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RESEARCH SUBMISSION

Safety and tolerability of ubrogepant for the acute treatment of migraine in participants taking atogepant for the preventive treatment of episodic migraine: Results from the TANDEM study

Jessica Ailani MD[1] | Richard B. Lipton MD[2] | Andrew M. Blumenfeld MD[3] | Laszlo Mechtler MD[4] | Brad C. Klein MD, MBA[5] | Molly Yizeng He PhD[6] | Jonathan H. Smith MD[6] | Joel M. Trugman MD[6] | Rosa de Abreu Ferreira MD[6] | Elimor Brand-Schieber PhD[6]

[1]Department of Neurology, MedStar Georgetown University Hospital, Washington, DC, USA

[2]Department of Neurology, Albert Einstein College of Medicine, Bronx, New York, USA

[3]The Los Angeles Headache Center, Los Angeles, California, USA

[4]Dent Neurologic Institute, Buffalo, New York, USA

[5]Abington Neurological Associates, Abington, Pennsylvania, USA

[6]AbbVie, North Chicago, Illinois, USA

Correspondence
Jessica Ailani, Department of Neurology, Medstar Georgetown University Hospital, 3800 Reservoir Road NW, 7PHC, Washington, DC 20007, USA.
Email: jessica.ailani@medstar.net

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AbbVie

Abstract

Objective: To evaluate the safety and tolerability of ubrogepant for the acute treatment of migraine in participants taking atogepant for the preventive treatment of episodic migraine (EM).

Background: Atogepant is an oral calcitonin gene-related peptide (CGRP) receptor antagonist approved for the preventive treatment of migraine in adults and ubrogepant is an oral CGRP receptor antagonist approved for the acute treatment of migraine in adults, with or without aura. The safety and tolerability of the concomitant use of ubrogepant and atogepant have not been previously evaluated in a clinical setting.

Methods: The TANDEM study, a phase 4, two-period, multicenter, open-label study conducted in the United States, enrolled adults with migraine, with or without aura, and <15 headache days/month. In Treatment Period 1, participants took atogepant 60 mg once daily (QD) for 12 weeks and their own non-gepant acute headache medication for breakthrough migraine attacks. In Treatment Period 2, participants continued taking atogepant 60 mg QD and ubrogepant 100 mg was taken as needed (PRN) for the treatment of breakthrough migraine attacks (up to eight per 4-week interval) for 12 weeks. In Treatment Period 2, an optional second ubrogepant dose or the participant's own acute medication could be used to rescue headaches that did not resolve within 2–24 h post initial ubrogepant dose. The primary objective evaluated the safety and tolerability of the concomitant use of ubrogepant and atogepant.

Results: Of 263 participants enrolled, 262 were treated in Treatment Period 1 (Safety Population 1) and 218 continued and were treated in Treatment Period 2 (Safety

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CGRP, calcitonin gene-related peptide; CI, confidence interval; ECG, electrocardiogram; EM, episodic migraine; ICHD-3, International Classification of Headache Disorders, third edition; PRN, as needed; QD, once daily; SD, standard deviation; TEAE, treatment-emergent AE; ULN, upper limit of normal.

Population 2). The mean (standard deviation) number of ubrogepant use days in Treatment Period 2 was 6.6 (5.03) over the 12 weeks. In Treatment Periods 1 and 2, 49.6% and 43.1% of participants experienced a treatment-emergent adverse event (TEAE), respectively. The most common TEAEs (≥5%) in Treatment Period 1 and Treatment Period 2 were COVID-19 (8.4%, 3.2%), fatigue (6.5%, 1.4%), nausea (6.1%, 0.9%), decreased appetite (5.7%, 0.9%), and constipation (5.3%, 0.9%). In Treatment Period 2, no increase in the incidence and types of TEAEs in relation to the number of ubrogepant use days or doses taken were identified. During the whole treatment period, 9.9% of participants discontinued atogepant or ubrogepant treatment due to TEAEs. There was one serious TEAE in Treatment Period 1 (ureterolithiasis) and one in Treatment Period 2 (cervical myelopathy), and both were considered not related to study treatment by the study investigators.

Conclusion: The use of atogepant 60 mg QD for the preventive treatment of EM and ubrogepant 100 mg PRN for the acute treatment of migraine over the 12-week open-label concomitant use treatment period was safe and well tolerated. The overall safety results were consistent with the known safety profiles of atogepant and ubrogepant when used alone and no new safety signals were identified.

