A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Atogepant for the Prophylaxis of Migraine in Participants with Episodic Migraine Who Have Previously Failed 2 to 4 Classes of Oral Prophylactic Treatments (ELEVATE)

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To prospectively test for superiority of atogepant 60 mg QD versus placebo for the prevention of migraine in participants with episodic migraine who have previously failed 2 to 4 classes of oral medications for the prophylaxis of migraine

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Headaches
Study type	Interventional

Summary

ID

NL-OMON52713

Source
ToetsingOnline

Brief title
Allergan 3101-304-002 (ELEVATE) Study

Condition

- Headaches

Synonym
Episodic migraine; Headache

Research involving
Human

Sponsors and support

Primary sponsor: AbbVie Deutschland GmbH & Co. KG
Source(s) of monetary or material Support: AbbVie B.V.

Intervention

Keyword: Atogepant, Episodic Migraine, Phase 3, Prohylaxis

Outcome measures

Primary outcome

Change from Baseline (CFB) in mean monthly migraine days across the 12-week treatment period.

Secondary outcome

- Achievement of at least a 50% reduction in mean monthly migraine days across the 12-week treatment period.

- CFB in mean monthly headache days across the 12 week treatment period.

- CFB in mean monthly acute medication use days across the 12-week treatment period.

- CFB in MSQ v2.1 Role Function-Restrictive domain score at Week 12

- CFB in mean monthly Physical Impairment domain score of the AIM-D across the 12 week treatment period

- CFB in the HIT-6 total score at Week 12

Study description

Background summary

Migraine affects 18% of women and 6% of men in the United States with peak prevalence occurring between the ages of 25 to 55 years. Approximately one-third of these migraineurs have 3 or more migraine headaches per month, and over half report severe impairment or the need for bed rest. Prevalence is similar in Europe, with migraine headache affecting on average 17.6% of women and 8% of men. As of 2016, migraine is the second leading cause of disability worldwide.
Migraine is typically characterized by attacks of throbbing, unilateral headache of moderate or severe pain intensity, associated with nausea, vomiting, and/or sensitivity to light (photophobia) and sound (phonophobia). In about 25% of individuals, the migraine headache is preceded by focal neurological dysfunction (aura). Improving diagnosis and optimizing treatments for migraine have been recognized as critically important to overcoming current barriers to reduce the global burden of migraine.
Because there are no biological markers for migraine, diagnosis is based on clinical history, exam, and the exclusion of other headache disorders. Physicians apply clinical criteria to guide diagnoses and subsequent treatment. Episodic migraine (EM) can be divided into low frequency (LFEM) and high frequency episodic migraine (HFEM) depending on the headache days suffered per month (GBD 2017).
Episodic migraine (EM) is a syndrome diagnosis applied to patients with migraine (with or without aura) who have 1 to 14 headache days per month. Chronic migraine is a specific ICHD-3diagnosis applied to a subset of patients with >=15 headache days per month.
This study will include participants with episodic migraine who had failed 2-4 classes of prior oral prophylactic medications. The rationale for targeting this population is 2-fold. Firstly, patients on currently available oral prophylactic medications may experience poor tolerability; secondly, many of these treatments have shown insufficient efficacy (did not sufficiently reduce either severity or frequency) of migraine for many patients.
The consequences of the limitations in current oral prophylactic migraine treatments amount to both poor adherence and reluctance to initiate prophylactic treatment. In fact, recent studies have indicated that approximately half of migraine patients discontinued their initial oral migraine prophylactic treatment within 60 days, which might be explained by poor tolerability or lack of efficacy.
Moreover, in a US-based retrospective database study it was concluded that approximately 70% of patients who begin migraine prophylaxis with antidepressants, antiepileptics, or beta-blockers are no longer taking these medications at 6 months. Of those patients who continue to take a prophylactic medication, many still have substantial disease burden.

