

5-21-2024

Sustained Response to Atogepant in Episodic Migraine: Post Hoc Analyses of a 12-Week Randomized Trial and a 52-Week Long-Term Safety Trial

Richard Lipton

Stephanie J. Nahas


Patricia Pozo-Rosich

Tanya Bilchik

Peter McAllister

See next page for additional authors

Follow this and additional works at: <https://jdc.jefferson.edu/neurologyfp>

 Part of the [Anesthesia and Analgesia Commons](#), [Nervous System Diseases Commons](#), and the [Neurology Commons](#)

[Let us know how access to this document benefits you](#)

This Article is brought to you for free and open access by the Jefferson Digital Commons. The Jefferson Digital Commons is a service of Thomas Jefferson University's [Center for Teaching and Learning \(CTL\)](#). The Commons is a showcase for Jefferson books and journals, peer-reviewed scholarly publications, unique historical collections from the University archives, and teaching tools. The Jefferson Digital Commons allows researchers and interested readers anywhere in the world to learn about and keep up to date with Jefferson scholarship. This article has been accepted for inclusion in Department of Neurology Faculty Papers by an authorized administrator of the Jefferson Digital Commons. For more information, please contact: JeffersonDigitalCommons@jefferson.edu.

Authors

Richard Lipton, Stephanie J. Nahas, Patricia Pozo-Rosich, Tanya Bilchik, Peter McAllister, Michelle Finnegan, Yingyi Liu, Natty Chalermpanupap, Brett Dabruzzo, and David Dodick

RESEARCH

Open Access



Sustained response to atogepant in episodic migraine: post hoc analyses of a 12-week randomized trial and a 52-week long-term safety trial

Richard B. Lipton¹, Stephanie J. Nahas², Patricia Pozo-Rosich^{3,4}, Tanya Bilchik⁵, Peter McAllister⁶, Michelle Finnegan⁷, Yingyi Liu⁷, Natty Chalermpanupap⁷, Brett Dabruzzo^{7*} and David W. Dodick^{8,9}

Abstract

Background Atogepant is an oral calcitonin gene-related peptide receptor antagonist approved for the preventive treatment of migraine in adults. These analyses evaluated the proportions of clinical trial participants who experienced sustained responses to atogepant over 12 or 52 weeks of treatment.

Methods These were post hoc analyses of ADVANCE, a 12-week, double-blind, randomized trial of atogepant 10, 30, and 60 mg once daily vs. placebo for the preventive treatment of episodic migraine, and a separate open-label long-term safety (LTS) trial of atogepant 60 mg once daily over 52 weeks. The 60 mg dose of atogepant was used to detect safety issues. An initial response was defined as $\geq 50\%$, $\geq 75\%$, or 100% reduction from baseline in MMDs in month 1 for ADVANCE or quarter 1 for the LTS trial. The proportions of participants who continued to experience a response above each response-defining threshold through each subsequent month (for ADVANCE) or each quarter (for LTS) were calculated.

Results In ADVANCE, sustained response rates during months 2 and 3 varied with dose and were as follows: 70.8–81.1% following an initial $\geq 50\%$ response, 47.3–61.9% following an initial $\geq 75\%$ response, and 34.8–41.7% following an initial 100% response. Of those who experienced an initial $\geq 75\%$ or 100% response during month 1, more than 79% continued to experience at least a 50% response during both months 2 and 3. During the LTS trial, sustained response rates through quarters 2, 3, and 4 were 84.7% following an initial $\geq 50\%$ response, 72.6% following an initial $\geq 75\%$ response, and 37.8% following an initial 100% response. Of those who experienced an initial $\geq 75\%$ or 100% response during quarter 1, more than 90% continued to experience at least a 50% response through quarters 2, 3, and 4.

Conclusion Over 70% of participants who experienced an initial response with atogepant treatment had a sustained response with continued treatment.

Finnegan: Employee at the time of study conduct.