Plain Language Summary

Some individuals receiving preventive treatment for migraine, such as the oral medication atogepant, may continue to experience migraine attacks and migraine-related disability. This study aimed to evaluate the safety and tolerability of the dual use of ubrogepant, an oral medication used for the acute treatment of migraine, and atogepant in adults with episodic migraine. The study included a 12-week period of combined use of atogepant for daily preventive treatment and ubrogepant for acute treatment of migraine attacks and found that the using these treatments at the same time was safe and well-tolerated by participants.

KEYWORDS
atogepant, calcitonin gene-related peptide, gepant, safety, ubrogepant

INTRODUCTION

Migraine is a debilitating neurological disease that impacts ~1.1 billion individuals worldwide, with >90% of those individuals having episodic migraine (EM).[1–3] Migraine can be addressed using acute treatments to relieve pain and restore function and/or preventive treatments, which are aimed at preventing migraine attacks and reducing the symptom burden of attacks.[4] The American Headache Society Consensus Guidelines state the management of migraine may include both acute and preventive treatments.[4] The majority of individuals receiving preventive treatment for migraine continue to experience breakthrough migraine attacks and migraine-related disability. A combination of acute and preventive treatments is often required for optimal migraine management.[5,6]

Calcitonin gene-related peptide (CGRP) is a neuropeptide that has been well documented to play a pivotal role in the pathogenesis of migraine. CGRP levels in the cranial circulation are increased during a migraine attack, and CGRP infusion has been shown to trigger migraine-like headaches.[7–9] Eight treatments targeting either the CGRP ligand or its receptor have established efficacy for the acute and/or preventive treatment of migraine.[10,11] Additionally, the American Headache Society recently published a position statement indicating that CGRP-targeted therapies should be considered a first-line approach for preventive treatment due to the substantial volume, scope, and quality of available evidence.[12] Atogepant is an oral, small molecule, CGRP receptor antagonist, or gepant, approved in the United States and European Union for the preventive treatment of migraine in adults,[13,14] and ubrogepant is an oral CGRP receptor antagonist approved in the United States for the acute treatment of migraine in adults, with or without aura.[15] Atogepant was shown to be safe and well tolerated in three placebo-controlled, double-blind, randomized trials for the preventive treatment of EM (Phase 2b/3 [NCT02848326], ADVANCE [NCT03777059], ELEVATE [NCT04740827]) and a trial for the preventive treatment of chronic

migraine (PROGRESS [NCT03855137]).[16–19] Ubrogepant was shown to be safe and well tolerated in two placebo-controlled, double-blind, randomized controlled trials for the acute treatment of migraine (ACHIEVE I [NCT02828020], ACHIEVE II [NCT02867709]).[20,21] The combination of atogepant and ubrogepant was shown to be well tolerated and without clinically meaningful drug interactions in a pharmacokinetic study of 31 participants.[22] Additional safety and tolerability data regarding the concomitant use of atogepant and ubrogepant for the treatment of migraine were also sought. Here, we report the safety and tolerability of the concomitant use of ubrogepant for the acute treatment of breakthrough migraine attacks in participants taking atogepant for the preventive treatment of EM.

METHODS

Study design

The TANDEM study was a multicenter, two-period, open-label, phase 4 trial conducted in the United States from March 7, 2022, to April 4, 2023. Eligible participants were included in a screening period, two 12-week open-label treatment periods, and a 4-week follow-up period (Figure 1). Treatment Period 1 (Weeks 1–12) was a 12-week open-label treatment period with participants taking atogepant 60 mg once daily (QD) for the preventive treatment of EM. Participants took their own acute migraine treatment, except for any gepant, for any breakthrough migraine attack. In Treatment Period 2 (Weeks 13–24), participants continued atogepant 60 mg QD and were instructed to take ubrogepant 100 mg as needed (PRN) for all breakthrough migraine attacks (up to eight in a 4-week interval) for 12 weeks. An optional second ubrogepant dose, or the participant's own acute medication for migraine was allowed between 2 and 24 h after the initial ubrogepant dose if the breakthrough migraine attack did not resolve or recurred. All participants who took one or more dose of atogepant 60 mg QD entered the safety follow-up of 4 additional weeks after their last dose of study drug.

The trial was approved by a local or central Institutional Review Board at each participating institution and conducted in accordance with the International Conference for Harmonisation guidelines, applicable regulations, and the Declaration of Helsinki. Participants provided written informed consent before screening. The study is registered with ClinicalTrials.gov (NCT05264129).

Participants

The study enrolled adults aged 18–80 years, who had a ≥1-year history of migraine, with or without aura, consistent with a diagnosis according to the International Classification of Headache Disorders, third edition (ICHD-3),[2] age of migraine onset <50 years, and a history of 4–14 migraine days/month, on average, in the 3 months prior to screening (based on investigator's judgment). A history of <15 headache days/month across the 3 months prior to screening was also required (based on investigator's judgment).