Therefore, the proposed population for Study 3101-304-002 reflects clinical practice. There is severe unmet need in patients that have failed multiple migraine prophylactic oral medications, and these patients are currently often relying on ineffective treatments and many suffer from intolerability to currently available medications

Study objective

To prospectively test for superiority of atogepant 60 mg QD versus placebo for the prevention of migraine in participants with episodic migraine who have previously failed 2 to 4 classes of oral medications for the prophylaxis of migraine

Study design

A global, multicenter, randomized, double-blind, placebo-controlled, parallel group study in participants with episodic migraine who have previously failed 2 to 4 classes of oral medications for the prophylaxis of migraine

Intervention

Patient participation will begin with a 4-week screening/baseline period. Participants who complete the 4-week screening/baseline period and meet all entry criteria will be randomized to the doubleblind treatment period of the study at Visit 2 (Randomization Visit). The double-blind treatment period will last 12 weeks, with a subsequent safety follow-up period of 4 additional weeks. Total duration of study participation for one participant is approximately 20 weeks.

Study burden and risks

The study will include a total of 8 visits and will be up to 20 weeks in duration. Subjects are expected to undergo procedures/assessments as described in the section 1.3 of the study protocol, which include: Physical exam, vital signs, demographic and medical history; ECG; eDiary: reporting information on symptoms/signs of disease, (i.e. headache duration, frequency, characteristics, symptoms, acute medication use, etc.); Blood and urine tests (including urine drug screening); Completion of questionnaire and answering questions from the study team; Pregnancy tests in women of childbearing potential; Female patients: no breastfeeding allowed. Effective methods of birth control must be used from the time of signing the ICF, throughout the entire study; Male patients: due to the potential risk of the effect on the sperm appropriate method of contraception must be used starting at screening and throughout the entire study.
The following risks were the most common side effects in a study of patients with migraine receiving atogepant or placebo (medically inactive substance)

daily for 12 weeks: nausea, common cold, constipation, urinary tract infection, fatigue, increased creatine phosphokinase
The risks involved in taking this study medication have been carefully assessed by previous testing done in animal and human studies. Overall, the risks are considered to be acceptable although some risks are unforeseeable. In addition to the risks listed above, there may be some infrequent and unforeseeable risks associated with the use of atogepant. Atogepant is investigational, when taken alone or in combination with other medications, so there may be other risks that are unknown.
Older drugs in this class have been associated with an increased risk of liver problems. However, atogepant is a new drug that has been designed specifically to minimise this risk. Based on previous studies with this drug, no safety issues related to taking atogepant and liver problems have been detected.
Placebo Risks: If the study subject is in the group which is assigned placebo, study subject*s symptoms of migraine may not improve or may worsen. Even if the study subject is in the group that gets the active drug during the study, the symptoms may not improve or may worsen.
Blood Sample Risks: Subjects may feel a slight needle prick when blood is drawn. Some participants may have a slight bruise that will go away within a few days. Sometimes, participants feel light headed or feel dizzy. Other rare complications associated with the blood sample collection include: infections, nerve lesions, accidental arterial puncture (when the needle pierces an artery instead of a vein) and bleeding, inflammation of vein, and dizziness.
Electrocardiogram (ECG) Risks: The ECG procedure may cause minimal discomfort and skin irritation during or after the attachment/removal of the leads (and adhesive).
Allergic Reaction Risks: As with taking any treatment, there is a risk of allergic reaction. Some symptoms of allergic reactions are: Rash; Wheezing and difficulty breathing; Dizziness and fainting; Swelling around the mouth, throat or eyes; A fast pulse; Sweating.

