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Effect of Atogepant for Preventive Migraine Treatment on Patient-Reported Outcomes in the Randomized, Double-blind, Phase 3 ADVANCE Trial

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Abstract

Background and Objectives

The oral calcitonin gene–related peptide receptor antagonist atogepant is indicated for the preventive treatment of episodic migraine. We evaluated changes in patient-reported outcomes with atogepant in adults with migraine.

Methods

In this phase 3, 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial (ADVANCE), adults with 4–14 migraine days per month received atogepant (10, 30, or 60 mg) once daily or placebo. Secondary endpoints included changes from baseline in Migraine-Specific Quality-of-Life Questionnaire (MSQ) version 2.1 Role Function–Restrictive (RFR) domain at week 12 and mean monthly Activity Impairment in Migraine–Diary (AIM-D) Performance of Daily Activities (PDA) and Physical Impairment (PI) domains across the 12-week treatment period. Exploratory endpoints included change in MSQ Role Function–Preventive (RFP) and Emotional Function (EF) domains; AIM-D total scores; and change in Headache Impact Test (HIT)–6 scores.

Results

Of 910 participants randomized, 873 comprised the modified intent-to-treat population (atogepant: 10 mg [n = 214]; 30 mg [n = 223]; and 60 mg [n = 222]; placebo [n = 214]). All atogepant groups demonstrated significantly greater improvements vs placebo in MSQ RFR that exceeded minimum clinically meaningful between-group difference (3.2 points) at week 12 (least-square mean difference [LSMD] vs placebo: 10 mg [9.9]; 30 mg [10.1]; 60 mg [10.8]; all $p < 0.0001$). LSMDs in monthly AIM-D PDA and PI scores across the 12-week treatment period improved significantly for the atogepant 30 (PDA: −2.54; $p = 0.0003$; PI: −1.99; and $p = 0.0011$) and 60 mg groups (PDA: −3.32; $p < 0.0001$; PI: −2.46; $p < 0.0001$), but not for the 10 mg group (PDA: −1.19; $p = 0.086$; PI: −1.08; $p = 0.074$). In exploratory analyses, atogepant 30 and 60 mg were associated with nominal improvements in MSQ RFP and EF domains, other AIM-D outcomes, and HIT-6 scores at the earliest time point (week 4) and throughout the 12-week treatment period. Results varied for atogepant 10 mg.

Discussion

Atogepant 30 and 60 mg produced significant improvements in key patient-reported outcomes including MSQ-RFR scores and both AIM-D domains. Nominal improvements also occurred for other MSQ domains and HIT-6, reinforcing the beneficial effects of atogepant as a new treatment for migraine prevention.

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Glossary

AIM-D = Activity Impairment in Migraine–Diary; **CGRP** = calcitonin gene–related peptide; **CM** = chronic migraine; **eDiary** = electronic diary; **EF** = Emotional Function; **EM** = episodic migraine; **eTablet** = electronic tablet; **HA** = headache (day); **HIT-6** = Headache Impact Test–6; **FDA** = Food and Drug Administration; **HRQoL** = health-related quality of life; ***ICHD-3*** = *International Classification of Headache Disorders, third edition*; **LSMD** = least-square mean difference; **mAb** = monoclonal antibody; **MID** = minimally important difference; **mITT** = modified intent-to-treat; **MHD** = monthly headache day; **MMD** = monthly migraine days; **MMRM** = mixed models for repeated measure; **MSQ v2.1** = Migraine-Specific Quality-of-Life Questionnaire version 2.1; **nHA** = nonheadache (day); **PDA** = performance of daily activities; **PI** = physical impairment; **PRO** = patient-reported outcome; **QD** = once daily; **RFP** = Role Function–Preventive; **RFR** = Role Function–Restrictive.

Trial Registration Information

ClinicalTrials.gov NCT03777059. Submitted: December 13, 2018; First patient enrolled: December 14, 2018. clinicaltrials.gov/ct2/show/NCT03777059.

Classification of Evidence

This study provides Class II evidence that daily atogepant is associated with improvements in health-related quality-of-life measures in patients with 4–14 migraine days per month.

Migraine, a highly prevalent neurologic disease defined by recurrent attacks of headache pain and associated symptoms (e.g., aura, photophobia, nausea, and allodynia), is a leading cause of disease burden.[1-5] Migraine reduces the performance of daily activities, participation in social/leisure activities, physical/emotional functioning, and health-related quality of life (HRQoL), both during and between attacks.[6-11] Preventive migraine treatments aim to reduce the frequency, intensity, and duration of attacks and should reduce activity limitations and improve HRQoL.[12,13] Assessing the effect of migraine on HRQoL using patient-reported outcome (PRO) measures is important when evaluating preventive treatments.[12-15]

Atogepant is a recently approved oral, small-molecule, calcitonin gene–related peptide (CGRP) receptor antagonist (gepant)[16,17] that demonstrated efficacy, safety, and tolerability for preventive treatment of migraine in phase 2/3[16] and phase 3 (ADVANCE) trials in people with 4–14 monthly migraine days (MMDs).[18] In the ADVANCE trial, 10, 30, and 60 mg of atogepant once daily significantly reduced MMDs across the 12-week treatment period (primary endpoint) compared with placebo. In this study, we emphasized results from PROs that were selected as alpha-controlled secondary endpoints in the ADVANCE trial, in accordance with the US Food and Drug Administration (FDA) regulatory guidance.[19] These endpoints included changes from baseline in Migraine-Specific Quality-of-Life Questionnaire version 2.1 (MSQ v2.1) Role Function–Restrictive (RFR) domain score at week 12 and mean monthly Activity Impairment in Migraine–Diary (AIM-D) Performance of Daily Activities (PDA) and Physical Impairment (PI) domain scores across the 12-week treatment period. We also presented results from prespecified exploratory analyses of the MSQ v2.1 RFR and AIM-D PDA and PI domains at other time points and other MSQ v2.1 domains, total AIM-D score, and the Headache Impact Test (HIT)–6 score. The primary research question was the effect of daily atogepant on health-related qualify-of-life measures among patients with 4–14 migraine days per month.

Methods

Trial Design

Detailed methods of the ADVANCE trial have been published.[18] This multicenter, randomized, double-blind, placebo-controlled, parallel-group phase 3 trial was conducted from December 14, 2018, to June 19, 2020, at 136 sites in the United States. Participants were randomized to receive placebo and atogepant (10, 30, or 60 mg) once daily (QD) at a 1:1:1:1 ratio. Randomization was stratified by previous exposure to a migraine prevention medication with proven efficacy. The randomization sequence was generated by an automated interactive web response system. Blinding was maintained by providing treatments in identical blister cards and masking treatment assignment from participants and site and sponsor personnel. The study included a 4-week baseline period, 12-week double-blind treatment period, and 4-week safety follow-up period. Participants were instructed to take study treatment once daily, orally, at approximately the same time each day.

Participants

Eligible participants were adults aged 18–80 years with 4–14 MMDs in the 3 months before screening and 4–14 migraine days recorded in an electronic diary (eDiary) during the 28-day baseline run-in period. Additional inclusion criteria required ≥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] and migraine onset before 50 years of age. Participants were excluded if they had a

current diagnosis of chronic migraine (CM), new persistent daily headache, trigeminal autonomic cephalalgia (e.g., cluster headache), or painful cranial neuropathy as defined by *ICHD-3*[2]; ≥15 monthly headache days (MHDs) on average across 3 months before visit 1 or during the 28-day baseline period; a history of inadequate response to >4 medications (2 with different mechanisms of action) prescribed for preventive migraine treatment; use of opioids >2 days per month, triptans or ergots ≥10 days per month, or simple analgesics (e.g., aspirin, nonsteroidal anti-inflammatory drugs, and acetaminophen) ≥15 days per month during the 3 months before screening or baseline period; or the use of barbiturates >2 days per month in the 3 months before screening or any use within 30 days of screening.