Exclusion criteria included the following: participants with an ICHD-3-defined history of migraine accompanied by diplopia or

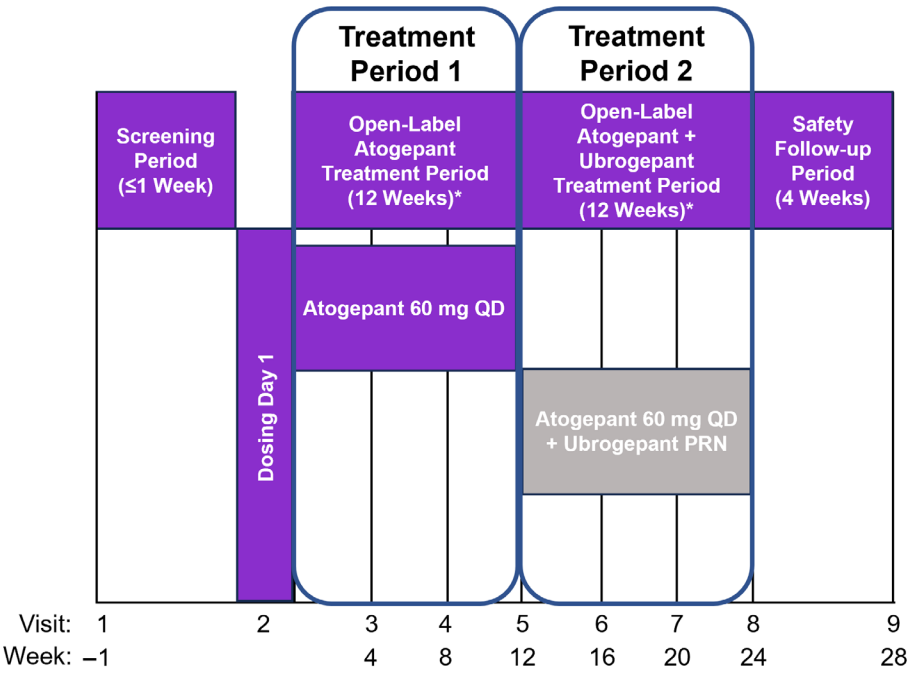

FIGURE 1 The TANDEM study design. *In Treatment Period 1, non-gepant acute treatment was allowed for any breakthrough migraine attack. In Treatment Period 2, participants were instructed to treat first with ubrogepant for all breakthrough migraine attacks. An optional second ubrogepant dose or a non-gepant acute treatment was allowed between 2 and 24 h after the initial ubrogepant dose if the breakthrough migraine attack did not resolve, or recurred. PRN, as needed; QD, once daily. [Colour figure can be viewed at wileyonlinelibrary.com]

decreased level of consciousness, or retinal migraine, or a current diagnosis of chronic migraine, new daily persistent headache, trigeminal autonomic cephalalgia, or painful cranial neuropathy; clinically significant laboratory values, including alanine transaminase (ALT) >1×upper limit of normal (ULN), total bilirubin >1×ULN (except those with a diagnosis of Gilbert's disease), or serum albumin <2.8 g/dL; history of an inadequate response to five or more prescription preventive migraine medications in two or more different mechanisms; clinically significant cardiovascular/cerebrovascular disease or clinically significant hematologic, endocrine, pulmonary, renal, hepatic, gastrointestinal, or neurologic diseases (unless stable for >1 year); participants who were pregnant, planning to become pregnant during the trial, or currently lactating; use of opioids >4 days/month in the 3 months prior to screening; previous exposure to atogepant, exposure to injectable CGRP monoclonal antibodies within the last 6 months, or exposure to rimegepant for preventive treatment within the last month.

Outcomes

The primary objective of this study was to evaluate the safety and tolerability of the concomitant use of ubrogepant 100 mg PRN for the acute treatment of migraine in participants taking atogepant 60 mg QD for the preventive treatment of EM. Safety evaluations included the incidence of adverse events (AEs), serious AEs, AEs leading to discontinuation, and vital sign measurements, electrocardiogram (ECG) variables, clinical laboratory evaluations (hematology, chemistry, urinalysis), and Columbia Suicide Severity Rating Scale for the entire study duration. Treatment-emergent AEs (TEAEs) were defined as AEs with a recorded onset date on or after the date of the first dose of study treatment in the respective treatment period. An AE that occurred >30 days after the last dose of the study treatment or Visit 8, whichever came later, was not counted as a TEAE. An AE in Treatment Period 1 that continued into Treatment Period 2 was counted as a TEAE only in Treatment Period 1. An AE that started during Treatment Period 2 was counted as a TEAE in Treatment Period 2 (even if the same preferred term was previously reported in Treatment Period 1). Treatment emergent ALT and/or aspartate aminotransferase (AST) ≥3×ULN and potential Hy's law cases were considered AEs of special interest and adjudicated by an external Hepatic Event Adjudication Committee and were followed until resolution. Clinically significant blood pressure was defined as sitting or standing systolic ≥180 mmHg and increase ≥20 or ≤90 mmHg and decrease of ≥20 mmHg or sitting or standing diastolic ≥105 mmHg and increase of ≥15 or ≤50 mmHg and decrease ≥15 mmHg.