*Correspondence:

Brett Dabruzzo

brett.dabruzzo@abbvie.com

Full list of author information is available at the end of the article



© The Author(s) 2024. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

Trial registration ClinicalTrials.gov: NCT03777059 (submitted: December 13, 2018); NCT03700320 (submitted: September 25, 2018).

Keywords CGRP, Responders, Migraine

Introduction

Migraine is a highly prevalent neurologic disease worldwide that is characterized by recurrent attacks of headache pain, often accompanied by phonophobia, photophobia, and nausea [1]. Migraine causes more years lived with disability than all other neurologic diseases combined and is the leading cause of disability in young adult women [2–4]. People with migraine report nearly double the rates of absenteeism, presenteeism, and overall work impairment compared with those without migraine, and approximately one third of people with migraine report a negative impact on their career and financial worry as a result of the disease [5, 6]. The Migraine in America Symptoms and Treatment (MAST) study found that people with migraine were upwards of three times more likely to suffer from insomnia, depression, anxiety, and gastric ulcer/gastrointestinal bleeding compared with those without migraine [7, 8].

Although migraine is common, it tends to be underdiagnosed and undertreated [9]. Many people with episodic migraine (EM) are highly disabled by the disease and are in need of preventive treatment [10]. Despite the high disability associated with migraine, only a minority (~10–20%) of people with migraine who are eligible for preventive treatment based on the 2021 American Headache Society consensus statement algorithm are currently taking a migraine preventive medication [11]. Ideally, preventive treatments for migraine should have both a rapid onset of action and sustained efficacy. However, current conventional oral preventive treatments require titration and may take weeks or months to demonstrate maximum efficacy.

Historically, oral medications for the preventive treatment of migraine tend to have low rates of adherence and persistence [12, 13]. Often, the reasons for poor adherence or discontinuation of oral preventive treatment include insufficient efficacy, insufficient tolerability, or both [13–15]. Results from the second International Burden of Migraine Study, a web-based, cross-sectional survey, revealed that 36.8–47.6% of respondents with EM discontinued their oral preventive treatment due to lack of efficacy, and 34.8–49.0% discontinued because of side effects [14]. In a cross-sectional study of disease burden and treatment patterns among people with migraine, over 70% of respondents with EM who reported switching or discontinuing preventive treatment indicated lack of efficacy or safety/tolerability as the reason [15]. These data suggest that both rapid onset and sustained

efficacy are important attributes of migraine preventive treatments.

Atogepant is an oral calcitonin gene-related peptide (CGRP) receptor antagonist approved for the preventive treatment of migraine (EM and chronic migraine [CM]) in adults [16]. The ADVANCE trial was a pivotal 12-week phase 3 trial that demonstrated the efficacy and safety of atogepant 10, 30, and 60 mg once daily for the preventive treatment of EM [17]. In order to evaluate the safety and tolerability of atogepant for the preventive treatment of EM over a longer period of time, a separate open-label, long-term safety (LTS) trial among participants who had either previously completed a phase 2b/3 atogepant trial or were naive to atogepant was conducted, evaluating the maximum dose (60 mg once daily) over 52 weeks [18].

In multiple clinical trials of atogepant, favorable tolerability and adequate efficacy have been demonstrated [17–20]. In the extension trial of ADVANCE, the tolerability of atogepant was demonstrated with more than 70% of the safety population continuing atogepant for at least 9 months [20]. Moreover, rates of discontinuation of atogepant due to adverse events were only 2.7% for the 60 mg dose in the ADVANCE trial [17]. Furthermore, efficacy was also favorable in both the ADVANCE and LTS trials. Over 60% of participants treated with atogepant 60 mg experienced a 50% or greater reduction from baseline in monthly migraine days (MMDs) over 12 weeks [17, 18]. This endpoint is considered an important clinical outcome, as a 50% reduction in MMDs is aligned with clinical trial guidelines for the development of preventive treatments for migraine [21].