Outcome Measures

Migraine-Specific Quality-of-Life Questionnaire Version 2.1

Participants completed the MSQ v2.1 through electronic tablet (eTablet) at study sites at baseline (treatment day 1) and at weeks 4, 8, and 12. The MSQ v2.1, a 14-item questionnaire designed to measure migraine-specific HRQoL over the past 4 weeks, has 3 domains.[20,21] The 7-item MSQ v2.1 RFR domain measures the degree to which migraine limits the performance of daily social and work-related activities. The 4-item MSQ v2.1 Role Function–Preventive (RFP) domain measures the degree to which migraine interrupts or prevents the performance of daily social and work-related activities. The 3-item Emotional Function (EF) domain assesses emotions associated with migraine. All MSQ v2.1 items use a 6-point ordinal scale with response options ranging from "none of the time" to "all of the time." Raw domain scores were computed as a sum of item responses and rescaled to a 0–100 scale, based on the developer's scoring scheme, where higher scores indicate better daily functioning (i.e., lesser effect of migraine) and positive changes in scores reflect improvement in quality of life. The MSQ v2.1 has been shown to be reliable, valid, and sensitive to changes in migraine with treatment.[20-22] The between-group minimally important difference (MID) for the MSQ-RFR is 3.2 points, MSQ-RFP is 4.6 points, and MSQ-EF is 7.5 points.[23] The meaningful within-group change for responder analyses is 5.0 points for the MSQ-RFR, 5.0–7.9 points for MSQ-RFP, and 8.0–10.6 points for MSQ-EF.[18,23] Change from baseline in MSQ-v2.1 RFR domain score at week 12 was a prespecified alpha-controlled secondary efficacy endpoint. Changes from baseline in the MSQ-v2.1 RFR domain score at weeks 4 and 8 and MSQ-v2.1 RFP and -EF domain scores at weeks 4, 8, and 12 were prespecified exploratory endpoints.

Per COVID-19–related protocol amendments, the MSQ v2.1 and HIT-6 at visit 7/week 12 were collected remotely by eTablet starting on 4/20/2020, according to the remote visit procedure. A total of 10 participants (1.1%) missed ≥1 PRO assessment at week 12 because of COVID-19.

Activity Impairment in Migraine–Diary

Participants completed the AIM-D in eDiaries once daily throughout the entire study, including during the 4-week baseline period. The AIM-D is a novel, rigorously developed, and psychometrically sound 11-item daily diary measure that assesses the effect of migraine.[24] The AIM-D has 2 domains: PDA (7 items) and PI (4 items). Validation studies for the AIM-D have been published.[24] Participants were asked to rate the level of difficulty experienced in the past 24 hours with PDA (i.e., difficulty with household chores, errands, leisure activities at home, leisure or social activities outside the home, strenuous physical activities, concentrating, and thinking clearly) and PI (i.e., difficulty walking, moving body, bending forward, and moving head) using a 6-point ordinal response scale ranging from "not difficult at all" to "I could not do it at all." Three items also include response options of "I did not…" (e.g., "I did not have errands planned."). The AIM-D was developed with similar questions and content for headache (HA) day and nonheadache (nHA) day items; the only difference is the instruction provided to the patient with "during your headache" indicated for the HA day version.

For both HA and nHA days, the daily AIM-D PDA domain score required availability of ≥4 item scores per day; otherwise, the domain score was considered missing. A raw daily AIM-D PDA score was calculated based on summation of scores for individual items 1–5, 10, and 11. Each of the 7 items had scores of 0–5, so that raw domain scores were 0–35. If the response category "I did not have errands, leisure or social, strenuous activities planned" (items 2, 4, and 5) was selected, the response was considered missing. The raw daily AIM-D PDA score was the sum of nonmissing item scores divided by the number of nonmissing items, given >50% of items have responses, and then multiplied by 7. Raw daily scores were transformed to a 0–100 daily domain score by multiplying by 100 and dividing by the highest possible raw score (35). Higher scores indicate greater difficulty in performing daily activities. A similar approach was used for computing the raw daily score for the AIM-D PI domain and required that ≥2 item scores were available; if not, the domain score was considered missing. The raw daily AIM-D PI score (range: 0–20) was the sum of scores for individual items 6–9.

For both HA and nHA days, the daily total raw score (range: 0–55) was the sum of scores for individual items 1–11, if ≥6 items had nonmissing responses. When the response category "I did not have errands, leisure or social, strenuous activities planned" (items 2, 4, and 5) was selected, the response was considered missing. The daily total raw score was transformed to a 0–100 scale by multiplying by 100 and dividing by the highest possible raw score (55), with higher scores indicating worse activity impairment. Monthly AIM-D PDA and PI domain and total scores were the average of daily scores, calculated by summing nonmissing daily scores (HA and nHA days combined) and dividing by the number of nonmissing daily scores, provided there were ≥14 nonmissing daily scores (HA and nHA days combined) in the corresponding 28-day period; otherwise, the monthly total score was set to missing.

Changes from baseline in the mean monthly AIM-D PDA domain score and the mean monthly PI domain score across the 12-week treatment period were prespecified alpha-controlled secondary efficacy endpoints and have been previously

reported.[18] Changes from baseline in monthly PDA and PI domain scores of the AIM-D at weeks 1–4, 5–8, and 9–12 and in monthly AIM-D total score at weeks 1–4, 5–8, 9–12 and average across the 12-week treatment period were prespecified exploratory efficacy endpoints.

Headache Impact Test–6

Participants completed the HIT-6 on an eTablet at study sites at baseline (day 1 of treatment) and at weeks 4, 8, and 12. The HIT-6 is a 6-item assessment used to measure the effect of headaches on normal daily life and ability to function on the job, at school, at home, and in social situations in the past 4 weeks.[25,26] Responses are based on frequency using a 5-point verbal response scale ranging from "never" to "always." The HIT-6 total score is the sum of all responses, each of which is assigned a score ranging from 6 points (never) to 13 points (always). HIT-6 total scores range from 36–78 and are interpreted as little or no effect (score ≤49), some effect (50–55), substantial effect (56–59), and severe effect (60–78) due to headache, with higher scores indicating greater effect and lower scores indicating improvement.[27] The HIT-6 has been validated in people with episodic migraine (EM)[28] and in those with CM.[28-30] The between-group MID for HIT-6 in people with EM is −1.5 points,[31] and the within-patient MID for responder analyses is a score reduction of 5.0 points.[28,31-33] Changes from baseline in HIT-6 total score at weeks 4, 8, and 12 and percentages of participants with ≥5-point reduction in HIT-6 (responders) at weeks 4, 8, and 12 were prespecified exploratory endpoints.

Statistical Analysis

All analyses were conducted on participants in the modified intent-to-treat (mITT) population with available data for each outcome measure and time point. The mITT population included all participants who received ≥1 dose of study drug, who had an evaluable baseline period of eDiary data, and who had ≥1 evaluable postbaseline 4-week period of eDiary data during the double-blind treatment period. Descriptive comparisons between the atogepant and placebo groups were reported as differences in change from baseline and corresponding odds ratios. Secondary endpoints of change from baseline in MSQ v2.1 RFR domain score at week 12 and changes from baseline in mean monthly AIM-D domain scores across the 12-week treatment period were analyzed using mixed models for repeated measures (MMRMs) that included the treatment group, visit, previous exposure to a migraine prevention medication (yes/no), and treatment group by visit as categorical fixed effects and baseline score and baseline-by-visit interaction as covariates. The overall type I error rate for multiple comparisons across the 3 atogepant doses and the secondary efficacy endpoints was controlled at the 0.05 level using a graphical approach with weighted-Bonferroni test procedure.[34] Within each dose, testing started from the primary endpoint, followed by testing of the secondary endpoints in a prespecified order.[18]

Continuous exploratory endpoints (i.e., changes from baseline in MSQ v2.1 domain scores, mean monthly AIM-D domain and total scores, and HIT-6 total scores) were analyzed using MMRM models that included treatment group, visit, previous exposure to a preventive migraine medication (yes/no), and treatment group by visit as categorical fixed effects; and baseline score and baseline-by-visit interaction as covariates. Binary exploratory endpoints (i.e., percentage of participants with ≥5-point improvement [decrease] from baseline in HIT-6 total score) were analyzed using a generalized linear mixed model that included treatment group, visit, previous exposure (yes/no) to a preventive migraine medication, and treatment group–by-visit interaction as categorical fixed effects; baseline value and baseline-by-visit interaction as covariates; and participants as random effects. Post hoc exploratory analyses of the proportions of participants reaching the within-group MID for each MSQ v2.1 domain used a similar generalized linear mixed model. *p* Values from the tests between each atogepant dose group and the placebo group are reported. Except for secondary efficacy endpoints, all analyses were performed at the nominal significance level, without adjusting for multiplicity.