Statistical analyses

Sample size was determined based on historical data from previously completed clinical studies. It was assumed that 15% of participants would discontinue from the study during the atogepant treatment period (Weeks 1–12). Therefore, 235 participants were assigned to receive open-label atogepant 60 mg QD for the preventive treatment of EM at baseline/Visit 2 (Day 1), with ~200 participants assigned to also receive ubrogepant 100 mg for the acute treatment of migraine starting at Visit 5 (Week 12). This sample size provided estimation for AEs of interest occurring in either the open-label atogepant Treatment Period 1 (Weeks 1–12) or the open-label atogepant and ubrogepant concomitant use Treatment Period 2 (Weeks 13–24) with a precision (defined as the half width of 95% confidence interval [CI]) of approximately ±3–5%.

Safety Population 1 consists of all participants who received at least one dose of study drug (atogepant) during Treatment Period 1. Safety Population 2 consists of all participants who received at least one dose of study drug (atogepant or ubrogepant) during Treatment Period 2. Safety Population 1 was used for all baseline analyses, and Safety Population 1 or Safety Population 2 were used for safety analyses.

The safety outcomes included AEs, clinical laboratory evaluations, vital sign measurements, ECG parameters, Columbia Suicide Severity Rating Scale, and pregnancy test. For each of the clinical laboratory, vital sign, and ECG parameters, the last non-missing safety assessment before the first dose of study drug was used as the baseline for all analyses of that safety parameter. Continuous variables were summarized by the number of participants, mean, standard deviation (SD), median, minimum, and maximum values. Categorical variables were summarized by number and percentage of participants. A post hoc sensitivity analysis was performed on Safety Population 2 to evaluate the incidence of TEAEs during Treatment Period 1. Statistical analyses were performed using Statistical Analysis System (SAS) software, version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Participants

Of the 352 participants screened, 263 were enrolled in the study. Safety Population 1 included 262 participants in the open-label atogepant Treatment Period 1. Safety Population 2 included 218 participants in the open-label atogepant and ubrogepant Treatment Period 2. Most of the participants in Safety Populations 1 and 2 were female (81.7%, 83.0%) and White (78.2%, 81.7%); the mean age was 43.7 and 43.4 years, respectively, and the mean body mass index was 29.6 kg/m^2 for both populations (Table 1). Prior treatment with a CGRP antagonist was reported in 23 (8.8%) participants, including 11 (4.2%) with prior ubrogepant exposure. No participant had prior atogepant exposure.

Among all enrolled participants, most completed Treatment Period 1 (221/263 [84.0%]) and continued into Treatment Period 2. The most common reasons for discontinuation of atogepant during Treatment Period 1 were AEs (16/263 [6.1%]), withdrawal by participant (11/263 [4.2%]), lost to follow-up (8/263 [3.0%]), and other

TABLE 1 Baseline demographics.

Variable	Treatment Period 1 (open-label atogepant treatment period) Safety Population 1 ($N=262$)	Treatment Period 2 (open-label atogepant + ubrogepant treatment period) Safety Population 2 ($N=218$)
Age, years, mean (SD)	43.7 (13.0)	43.4 (12.7)
Sex, *n* (%)		
Male	48 (18.3)	37 (17.0)
Female	214 (81.7)	181 (83.0)
Race, *n* (%)		
White	205 (78.2)	178 (81.7)
Black or African American	44 (16.8)	29 (13.3)
Asian	8 (3.1)	7 (3.2)
American Indian or Alaska Native	1 (0.4)	0
Native Hawaiian or Other Pacific Islander	0	0
Multiple[a]	4 (1.5)	4 (1.8)
Ethnicity, *n* (%)		
Hispanic or Latino	27 (10.3)	25 (11.5)
Not Hispanic or Latino	235 (89.7)	193 (88.5)
Body mass index, kg/m^2, mean (SD)	29.6 (7.7)	29.6 (7.6)
Prior CGRP antagonist use, *n* (%)	23 (8.8)	-

Abbreviations: CGRP, calcitonin gene-related peptide; SD, standard deviation.