Given that migraine is a chronic disease, it is imperative that preventive treatments for migraine provide continued efficacy with long-term benefits. In an interim analysis of data from the Chronic Migraine Epidemiology and Outcomes–International study, over one-third of respondents in the United States who discontinued a preventive medication reported insufficient efficacy as a factor contributing to their decision to discontinue [22]. While the safety and efficacy of atogepant have been previously established, the degree to which treatment response is sustained in people who report an initial response has not been evaluated. Sustained responses, based on thresholds of prespecified reductions in MMDs over a given period of time, allow for the evaluation of long-term efficacy. The objective of these post hoc analyses was to assess the proportions of participants who experienced sustained responses of ≥50%, ≥75%, or 100%

reduction in MMDs over 12 and 52 weeks of atogepant treatment.

Methods

Study design

Full study details of the ADVANCE and LTS trials have previously been published [17, 18]. Briefly, the ADVANCE trial was a 12-week, double-blind, placebo-controlled, phase 3 trial conducted in the United States from December 14, 2018, to June 19, 2020, that evaluated the safety and efficacy of atogepant for the preventive treatment of EM. Participants were randomized (1:1:1:1) to treatment with once-daily atogepant 10 mg, 30 mg, or 60 mg, or placebo. The LTS trial was a multicenter, randomized, open-label trial conducted in the United States from October 8, 2018, to May 29, 2020, that evaluated the safety and tolerability of atogepant for the preventive treatment of EM for up to 52 weeks. Eligible participants included those who had completed the phase 2b/3 atogepant trial and a group of atogepant-naïve participants. Participants from the phase 2b/3 trial had a minimum of a 6-month gap from the end of that trial to enrollment in the LTS study. At the time of enrollment, eligible participants met criteria for migraine according to the International Classification of Headache Disorders, 3rd edition, had 4 to 14 migraine days per month, and completed a pretreatment diary to establish MMDs at baseline. For the LTS study, participants were randomized (5:2) to treatment with once-daily atogepant 60 mg or standard care (SC). Participants randomized to the SC arm received a physician-selected oral migraine preventive medication (e.g., topiramate, amitriptyline, propranolol) as their initial treatment. Permitted preventive medications in the SC arm were those recognized as safe and effective for the preventive treatment of migraine, based on investigator's judgment, and full details have been previously described [18]. The SC arm was included to contextualize the long-term safety of atogepant by providing comparative data in a manner consistent with clinical practice; efficacy data were not collected in the SC arm. Post hoc analyses of ADVANCE and LTS trials were performed to assess sustained response associated with atogepant treatment. Data from ADVANCE and the LTS trial were analyzed separately.

The ADVANCE and LTS trials were approved by an institutional review board or independent ethics committee and were registered at ClinicalTrials.gov NCT03777059 (ADVANCE) and NCT03700320 (LTS trial). For each trial, participants provided written informed consent. All study conduct was in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice.

Participants

Inclusion and exclusion criteria for each trial were published previously [17, 18]. Briefly, eligible participants were adults with 4 to 14 migraine days per month in the 3 months before visit 1 and in the 28-day baseline period. Participants were diagnosed with migraine with or without aura according to the International Classification of Headache Disorders, 3rd edition [1], for a minimum of 1 year with the diagnosis made prior to the age of 50 years.

Outcomes

For these post hoc analyses, participants were categorized as having an initial response if they experienced $\geq 50\%$ reduction from baseline in MMDs in month 1 (4 weeks after starting treatment) for ADVANCE or in quarter 1 (first 12 weeks) for the LTS trial. Participants who experienced this initial $\geq 50\%$ response were further categorized using higher response thresholds of $\geq 75\%$, or 100%. The proportions of participants experiencing either the same initial response or $\geq 50\%$ response through each subsequent month for ADVANCE or through each quarter for the LTS study were calculated. Missing data were treated conservatively. If a participant with an initial response had missing data for some timepoint (month/quarter) later in the trial, and they did not experience response at the nonmissing timepoint, they were included in the analyses as not experiencing a sustained response. If they did experience the response in the nonmissing timepoint, but had missing data for other timepoints, they were excluded from the analyses.