Standard Protocol Approvals, Registrations, and Participant Consents

All participating sites obtained approval from a local or central Institutional Review Board. The trial was conducted according to Good Clinical Practice and the Declaration of Helsinki. Participants provided written informed consent before enrollment. The study is registered with ClinicalTrials.gov (NCT03777059). The study protocol and statistical analysis plan have been published.[18]

Data Availability

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 and Statistical Analysis Plan and execution of a Data Sharing Agreement. Data requests can be submitted at any time, and 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: abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

Results

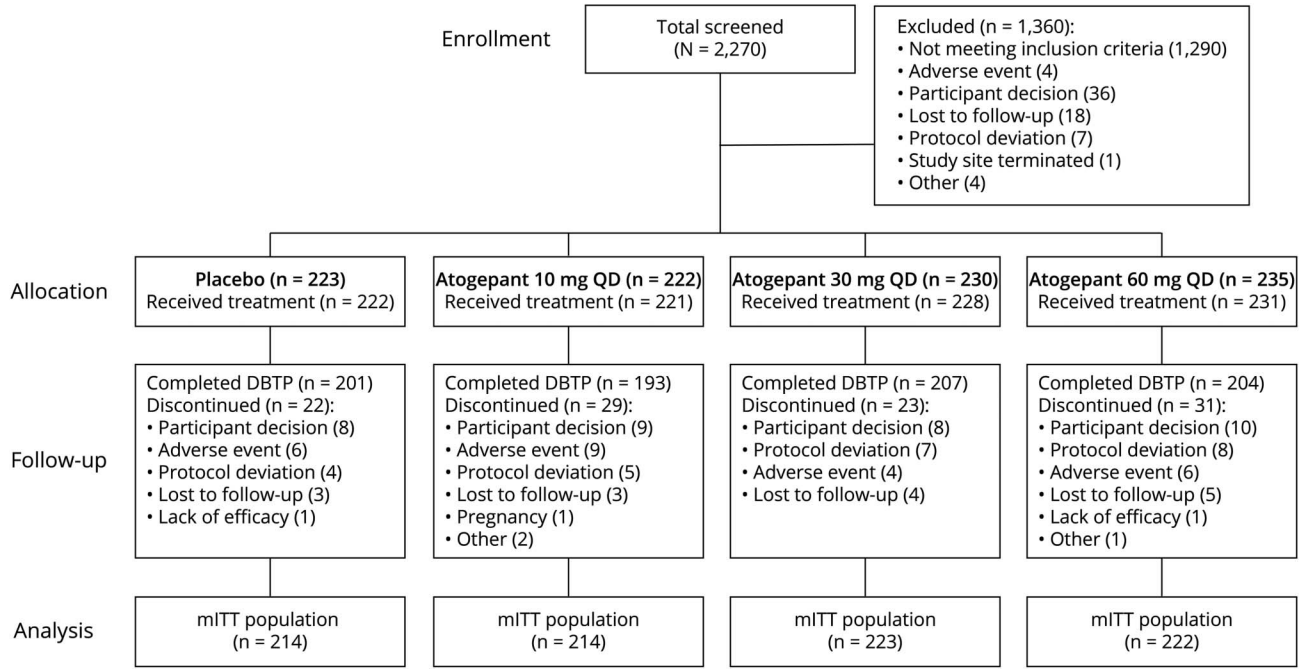
Participants and Baseline Characteristics

Of 910 participants randomized, 902 took ≥1 dose of trial treatment (safety population), and 873 were included in the mITT population (placebo, n = 214; atogepant [10 mg], n = 214; atogepant [30 mg], n = 223; and atogepant [60 mg], n = 222; Figure 1). Demographic and baseline characteristics are summarized in Table 1. In the mITT population, the mean (SD) age was 41.7 (12.3) years. Most participants were female (89%) and White (84%). Participants had a mean (SD) of 7.6 (2.4) MMDs and 8.7 (2.6) MHDs during the baseline period.

Migraine-Specific Quality-of-Life Questionnaire Version 2.1

MSQ v2.1 domain scores at baseline were similar among treatment groups and were reflective of substantial to

Figure 1 Participant Disposition



DBTP = double-blind treatment period; mITT = modified intent-to-treat; QD = once daily.

moderate effect on daily social and work-related activities with a mean MSQ-RFR score of 46, mean MSQ-RFP score of 61, and substantial emotional effect of migraine with a mean MSQ-EF score of 53 (Table 1). As previously reported,[18] the change from baseline in the MSQ-v2.1 RFR domain score at week 12 (secondary endpoint) demonstrated statistically significant and clinically meaningful (between-group difference exceeded MID of 3.2 points) improvements in the effect of migraine on daily social and work-related activities in all atogepant groups compared with placebo ($p < 0.0001$ for all comparisons after multiplicity adjustment; Figure 2).

Analysis of exploratory MSQ v2.1 endpoints demonstrated nominally greater ($p \leq 0.02$) improvements in all atogepant groups compared with placebo in MSQ-v2.1 RFR, MSQ-v2.1-RFP, and MSQ-v2.1-EF scores on the least-square mean difference (LSMD) scores from the earliest time point assessed (week 4) and throughout the 12-week double-blind treatment period (Figure 2). The LSMD between each atogepant group vs placebo in MSQ-v2.1 RFR, MSQ-v2.1-RFP, and MSQ-v2.1-EF scores achieved the between-group MID at all doses and time points evaluated, except for the EF domain in the 10 mg group at week 4 (Figure 2). Nominally greater proportions of participants in the atogepant groups than placebo had improvements in MSQ v2.1 scores that exceeded the established within-group MID (reflective of clinically meaningful improvement) for all 3 domains of the MSQ v2.1 at weeks 4, 8, and 12 ($p \leq 0.04$), except for the RFP and EF domains at week 4 in the 10 mg group (Table 2).

Activity Impairment in Migraine–Diary

At baseline, the mean AIM-D domain scores were similar among groups and reflected modest impairment in PDA (mean scores: 15–17) and PI (mean scores: 11–13; Table 1). As previously reported,[18] changes from baseline in mean monthly AIM-D PDA and PI scores across the entire 12-week double-blind treatment period (secondary endpoints) showed statistically significant improvement with atogepant (30 and 60 mg) compared with placebo ($p \leq 0.002$ after multiplicity adjustment); the 10 mg group did not show statistically significant improvement compared with placebo (PDA, $p = 0.086$; PI, $p = 0.074$; Figure 3).

Analysis of exploratory AIM-D endpoints demonstrated nominally greater improvements in mean monthly AIM-D PDA and PI domain scores and total scores vs placebo in all atogepant groups over the first month of treatment (weeks 1–4, $p \leq 0.012$) and for the 30 and 60 mg atogepant groups at weeks 5–8 ($p \leq 0.040$) and 9–12 ($p \leq 0.009$; Figure 3). Improvements in AIM-D scores increased with atogepant dose, with the largest improvements in AIM-D PDA, PI, and total scores consistently observed with 60 mg of atogepant at each time point (Figure 3).