[a]Participants who reported multiple races are only included in the "Multiple" category.

(6/263 [2.3%]). The most common reasons for discontinuation of atogepant in Treatment Period 2 were withdrawal by participant (8/263 [8.0%]), AEs (3/263 [1.1%]), lost to follow-up (2/263 [0.8%]), and other (2/263 [0.8%]), and the most common reasons for discontinuation of ubrogepant were withdrawal by participant (6/263 [2.3%]), lost to follow-up (2/263 [0.8%]), other (2/263 [0.8%]), and AEs (1/263 [0.4%]) (Figure 2).

Treatment duration

The mean (SD) treatment duration for atogepant during Treatment Period 1, Treatment Period 2, and across both treatment periods was 78.0 (20.2), 80.6 (14.5), and 145.2 (49.9) days, respectively. During Treatment Period 2, 25 (11.5%) participants never took ubrogepant treatment, and 59 (27.1%), 80 (36.7%), and 49 (22.5%) had 1–3 days, 4–9 days, and ≥10 days of ubrogepant treatment, respectively. Five participants were not included in the treatment duration analyses due to missing date data. Among the 188 participants who were evaluated based on ubrogepant use in Treatment Period 2, 113 participants (60.1%) took at least one optional second dose for breakthrough migraine attacks (individual participants may have had multiple attacks). Across Treatment Period 2, the mean (SD) ubrogepant use days for participants who took at least one dose of ubrogepant ($n=188$) was 6.6 (5.0) days, and the mean (SD) ubrogepant optional second dose use days for participants who took at least one optional second dose of ubrogepant ($n=113$) was 3.5 (3.4) days (Table 2).

Treatment-emergent AEs

Treatment-emergent AEs across the whole treatment period occurred in 174/262 (66.4%) participants (Table 3). TEAEs that occurred in ≥5% of participants were COVID-19 (11.1%), fatigue (7.6%), nausea (6.9%), decreased appetite (6.5%), constipation (6.1%), and upper respiratory tract infection (5.3%) (Table 4). No deaths were reported during the study. There was one serious TEAE in each period (Treatment Period 1, ureterolithiasis; Treatment Period 2, cervical myelopathy), and both were considered not related to study treatment by the investigator. Overall, 26 (9.9%) participants experienced TEAEs leading to study drug discontinuation during the whole treatment period. TEAEs that led to study drug discontinuation by more than one participant during the whole treatment period were constipation (5/262 [1.9%]), nausea (4/262 [1.5%]), decreased appetite (4/262 [1.5%]), fatigue (3/262 [1.1%]), dizziness (2/262 [0.8%]), migraine (2/262 [0.8%]), somnolence (2/262 [0.8%]), depression (2/262 [0.8%]), and insomnia (2/262 [0.8%]).

Treatment-emergent AEs in Safety Population 1 during Treatment Period 1 occurred in 130/262 (49.6%) participants (Table 3). TEAEs that occurred in ≥5% of participants were COVID-19 (8.4%), fatigue (6.5%), nausea (6.1%), decreased appetite (5.7%), and constipation (5.3%) (Table 4). TEAEs that led to study drug discontinuation by more than one participant during Treatment Period 1 were nausea (4/262 [1.5%]), constipation (5/262 [1.9%]), fatigue (3/262 [1.1%]), decreased appetite (3/262 [1.1%]), and somnolence (2/262 [0.8%]). TEAEs in Safety Population 2 during Treatment Period 2 occurred in 94/218 (43.1%) participants (Table 3). There were no TEAEs that

occurred in ≥5% of participants (Table 4). During Treatment Period 2, three (1.4%) participants experienced a TEAE leading to study drug discontinuation; one due to decreased appetite, one due to depression, and one due to vomiting and dizziness. An additional analysis evaluating TEAEs in Safety Population 2 during Treatment Period 1 found that the incidence of TEAEs was consistent between Safety Populations 1 and 2 during Treatment Period 1, so participant discontinuation during Treatment Period 1 does not appear to have led to the differences in the incidence of TEAEs between the treatment periods (Table S1).