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Moreover, in a US-based retrospective database study it was concluded that approximately 70% of patients who begin migraine prophylaxis with antidepressants, antiepileptics, or beta-blockers are no longer taking these medications at 6 months. Of those patients who continue to take a prophylactic

medication, many still have substantial disease burden.
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Contacts

Public
AbbVie Deutschland GmbH & Co. KG

Knollstrasse -
Ludwigshafen 67061
DE
Scientific
AbbVie Deutschland GmbH & Co. KG

Knollstrasse -
Ludwigshafen 67061
DE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1.01 Male or female participants ages 18 (or age of legal majority) to 80 years, inclusive, at Visit 1
2.01 At least a 1-year history of migraine with or without aura consistent with a diagnosis according to the ICHD-3, 2018.

2.02 Age of the participant at the time of migraine onset < 50 years
2.03 History of 4 to 14 migraine days per month on average in the 3 months prior to Visit 1 in the investigator's judgment
2.04 4 to 14 migraine days in the 28-day baseline period per eDiary (Note: A randomization cap of 20% will be instituted to ensure that the planned randomized participants include no more than 20% of participants with 4 to <8 migraine days at baseline.)
2.05 Completed at least 20 out of 28 days in the eDiary during the baseline period and is able to read, understand, and complete the study questionnaires and eDiary per investigator's judgment.
2.06 Participants must meet both criteria below (ie, a and b). Participants must have:
a. Failed oral migraine prophylaxis medications from 2 to 4 of the medication classes as listed below:
i. Propranolol, metoprolol, atenolol, bisoprolol, timolol, or nadolol;
ii. Topiramate;
iii. Flunarizine;
iv. Valproate or divalproex;
v. Amitriptyline or nortriptyline;
vi. Venlafaxine or desvenlafaxine;
vii. Lisinopril;
viii. Candesartan;
ix. Locally approved products (eg, oxeterone or pizotifen)
b. Failed at least one treatment from the list below:
i. Propranolol OR metoprolol;
ii. Topiramate;
iii. Flunarizine;
iv. Amitriptyline

3.01 Male participants willing to minimize the risk of inducing pregnancy as detailed below:
A male participant must agree to use contraception during the intervention period and for at least 3 days after the last dose of study intervention and refrain from donating sperm during this period.
Female participants willing to minimize the risk of inducing pregnancy as detailed below:
A female participant is eligible to participate if she is not pregnant (ie, has a negative urine pregnancy result at the Screening Visit (Visit 1) and Randomization Visit (Visit 2), is not planning to become pregnant during the course of the study, is not breastfeeding, and fulfills at least one of the following conditions:
a. Not a WOCBP as defined in Appendix 7 of the protocol
OR
b. A WOCBP who agrees to follow the contraceptive guidance of using a medically acceptable and effective contraceptive method as defined in Appendix 7 of the protocol during the intervention period and for 3 days after the last dose of study intervention.

4.01 Written informed consent and participant privacy information (eg, Written Authorization for Use and Release of Health and Research Study Information [US sites] and written Data Protection consent [EU sites]) obtained from the participant prior to any study-related procedures.