Headache Impact Test–6

The mean baseline HIT-6 total scores were similar among treatment groups and reflective of a severe effect of headaches (HIT-6 total score >60; Table 1). All atogepant groups had nominal improvement ($p \leq 0.006$) vs placebo in HIT-6 total

Table 1 Demographics and Baseline Characteristics (Modified Intent-to-Treat Population)

		Atogepant			
	Placebo (n = 214)	10 mg QD (n = 214)	30 mg QD (n = 223)	60 mg QD (n = 222)	Total (N = 873)
Age, y	40.3 (12.9)	41.5 (12.0)	42.2 (11.7)	42.8 (12.3)	41.7 (12.3)
Female, n (%)	190 (88.8)	193 (90.2)	199 (89.2)	191 (86.0)	773 (88.5)
Race, n (%)					
White	188 (87.9)	176 (82.2)	181 (81.2)	184 (82.9)	729 (83.5)
Black or African American	22 (10.3)	32 (15.0)	37 (16.6)	27 (12.2)	118 (13.5)
Asian	2 (0.9)	2 (0.9)	1 (0.4)	7 (3.2)	12 (1.4)
Other or unknown	2 (0.9)	4 (1.9)	4 (1.8)	4 (1.8)	14 (1.6)
Ethnicity, non-Hispanic, n (%)	192 (89.7)	193 (90.2)	205 (91.9)	209 (94.1)	799 (91.5)
MMDs	7.5 (2.4)	7.5 (2.5)	7.9 (2.3)	7.8 (2.3)	7.6 (2.4)
MHDs	8.4 (2.6)	8.4 (2.8)	8.8 (2.6)	9.0 (2.6)	8.7 (2.6)
Monthly acute medication use days	6.5 (3.2)	6.6 (3.0)	6.7 (3.0)	6.9 (3.2)	6.7 (3.1)
MSQ v2.1	n = 213	n = 212	n = 222	n = 222	n = 869
Role Function–Restrictive	46.8 (19.7)	44.9 (21.4)	44.0 (19.6)	46.8 (20.4)	45.6 (20.3)
Role Function–Preventive	63.0 (21.9)	60.9 (23.4)	57.6 (24.0)	61.1 (24.2)	60.6 (23.4)
Emotional Function	54.0 (26.1)	53.5 (28.3)	49.9 (27.0)	53.3 (29.4)	52.6 (27.8)
AIM-D	n = 188	n = 191	n = 188	n = 192	n = 759
Performance of Daily Activities	15.2 (8.3)	15.5 (8.9)	16.9 (8.0)	15.9 (8.3)	15.9 (8.4)
Physical Impairment	11.2 (8.1)	11.7 (8.5)	13.0 (8.0)	11.6 (7.9)	11.9 (8.1)
Total score	13.6 (7.9)	14.0 (8.4)	15.4 (7.7)	14.2 (7.9)	14.3 (8.0)
HIT-6 total score	n = 213 64.5 (4.6)	n = 212 64.2 (5.3)	n = 223 64.3 (4.7)	n = 222 63.8 (5.5)	n = 870 64.2 (5.0)

Abbreviations: AIM-D = Activity Impairment in Migraine–Diary; HIT-6 = Headache Impact Test–6; MHD = monthly headache day; MMD = monthly migraine day; MSQ v2.1 = Migraine-Specific Quality-of-Life Questionnaire version 2.1; QD = once daily.
Data represent mean (SD) unless otherwise indicated.

score at the earliest time point assessed (week 4) and throughout the double-blind treatment period (exploratory endpoints; Figure 4A). The LSMD in change from baseline for atogepant vs placebo exceeded the between-group MID (1.5 points) in all atogepant groups at weeks 4, 8, and 12. Greater proportions of atogepant-treated participants vs placebo-treated participants were HIT-6 responders (≥5-point improvement from baseline) with all atogepant doses at all time points ($p \leq 0.03$), with the exception of 30 mg of atogepant at week 4 ($p = 0.07$; Figure 4B).

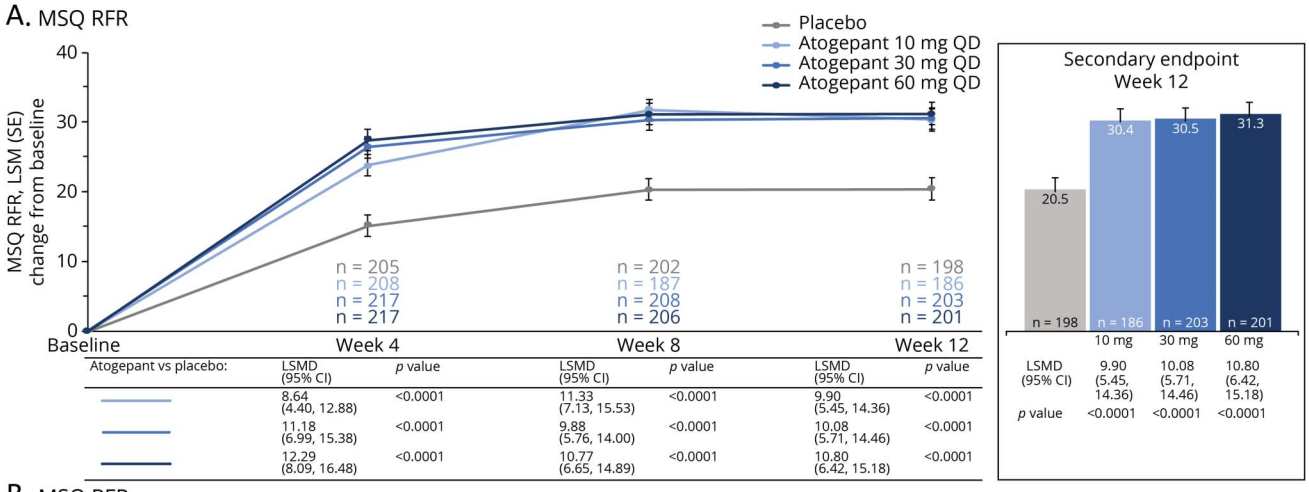
Classification of Evidence

This study provides Class II evidence that daily atogepant is associated with improvements in health-related quality-of-life measures in patients with 4–14 migraine days per month. Further, it was associated with HRQoL improvement in the RFR domain of the MSQ v2.1 at week 12, a prespecified alpha-controlled secondary efficacy endpoint, for all 3 doses. In addition, atogepant is associated with reductions (i.e., improvements) in other alpha-controlled secondary efficacy endpoints (e.g., AIM-D PI and PDA across 12 weeks of treatment) for the 30 and 60 mg doses. Although atogepant (10 mg) produced reductions on these outcomes, the differences were not uniformly significant.