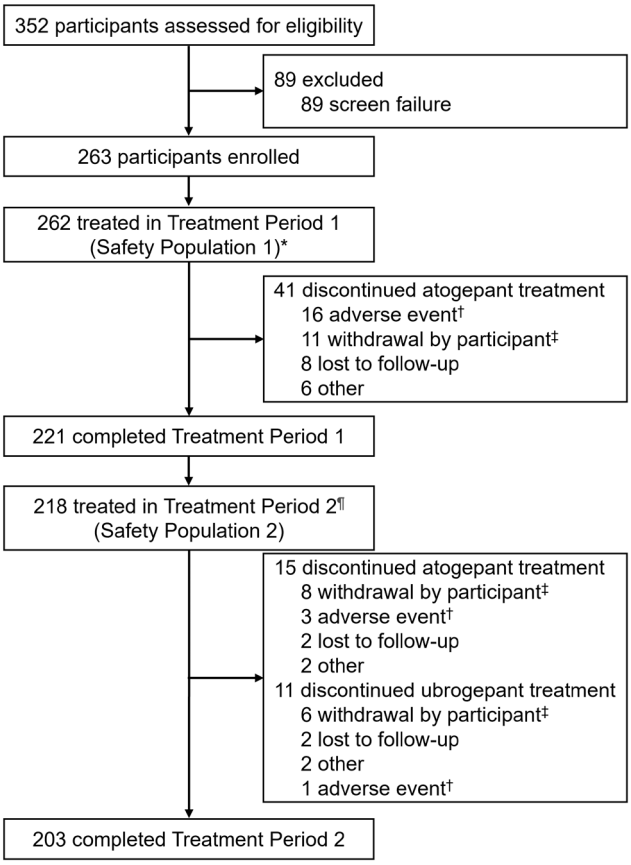

FIGURE 2 The TANDEM study disposition. The total completed for study includes all participants who completed all regular visits in the open-label atogepant and ubrogepant treatment period and the safety follow-up visit. *One participant withdrew consent before starting study intervention. †Number of adverse events that are deemed necessary to discontinue treatment as assessed by the investigator. ‡Adverse events that led to study drug discontinuation but not deemed necessary as assessed by the investigator. ¶Three participants had no treatment records in Treatment Period 2 for either atogepant or ubrogepant.

Analyses also evaluated TEAEs by the number of ubrogepant use days and dose subgroups. TEAEs occurred in 10/25 (40.0%) participants who never used ubrogepant and 83/188 (44.1%) participants who had any use of ubrogepant in Safety Population 2. Among participants with any use, those who had low use (1–3 days), moderate use (4–9 days), or high use (≥10 days) of ubrogepant, TEAEs occurred in 33/59 (55.9%), 30/80 (37.5%), and 20/49 (40.8%) participants in Safety Population 2, respectively. In participants who had low dose use (1-6 doses), moderate dose use (7-18 doses), and high dose use (≥19 doses) of ubrogepant, TEAEs occurred in 48/101 (47.5%), 25/66 (37.9%), and 10/21 (47.6%) participants in Safety Population 2, respectively. There were no clinically relevant increases in the incidence of TEAEs in the subgroups with higher average number of ubrogepant use days or number of ubrogepant doses taken during Treatment Period 2 (Table S2).

Clinical laboratory evaluation and vital signs

In Safety Populations 1 and 2, <3% of participants had potentially clinically significant values for sitting or standing systolic or diastolic blood pressure or pulse rate. A decrease of ≥7% of baseline weight was observed for 34/257 (13.2%) participants during one or more postbaseline visit during the whole 24-week treatment period. During Treatment Periods 1 and 2, 6.2% and 12.9% of participants had a weight decrease of ≥7% from baseline, respectively. An increase of ≥7% of baseline weight was observed for 9/257 (3.5%) participants during one or more postbaseline visit during the whole 24-week treatment period.

Three participants had postbaseline ALT or AST elevations ≥3 × ULN during Treatment Period 1. All three cases were considered

TABLE 2 Ubrogepant use days.

	Treatment Period 2 (open-label atogepant + ubrogepant treatment period)	
	Safety Population 2 (*N* = 218)	
	Ubrogepant use days for participants with ≥1 dose of ubrogepant	Ubrogepant optional second dose use days for participants with ≥1 dose of the optional second ubrogepant dose
n	188	113
Mean (SD)	6.6 (5.0)	3.5 (3.4)
Median (IQR)	5.0 (3.0, 10.0)	3.0 (1.0, 5.0)
Minimum, maximum	1, 24	1, 24
Subject-years[a]	3.4	1.1

Abbreviations: IQR, inter-quartile range; SD, standard deviation.

[a]Subject-years was calculated as the total treatment duration in days/365.25.

TABLE 3 Treatment-Emergent Adverse Events.