Exclusion criteria

1.01 Any clinically significant hematologic, endocrine, pulmonary, hepatic, gastrointestinal, or neurologic disease
1.02 Participant has any other concurrent pain condition that, in the opinion of the investigator, may significantly impact the current headache disorder
1.03 In the opinion of the investigator, confounding psychiatric conditions, dementia, epilepsy, or significant neurological disorders other than migraine
1.04 History of malignancy in the 5 years prior to Visit 1, except for adequately treated basal cell or squamous cell skin cancer, or in situ cervical cancer
1.05 History of any prior gastrointestinal procedures or gastrointestinal conditions that may affect the absorption or metabolism of study intervention; participants with prior gastric bariatric interventions which have been reversed are not excluded
1.06 Clinically significant cardiovascular or cerebrovascular disease per the investigator's opinion
1.07 Significant risk of self-harm based on clinical interview and responses on the C-SSRS, or of harm to others in the opinion of the investigator; participants must be excluded if they report suicidal ideation with intent, with or without a plan, in the past 6 months or report suicidal behavior in the 6 months prior to Visit 1 or Visit 2 assessments
1.08 At Visit 1, a user of recreational or illicit drugs or has had a history within the past year of drug or alcohol abuse or dependence
2.01 Has >= 15 headache days per month on average across the 3 months prior to Visit 1 in the investigator's judgment
2.02 Has >= 15 headache days in the 28-day baseline period per eDiary
2.03 Difficulty distinguishing migraine headaches from tension-type or other headaches
2.04 Has a history of migraine accompanied by diplopia or decreased level of consciousness or retinal migraine as defined by ICHD-3, 2018
2.05 Has a current diagnosis of chronic migraine, new persistent daily headache, medication overuse headache, trigeminal autonomic cephalgia (eg, cluster headache), or painful cranial neuropathy as defined by ICHD-3, 2018
3.01 Usage during 30 days prior to Visit 1 and throughout the study period of and requirement for any medication, diet, or nonpharmacological treatment that is on the list of prohibited concomitant medications or treatments that cannot be discontinued or switched to an allowable alternative medication or treatment. This includes concomitant medications with demonstrated efficacy for

the prevention of migraine regardless of indication.
3.02 Usage of therapeutic or cosmetic botulinum toxin injections into areas of the head, face, or neck within 6 months prior to Visit 1 and throughout the study period.
3.03 Usage of barbiturate-containing or opioid-containing analgesics > 2 days/month, triptans or ergots >= 10 days/month, or simple analgesics (eg, aspirin, NSAIDs, acetaminophen) >= 15 days/month in the 3 months prior to Visit 1 per investigator*s judgment, or during the baseline period.
(Note: barbiturate-containing analgesics are excluded 30 days prior to screening, during the screening/baseline period, and for the duration of the study. Opioid-containing analgesics are excluded during the screening/baseline period and throughout the study, however, episodic use of opioids for purposes not related to migraine or headache, eg, surgery, is not exclusionary.)

3.04 Previous exposure to:
• Atogepant
• Injectable monoclonal antibodies blocking the CGRP pathway within the last 6 months prior to Visit 1
• Any other investigational CGRP-RA
3.05 History of hypersensitivity or clinically significant adverse reaction to a CGRP-RA or hypersensitivity to any component of the study interventions.
4.01 Currently participating or has participated in a study with an investigational compound or device within 30 days prior to Visit 1
5.01 Hypertension as defined by sitting systolic blood pressure > 160 mm Hg or sitting diastolic blood pressure > 100 mm Hg at Visits 1 or
Visit 2. Vital sign measurements that exceed these limits may be repeated only once
5.02 An ECG with clinically significant abnormalities at screening as determined by the investigator
5.03 QTcF > 450 msec for males and QTcF > 470 msec for females at Visit 1 based on the ECG report of the central reviewer
5.04 Clinically significant laboratory values (see protocol section 5.2)
5.05 Positive result on the urine drug screen at Visit 1 unless explained by concomitant medication use
5.06 History of acute hepatitis within 6 months of screening ; or chronic hepatitis; or a positive result on anti-hepatitis A IgM antibody, hepatitis B surface antigen, anti-hepatitis C antibody or anti-hepatitis E IgM antibody testing at screening
6.01 Employed by or is an immediate family member of one of the investigators, study staff, or sponsor
6.02 Participant has a condition or is in a situation which in the investigator's opinion may put the participant at significant risk, may confound the study results, or may interfere significantly with the participant's participation in the study
6.03 Any medical or other reasons that, in the investigator's opinion, might indicate that the participant is unsuitable for the study

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-10-2021
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	-
Generic name:	Atogepant

Ethics review

Approved WMO Date:	10-06-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-10-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	06-03-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-04-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-10-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-11-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-01-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-01-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-03-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-04-2022

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2019-003448-58-NL
ClinicalTrials.gov	NCT04740827
CCMO	NL72795.056.20