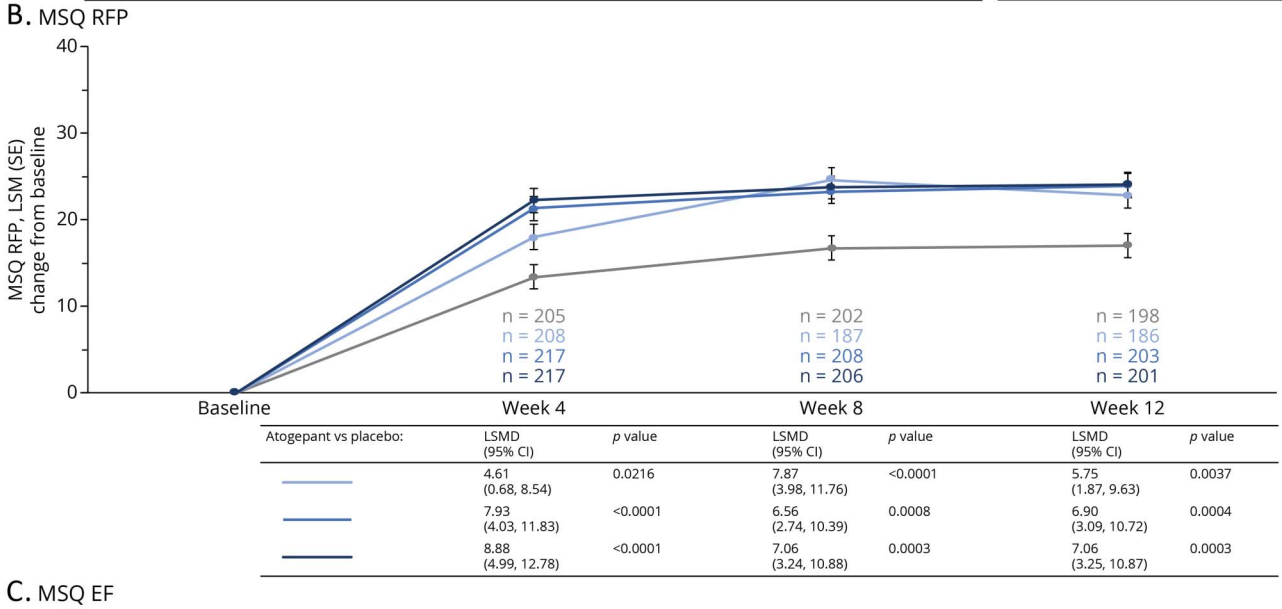
Discussion

Atogepant is a daily oral CGRP receptor antagonist for the preventive treatment of migraine. The ADVANCE trial compared 3 doses of atogepant with placebo for the preventive treatment of migraine in participants with 4–14 MMDs. A previous publication reported significant reductions in MMDs with corresponding significant increases in 50% responder rates, low discontinuation rates, and evidence of safety and tolerability for all 3 doses of atogepant vs placebo.[18] In addition to decreasing MMDs, reducing the effect of migraine on functioning in daily activities and improving overall HRQoL are important

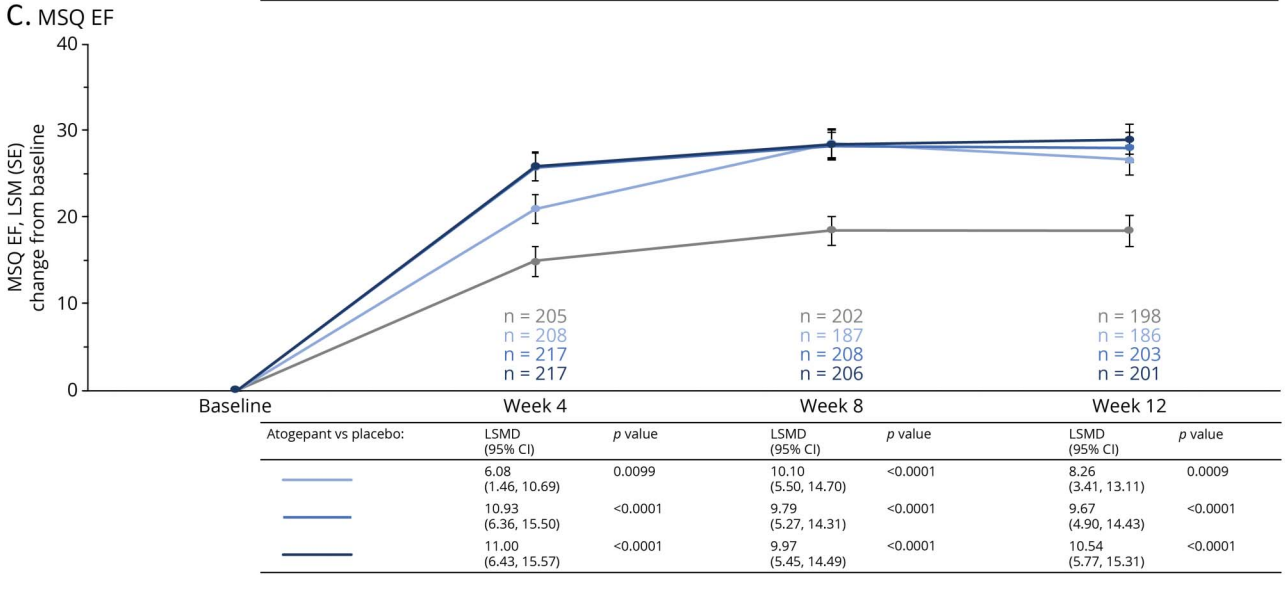
Figure 2 Change in MSQ v2.1 Scores



Atogepant vs placebo:	LSMD (95% CI)	p value	LSMD (95% CI)	p value	LSMD (95% CI)	p value
	8.64 (4.40, 12.88)	<0.0001	11.33 (7.13, 15.53)	<0.0001	9.90 (5.45, 14.36)	<0.0001
	11.18 (6.99, 15.38)	<0.0001	9.88 (5.76, 14.00)	<0.0001	10.08 (5.71, 14.46)	<0.0001
	12.29 (8.09, 16.48)	<0.0001	10.77 (6.65, 14.89)	<0.0001	10.80 (6.42, 15.18)	<0.0001



Atogepant vs placebo:	LSMD (95% CI)	p value	LSMD (95% CI)	p value	LSMD (95% CI)	p value
	4.61 (0.68, 8.54)	0.0216	7.87 (3.98, 11.76)	<0.0001	5.75 (1.87, 9.63)	0.0037
	7.93 (4.03, 11.83)	<0.0001	6.56 (2.74, 10.39)	0.0008	6.90 (3.09, 10.72)	0.0004
	8.88 (4.99, 12.78)	<0.0001	7.06 (3.24, 10.88)	0.0003	7.06 (3.25, 10.87)	0.0003



Atogepant vs placebo:	LSMD (95% CI)	p value	LSMD (95% CI)	p value	LSMD (95% CI)	p value
	6.08 (1.46, 10.69)	0.0099	10.10 (5.50, 14.70)	<0.0001	8.26 (3.41, 13.11)	0.0009
	10.93 (6.36, 15.50)	<0.0001	9.79 (5.27, 14.31)	<0.0001	9.67 (4.90, 14.43)	<0.0001
	11.00 (6.43, 15.57)	<0.0001	9.97 (5.45, 14.49)	<0.0001	10.54 (5.77, 15.31)	<0.0001

LS mean changes from baseline in MSQ v2.1 (A) RFR, (B) RFP, and (C) EF scores at weeks 4, 8, and 12. The LSMD for each atogepant group vs placebo was at least the between-group minimally important difference for each domain (MSQ-RFR: 3.2; MSQ-RFP: 4.6, and MSQ-EF: 7.5)[23] at each time point evaluated, with the exception of the EF domain at week 4 in the 10 mg group. Data for change from baseline MSQ v2.1 RFR at week 12 have been previously published.[18] EF = Emotional Function; LSM = least-square mean; LSMD = least-square mean difference; MSQ v2.1 = Migraine-Specific Quality-of-Life Questionnaire version 2.1; QD = once daily; RFP = Role Function-Preventive; RFR = Role Function-Restrictive.