	Treatment Period 1 (Open-label atogepant treatment period)	Treatment Period 2 (Open-label atogepant + ubrogepant treatment period)	Whole treatment period (*N* = 262), *n* (%)
	Safety Population 1 (*N* = 262), *n* (%)	Safety Population 2 (*N* = 218), *n* (%)	
Treatment-emergent adverse events (TEAEs)	130 (49.6)	94 (43.1)	174 (66.4)
Treatment-related TEAEs atogepant	68 (26.0)	3 (1.4)	70 (26.7)
Treatment-related TEAEs ubrogepant	0	12 (5.5)	12 (4.6)
Serious TEAEs	1 (0.4)	1 (0.5)	2 (0.8)
Severe TEAEs	7 (2.7)	4 (1.8)	11 (4.2)
TEAEs leading to any study drug discontinuation[a]	23 (8.8)	3 (1.4)	26 (9.9)
TEAEs leading to atogepant discontinuation	23 (8.8)	2 (0.9)	25 (9.5)
TEAEs leading to ubrogepant discontinuation	0	3 (1.4)	3 (1.1)
All deaths	0	0	0

[a]Participants are only counted once for either atogepant or ubrogepant discontinuation.

TABLE 4 Most common treatment-emergent adverse events (≥5%).

Treatment-emergent adverse events	Treatment Period 1 (open-label atogepant treatment period)	Treatment Period 2 (open-label atogepant + ubrogepant treatment period)	Whole treatment period (*N* = 262), *n* (%)
	Safety Population 1 (*N* = 262), *n* (%)	Safety Population 2 (*N* = 218), *n* (%)	
COVID-19	22 (8.4)	7 (3.2)	29 (11.1)
Fatigue	17 (6.5)	3 (1.4)	20 (7.6)
Nausea	16 (6.1)	2 (0.9)	18 (6.9)
Decreased appetite	15 (5.7)	2 (0.9)	17 (6.5)
Constipation	14 (5.3)	2 (0.9)	16 (6.1)
Upper respiratory tract infection	6 (2.3)	8 (3.7)	14 (5.3)

to be unlikely related to atogepant by an external Hepatic Event Adjudication Committee. No participant had postbaseline ALT or AST elevations ≥3×ULN during Treatment Period 2. No participant met criteria for Hy's law. No hepatic safety issues related to the combination of atogepant and ubrogepant were identified and there were no discontinuations due to ALT or AST elevations during Treatment Period 2 (Table S3).

There were no other clinically relevant laboratory parameters or vital sign changes noted during the study.

DISCUSSION

Migraine is a complex neurological disease and personalized management may require the use of both acute and preventive treatments.[5,6] The "TANDEM" study is the first large study to evaluate the safety and tolerability of the concomitant use of two gepants, ubrogepant and atogepant, though lack of clinically meaningful pharmacokinetic interactions has been previously demonstrated.[22] The "TANDEM" study met the primary objective of demonstrating the safety and tolerability of the concomitant use of ubrogepant 100 mg PRN for the acute treatment of breakthrough migraine attacks in participants taking atogepant 60 mg QD for the preventive treatment of EM. The concomitant use of atogepant and ubrogepant was safe and well tolerated over the 12-week open-label combined treatment period, and the overall safety results were consistent with the known safety profiles of atogepant and ubrogepant. Overall, no increases in TEAEs were identified with the concomitant use of atogepant and ubrogepant.

A sensitivity analysis to evaluate the incidence of TEAEs in Safety Population 2 during Treatment Period 1 demonstrated that the incidence of TEAEs during Treatment Period 1 was consistent between Safety Populations 1 and 2. This suggests that differences in TEAEs between the two treatment periods cannot be attributed to the discontinuation of participants with AEs in Treatment Period 1. Moreover, during Treatment Period 2, there were no apparent

increases in the incidence of TEAEs with a higher number of ubrogepant use days or number of ubrogepant doses taken. These data demonstrate that ubrogepant had no notable impact on tolerability when used concomitantly with atogepant.

Treatment options for the management of migraine involving combined acute and preventive approaches should be tailored to the individual patient. Currently, there are a limited number of studies evaluating the concomitant use of gepants with CGRP monoclonal antibodies or the concomitant use of two gepants.[23] A case report of two patients taking rimegepant for acute treatment and erenumab for preventive treatment found no related AEs.[24] A multicenter, open-label, long-term safety study in 13 patients taking rimegepant for acute treatment and either erenumab, fremanezumab, or galcanezumab for preventive treatment found no safety issues with combination treatment.[25] A randomized phase 1b drug–drug interaction study demonstrated no safety concerns with the combination use of ubrogepant for acute treatment with erenumab or galcanezumab for preventive treatment.[26] Additionally, several observational studies suggest that using gepants as an acute treatment with monoclonal antibodies as preventive treatment is a safe treatment strategy.[27,28] Lastly, a phase 1b open-label, fixed-sequence study demonstrated that the concomitant use of atogepant and ubrogepant was safe and well tolerated in adults with a history of migraine.[22] These preliminary studies support that combination of CGRP-pathway targeted therapies, at the doses and dose-frequencies studied, is safe and well tolerated. The results reported in this large-scale trial are the first to show that the concomitant use of ubrogepant for acute treatment and atogepant for preventive treatment is safe and well tolerated.

