUSAR reporting.
- **The following additional clarifications were made**:
  - Section 4.1 Clarified that subjects who permanently discontinue study drug during the DB treatment period are not eligible to enter the 52-week OL treatment period.
  - Section 5.10 Clarified the description of the DSMB responsibilities to align with the removal of the planned unblinded interim analysis.
  - Section 5.1 Inclusion Criterion 7 and Criterion 8 Clarified the text that describes the extent of eDiary data required just prior to Visit 2/Randomization.
  - Section 5.1 Exclusion Criterion 6 Clarified that subjects who are currently being treated for epilepsy are excluded from the study.
  - Section 5.3 and Appendix E Clarified the examples of prohibited strong and moderate CYP3A4 inducers and strong OATP1B1/OATP1B3 inhibitors.
  - Section 8.3 Clarified subject confidentiality language in accordance with the sponsor's current protocol template.
  - Appendix F Clarified visit windows for Visit 8 and Visit 13

The following updates were made to Appendix H Operations Manual

- Section 1 and Section 4.2 Updated the pharmacovigilance contact email and fax numbers in accordance with current sponsor process, and clarified reporting procedure for AESI or pregnancy.
- Section 2.3, Section 3.4, Section 3.10, and Section 3.14 Potential remote visit procedures (previously specified for the COVID-19 pandemic) were extended to exceptional situations of geopolitical conflict in Israel and surrounding impacted areas.

- Section 3.8 Clarified PK sampling during the DB treatment period and at the Early DB Treatment Discontinuation visit.
- Table 1 Updated footnote "a" to clarify the purpose for collecting the specified laboratory parameters. Removed "Visit 2 (randomization)" from footnote "c" to align with the activities schedule.
- Section 5.2 Clarified language for SUSAR reporting in accordance with the sponsor's current protocol template.
- Section 6.5 Clarified language regarding subjects who discontinue study drug during the up-titration phase and who may require taper off of topiramate at the investigator's discretion.