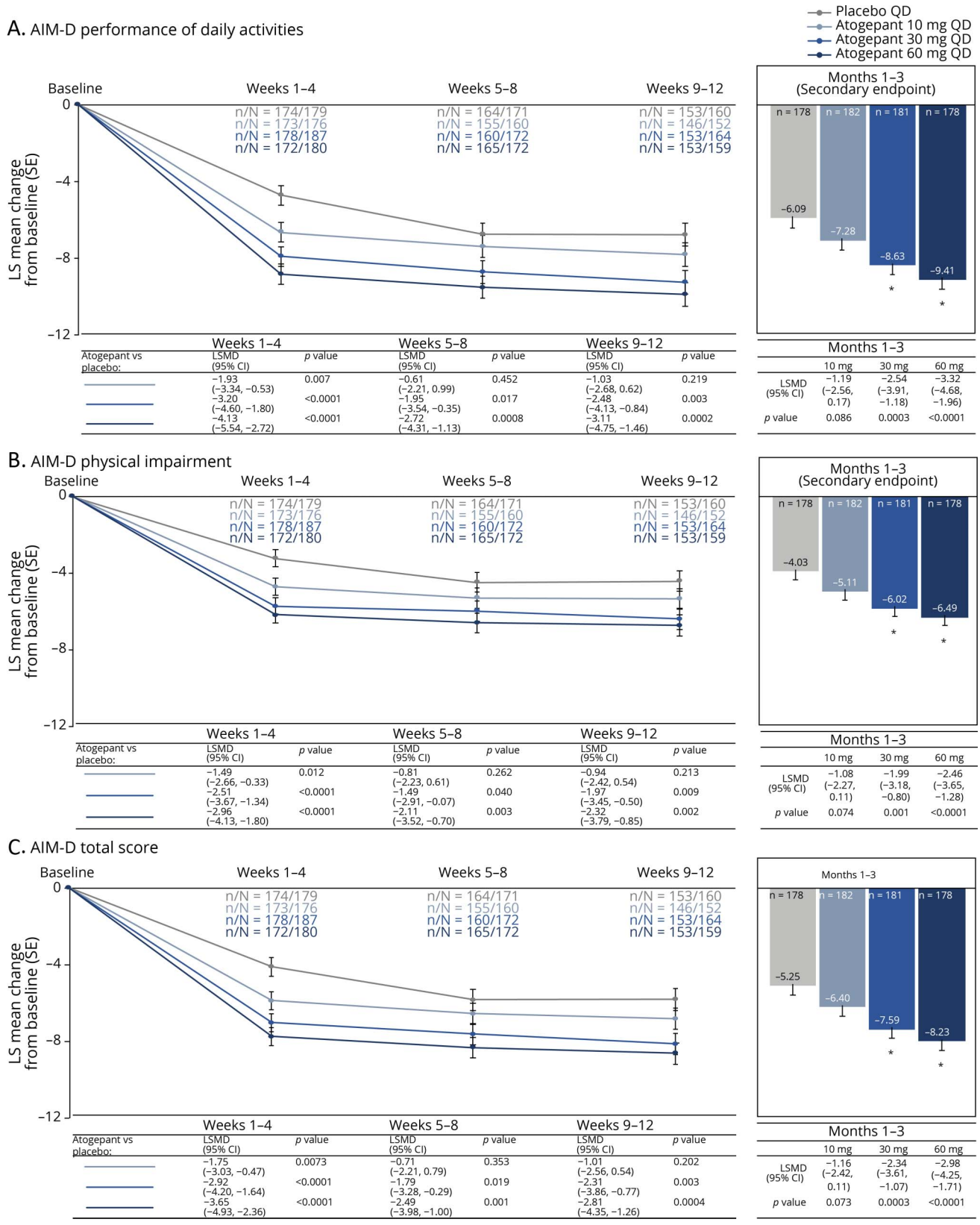
Table 2 Migraine-Specific Quality-of-Life Questionnaire Version 2.1 Responder Rates

	Placebo (N = 214)	Atogepant 10 mg QD (N = 214)	Atogepant 30 mg QD (N = 223)	Atogepant 60 mg QD (N = 222)
Role Function–Restrictive domain (≥5-point improvement from baseline)				
Week 4, n/N (%)[a]	135/205 (65.9)	159/208 (76.4)	177/217 (81.6)	179/217 (82.5)
Odds ratio vs placebo (95% CI)[b]		1.63 (1.03, 2.59)	2.22 (1.38, 3.57)	2.54 (1.57, 4.11)
***p* Value**		0.036	0.001	<0.001
Week 8, n/N (%)[a]	146/202 (72.3)	162/187 (86.6)	179/208 (86.1)	178/206 (86.4)
Odds ratio vs placebo (95% CI)[b]		2.44 (1.43, 4.18)[a]	2.36 (1.40, 3.96)	2.43 (1.45, 4.07)
***p* Value**		0.001	0.001	<0.001
Week 12, n/N (%)[a]	141/198 (71.2)	158/186 (84.9)	178/203 (87.7)	172/201 (85.6)
Odds ratio vs placebo (95% CI)[b]		2.22 (1.33, 3.69)	2.79 (1.66, 4.71)	2.44 (1.47, 4.03)
***p* Value**		0.002	<0.001	<0.001
Role Function–Preventive domain (≥5-point improvement from baseline)				
Week 4, n/N (%)[a]	133/205 (64.9)	154/208 (74.0)	178/217 (82.0)	171/217 (78.8)
Odds ratio vs placebo (95% CI)[b]		1.49 (0.95, 2.33)	2.33 (1.45, 3.75)	2.00 (1.26, 3.16)
***p* Value**		0.082	<0.001	0.003
Week 8, n/N (%)[a]	141/202 (69.8)	158/187 (84.5)	168/208 (80.8)	168/206 (81.6)
Odds ratio vs placebo (95% CI)[b]		2.35 (1.39, 3.98)	1.66 (1.02, 2.70)	1.75 (1.08, 2.84)
***p* Value**		0.002	0.041	0.024
Week 12, n/N (%)[a]	140/198 (70.7)	153/186 (82.3)	170/203 (83.7)	169/201 (84.1)
Odds ratio vs placebo (95% CI)[b]		1.85 (1.10, 3.08)	2.04 (1.22, 3.42)	2.05 (1.23, 3.41)
***p* Value**		0.019	0.007	0.006
Emotional Function domain (≥8-point improvement from baseline)				
Week 4, n/N (%)[a]	110/205 (53.7)	130/208 (62.5)	142/217 (65.4)	144/217 (66.4)
Odds ratio vs placebo (95% CI)[b]		1.49 (0.97, 2.30)	1.56 (1.01, 2.40)	1.80 (1.17, 2.78)
***p* Value**		0.069	0.043	0.008
Week 8, n/N (%)[a]	109/202 (54.0)	137/187 (73.3)	149/208 (71.6)	138/206 (67.0)
Odds ratio vs placebo (95% CI)[b]		2.42 (1.51, 3.88)	2.15 (1.36, 3.39)	1.85 (1.18, 2.91)
***p* Value**		<0.001	0.001	0.007
Week 12, n/N (%)[a]	112/198 (56.6)	129/186 (69.4)	148/203 (72.9)	137/201 (68.2)
Odds ratio vs placebo (95% CI)[b]		1.69 (1.07, 2.67)	1.92 (1.22, 3.03)	1.70 (1.09, 2.67)
***p* Value**		0.025	0.005	0.020

Abbreviation: QD = once daily.
[a] Percentages are relative to the number of participants available for analysis at a specific time point in the modified intent-to-treat population.
[b] Analyses are based on a generalized linear mixed model for repeated measures. The model includes baseline as a covariate, previous exposure to migraine prevention medications (Y/N), treatment group and visit (month) as fixed factors, and treatment group–by-visit and baseline-by-visit as interaction terms. Participants are included as random effects with unstructured covariance matrix in the model.