There is a potential for related AEs when combining CGRP antagonists due to the physiologic effects of the CGRP neuropeptide. CGRP is a potent vasodilator and is involved in the regulation of blood pressure and maintenance of cardiovascular homeostasis.[29] Additionally, in the gastrointestinal tract, CGRP has been shown to accelerate intestinal transit via motor-stimulating and prosecretory activities.[30] In this study, few participants (<3%) had potentially clinically significant values for sitting or standing systolic or diastolic blood pressure or pulse rate. The rates of constipation observed in this study (6.1% across the whole treatment period) were consistent with rates seen in previous atogepant studies.[16–19] During Treatment Periods 1 and 2, 6.2% and 12.9% of participants had a decrease of ≥7% in baseline weight, respectively. The higher percentage of participants with a weight decrease of ≥7% from baseline during Treatment Period 2 compared to Treatment Period 1 is within the expected rate for up to 24 weeks of treatment with atogepant alone.[31,32] Collectively, 66.4% (174/262) of participants experienced a TEAE during the whole treatment period. Of these, the majority (93.7% [163/174]) were mild to moderate in severity. Across the whole treatment period, 9.9% of participants discontinued treatment due to TEAEs. TEAEs that led to study drug discontinuation by more than one participant included constipation, nausea, decreased appetite, fatigue, dizziness, migraine, somnolence, depression, and insomnia. The incidence, type, and severity of TEAEs in this trial were consistent with the safety profile in previous atogepant and ubrogepant clinical trials.[16–21] There were no new safety signals observed with the concomitant treatment of ubrogepant and atogepant.

Limitations of this study include a study population of mostly women and mostly White participants, and results may not be generalizable. This study excluded participants if they used opioids ≥4 days/month in the 3 months before Visit 1 or during the baseline period. Participants with significant cardiovascular disease were also excluded. Therefore, inferences cannot be made about these patient populations. This study did not include a placebo control and was not blinded due to the logistical complexities of a two-treatment period, combination study of a daily preventive treatment with an as needed acute treatment including a double-blind, placebo-controlled design. The number of participants who used ubrogepant during Treatment Period 2 was small; however, within Safety Population 2, no new safety signals were identified. Efficacy outcomes were exploratory in this open-label study and may be reported in a future publication. Given the short duration of the open-label atogepant and ubrogepant treatment period (12 weeks), long-term studies are needed to evaluate the sustained safety and tolerability of the concomitant use of ubrogepant and atogepant.

CONCLUSION

In summary, the concomitant use of ubrogepant for the acute treatment of breakthrough migraine attacks and atogepant for the preventive treatment of EM in this study was safe and well tolerated. No clinically relevant increases in the incidence, type, or severity of TEAEs were identified for the concomitant use of atogepant and ubrogepant. The overall safety results were consistent with the known safety profiles of atogepant and ubrogepant alone.

AUTHOR CONTRIBUTIONS

Jessica Ailani: Conceptualization; investigation; visualization; writing – review and editing. **Richard B. Lipton:** Conceptualization; visualization; writing – review and editing. **Andrew M. Blumenfeld:** Conceptualization; visualization; writing – review and editing. **Laszlo Mechtler:** Conceptualization; investigation; visualization; writing – review and editing. **Brad C. Klein:** Conceptualization; investigation; visualization; writing – review and editing. **Molly Yizeng He:** Conceptualization; formal analysis; methodology; validation; visualization; writing – review and editing. **Jonathan H. Smith:** Conceptualization; project administration; visualization; writing – review and editing. **Joel M. Trugman:** Conceptualization; supervision; visualization; writing – review and editing. **Rosa de Abreu Ferreira:** Conceptualization; project administration; visualization; writing – review and editing. **Elimor Brand-Schieber:** Conceptualization; methodology; project administration; visualization; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (e.g., protocols, clinical study reports, or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent, scientific research, and will be provided following review and approval of a research proposal, Statistical Analysis Plan, and execution of a Data Sharing Agreement. Data requests can be submitted at any time after approval in the United States and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://vivli.org/ourmember/abbvie/ then select "Home".

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ORCID

Molly Yizeng He https://orcid.org/0009-0008-6353-8437

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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