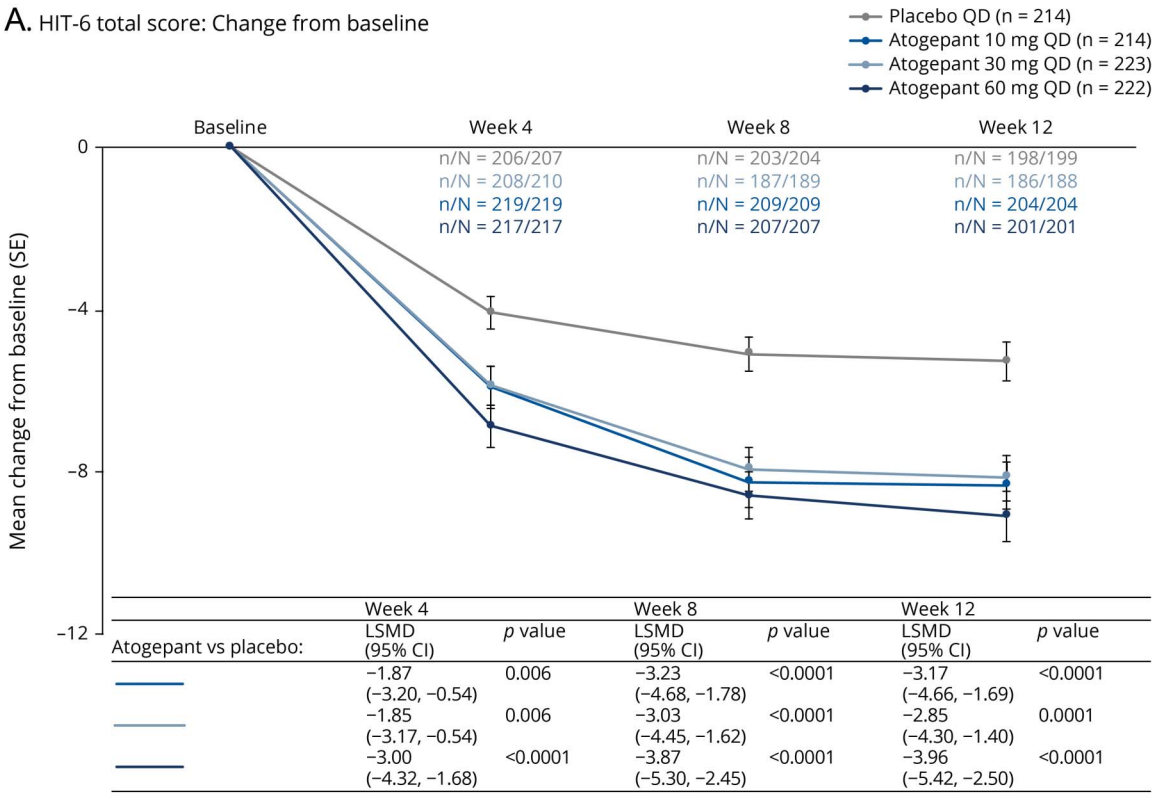
goals of migraine treatment from the perspectives of the patient, their family, employers, and payers.[12,35,36] Our results demonstrated significant improvements in PROs that assessed functioning in daily social and work-related activities and performance of daily activities, emotional effect, physical impairment, and overall effect of headaches. Atogepant (30 and 60 mg) was associated with significant improvements in key alpha-controlled secondary endpoints (MSQ v2.1 RFR and AIM-D PDA and PI) over the 12-week treatment period; for the 10 mg dose, differences were statistically significant for MSQ

Figure 3 Change in AIM-D Scores

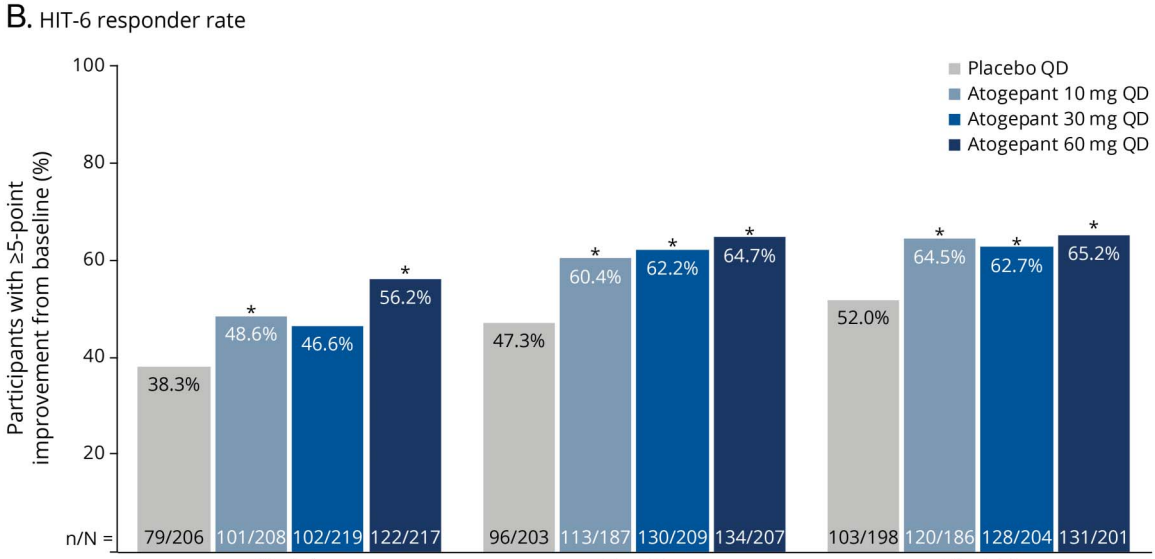


LS mean changes from baseline in average monthly AIM-D (A) Performance of Daily Activities, (B) Physical Impairment, and (C) Total Score. Data for Performance of Daily Activities and Physical Impairment across the 12-week treatment period (months 1–3; secondary endpoint) have been previously published.[18] *$p < 0.05$ vs placebo. AIM-D = Activity Impairment in Migraine–Diary; LSMD = least-square mean difference; QD = once daily.

Figure 4 Change in HIT-6 Score



Atogepant vs placebo:	Week 4 LSMD (95% CI)	Week 4 *p* value	Week 8 LSMD (95% CI)	Week 8 *p* value	Week 12 LSMD (95% CI)	Week 12 *p* value
10 mg	−1.87 (−3.20, −0.54)	0.006	−3.23 (−4.68, −1.78)	<0.0001	−3.17 (−4.66, −1.69)	<0.0001
30 mg	−1.85 (−3.17, −0.54)	0.006	−3.03 (−4.45, −1.62)	<0.0001	−2.85 (−4.30, −1.40)	0.0001
60 mg	−3.00 (−4.32, −1.68)	<0.0001	−3.87 (−5.30, −2.45)	<0.0001	−3.96 (−5.42, −2.50)	<0.0001



	Week 4 10 mg	Week 4 30 mg	Week 4 60 mg	Week 8 10 mg	Week 8 30 mg	Week 8 60 mg	Week 12 10 mg	Week 12 30 mg	Week 12 60 mg
Odds ratio vs placebo (95% CI)	1.53 (1.03, 2.27)	1.43 (0.97, 2.12)	2.18 (1.47, 3.25)	1.79 (1.19, 2.68)	1.95 (1.31, 2.90)	2.25 (1.50, 3.37)	1.74 (1.15, 2.62)	1.54 (1.03, 2.30)	1.77 (1.18, 2.66)
p value	0.037	0.074	0.0001	0.005	0.001	<0.0001	0.009	0.033	0.006

(A) Mean changes from baseline in HIT-6 total score. The between-group MID for HIT-6 is 1.5 points.[31] (B) Percentage of participants with ≥5-point improvement (responders) from baseline in HIT-6 total score. *$p < 0.05$ vs placebo. HIT-6 = Headache Impact Test–6; LSMD = least-square mean difference; QD = once daily.

v2.1 RFR but not for AIM-D among the alpha-controlled endpoints. Atogepant was also associated with nominal improvements in a series of exploratory endpoints as early as week 4.

For the MSQ v2.1, change in the RFR domain from baseline to week 12 was a key secondary endpoint, and earlier time points for the RFR domain and all time points for the RFP and

EF domains were exploratory endpoints. At week 12, each of the 3 atogepant groups demonstrated statistically significant and clinically meaningful improvement compared with placebo in the effect of migraine on daily social and work-related activities as measured by the MSQ v2.1 RFR domain. In addition, all 3 doses of atogepant achieved nominal improvements relative to placebo for all 3 MSQ v2.1 domains at weeks 4 and 8. All atogepant groups achieved the between-group MID vs placebo for the mean improvement in each MSQ v2.1 domain as early as week 4 and throughout the double-blind treatment period, except for the EF domain in the 10 mg group at week 4. The proportion of individuals with clinically meaningful improvements (i.e., responders with score improvement exceeding the within-group MID) in the MSQ v2.1 at week 12 was 85%–88% with atogepant 10–60 mg (vs 71% placebo) for the MSQ-RFR; 82%–84% (vs 71% placebo) for the MSQ-RFP; and 68%–73% (vs 57% placebo) for the MSQ-EF.

The AIM-D, a novel migraine-specific PRO, provides a daily diary-based assessment of performance of daily activities and reduction of physical impairment related to migraine. The 1-day recall period and daily diary format of the AIM-D are intended to minimize the bias that influences measures with longer recall intervals. The other validated daily diary PRO for migraine, the Migraine Physical Function Impact Diary,[37] was not available when study was planned, as exemplified by the 4-week recall interval of the MSQ v2.1 and the 3-month recall interval of the Migraine Disability Assessment Scale.[15,38] Both the MSQ v2.1 and the AIM-D contribute valuable information regarding the effect of migraine on functioning and performance of daily activities and therefore provide a more complete evaluation of migraine burden and treatment benefits. In particular, the AIM-D's assessment of difficulty in performance of daily activities and physical impairment provides complimentary measurement to the MSQ v2.1 RFR domain's evaluation of the frequency of migraine effect on daily social and work activities. The AIM-D PDA and PI domains and total score demonstrated good internal consistency reliability, test-retest reliability, construct validity, known-groups validity, and responsiveness. In the ADVANCE trial, changes from baseline in mean monthly AIM-D PDA and PI domain scores across the 12-week treatment period were alpha-controlled secondary endpoints, and PDA and PI domain scores at monthly time points and AIM-D total scores were exploratory endpoints. Atogepant (30 and 60 mg) demonstrated statistically significant improvements from baseline compared with placebo in mean monthly AIM-D PDA and PI scores across the 12-week treatment period; the 10 mg group also showed improvement in both domains, but the mean change was not significantly different from placebo. The 30 and 60 mg atogepant groups had numerically greater improvements than the placebo group in exploratory endpoints of AIM-D PDA, PI, and total scores across weeks 1–4 that were maintained through the end of the trial.

Changes from baseline in HIT-6 total score (exploratory endpoint) showed that each atogepant dose was associated with nominal and clinically meaningful reductions in headache effect vs placebo at first assessment (week 4) and throughout the double-blind treatment period. The HIT-6 responder rate (proportion of individuals ≥5-point improvement) at week 12 was 63%–65% across atogepant dose groups compared with 52% with placebo.

Previous studies have demonstrated that preventive migraine treatments from various drug classes, including oral preventives and injectable CGRP-targeted monoclonal antibodies (mAbs), improved HRQoL and functioning and reduced headache effect and disability in people with EM.[39-43] Multiple placebo-controlled clinical trials of CGRP-targeted mAbs in participants with EM demonstrated significant and clinically meaningful improvements in the MSQ v2.1 RFR, RFP, and EF domains and in HIT-6 scores with mAbs vs placebo for up to 6 months of treatment.[41-46] Methodological differences limit cross-study comparisons. However, all CGRP-targeted treatments were associated with improvements in MSQ v2.1 domains and HIT-6 total scores. This is the first randomized controlled trial to assess treatment benefits using AIM-D.

This trial has strengths and limitations. This rigorously designed double-blind placebo-controlled trial used established validated PRO instruments that measure changes in functional ability, activity impairment, and headache effect over time. The trial was not powered for key secondary endpoints, including the change from baseline in MSQ v2.1 RFR at week 12 and AIM-D PDA and PI across the 12-week treatment period, although these were prespecified alpha-controlled secondary efficacy endpoints. The MSQ v2.1 RFR measure has been included in the US labeling for migraine preventives; however, the HIT-6 has not.[47] The National Institute of Neurological Disorders and Stroke highly recommends both the MSQ v2.1 and HIT-6 for headache studies.[48] The MSQ v2.1 and HIT-6 have 4-week recall periods, raising recall bias as a potential limitation. There are other recall-based PROs, which were not included or available during the study, including the Migraine Functional Impact Questionnaire.[49] By contrast, as a daily diary, the AIM-D has a same-day recall period. The AIM-D, which was specifically constructed based on FDA guidance for PRO development[19] for use in clinical trials of migraine treatments, provides some unique insights into the effects of atogepant on migraine-related activity impairment. The lack of statistically significant changes in AIM-D scores in the 10 mg dose group is surprising, considering the significant changes with MSQ v2.1 and HIT-6. AIM-D scores are averaged across the month for HA and nHA days. In an EM study, by definition, participants do not have headaches on most days, truncating the potential range of AIM-D scores and creating a potential for floor effects. The baseline AIM-D total score for the overall population was 14.3 (range: 13.6–15.4), on a scale with a maximum value of 100. In addition, the benefits of atogepant might be greater on HA days than on nHA days. Combining HA days and nHA days may generate an AIM-D metric that is less sensitive than an HA day measure, particularly for a lower dose of a preventive treatment. The AIM-D has not been compared directly with other diary data or scales. Finally, the

duration of follow-up was only 12 weeks; some PRO outcomes may continue to improve beyond 12 weeks, so longer studies could be helpful.[50] Future work should separately score HA and nHA days to distinguish the benefits of atogepant on ictal and interictal burden. Only participants with 4–14 MMDs were included in the ADVANCE trial, but a phase 3 atogepant trial in people with CM is ongoing (NCT03855137).

In conclusion, atogepant demonstrated significant and clinically meaningful improvements in functioning in daily social and work-related activities and performance of daily activities and reductions in emotional effect, physical impairment, and overall effect of headaches. Improvements were observed at the earliest assessment point (4 weeks) and throughout the 12-week double-blind treatment period for the 30 and 60 mg doses. In addition, atogepant (10 mg), the lowest dose assessed, improved MSQ v2.1 domain and HIT-6 scores. The early onset of improved functioning is important to patients and payers.[35,36] Together, these results reinforce the beneficial effects of atogepant as a promising new treatment for the prevention of migraine.

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Continued

Appendix *(continued)*

Name	Location	Contribution
Patricia Pozo-Rosich, MD, PhD	Headache Unit, Neurology Department, Vall d'Hebron University Hospital, Barcelona; Headache Research Group, VHIR, Departamento de Medicina, Universitat Autonoma of Barcelona, Spain	Revised the article for intellectual content
Andrew M. Blumenfeld, MD	Headache Center of Southern California, Carlsbad	Revised the article for intellectual content
Ye Li, PhD*	AbbVie, Madison, NJ *Employee during this study	Revised the article for intellectual content
Lawrence Severt, MD*	AbbVie, Madison, NJ *Employee during this study	Revised the article for intellectual content
Jonathan Stokes, MBA	AbbVie, Madison, NJ	Analyzed and interpreted the data; revised the article for intellectual content
Lela Creutz, PhD*	Peloton Advantage, an OPEN Health company, Parsippany, NJ *Employee during manuscript development	Drafted and revised the article under the guidance of the authors
Pranav Gandhi, PhD	AbbVie, Madison, NJ	Designed study; analyzed and interpreted the data; and drafted and revised the article for intellectual content
David W. Dodick, MD	Department of Neurology, Mayo Clinic, Scottsdale, AZ; Atria Institute, New York	Revised the article for intellectual content

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