For ADVANCE, the proportions of participants who experienced a $< 50\%$ response in month 1 but proceeded to experience a $\geq 50\%$ response in subsequent months were calculated.

Statistical analysis

Response rates were previously presented in the overall modified intent-to-treat (mITT) population for both trials [17, 18]. These post hoc analyses focused on the subgroups of participants with an initial response in each trial and evaluated the proportions of those who continued to experience a given response threshold (e.g., $\geq 50\%$, $\geq 75\%$, or 100% reduction in MMDs from baseline) during the remainder of the 12- or 52-week trial. An initial response was defined as a $\geq 50\%$, $\geq 75\%$, or 100% reduction in MMDs from baseline during the first month of treatment in ADVANCE or during the first quarter of open-label treatment in the 52-week LTS trial. For ADVANCE, the subgroup of participants with a $< 50\%$ reduction in MMDs from baseline in month 1 who proceeded to experience a $\geq 50\%$ reduction in MMDs from baseline in month 2 and month 2 or 3 was assessed. These analyses used observed data for all participants at each assessment period. A month was defined as each 4-week treatment

interval. Data for each quarter of the LTS trial were based on the monthly average of MMDs (3 months for quarters 1–3, 4 months for quarter 4).

Results

Participants

Of 659 participants included in the mITT population in the ADVANCE trial, 214 participants received atogepant 10 mg, 223 participants received atogepant 30 mg, and 222 participants received atogepant 60 mg (Table 1). Mean MMDs at baseline were similar across dose groups, ranging from 7.5 to 7.9 days. In month 1 of the ADVANCE trial, a ≥50% initial MMD response was experienced by 48.9% (109/223; 30 mg) to 61.1% (135/221; 60 mg) of participants, a ≥75% initial response was experienced by 26.9% (60/223; 30 mg) to 39.4% (87/221; 60 mg) of participants, and a 100% initial response was experienced by 11.7% (26/223; 30 mg) to 19.0% (42/221; 60 mg) of participants.

In the LTS trial, 744 participants underwent randomization. Of these, 14.4% had participated in the phase 2b/3 atogepant trial and 85.6% had not previously taken atogepant. A total of 521 participants were included in the mITT population and received atogepant 60 mg. Participants reported a mean of 7.3 MMDs. Of these, 62.4% (325/521) experienced a ≥50% initial response in the first quarter, 38.0% (198/521) experienced a ≥75% initial response in the first quarter, and 10.6% (55/521) experienced a 100% initial response in the first quarter.

Efficacy results

ADVANCE

Of ADVANCE participants who experienced a ≥50% response within month 1, 70.8% (68/96; 30 mg) to 81.1% (103/127; 60 mg) continued to experience this initial ≥50% response through the remainder of the

12-week double-blind treatment period (months 2 and 3) (Fig. 1). Among those with an initial ≥75% response, 47.3% (26/55; 30 mg) to 61.9% (52/84; 60 mg) continued to experience a ≥75% response through months 2 and 3, and 79.2% (42/53; 30 mg) to 86.9% (73/84; 60 mg) had a ≥50% response through months 2 and 3 (Fig. 2). Among those with an initial 100% response, 34.8% (8/23; 30 mg) to 41.7% (10/24; 10 mg) continued to experience a 100% response, 66.7% (16/24; 10 mg) to 69.6% (16/23; 30 mg) had a ≥75% response, and 86.4% (19/22; 30 mg) to 95.0% (38/40; 60 mg) had a ≥50% response through months 2 and 3 (Fig. 3).

Of ADVANCE participants who did not experience a ≥50% response within month 1, 33.8% (26/77; 60 mg) to 41.3% (45/109; 30 mg) had ≥50% reduction from baseline in MMDs in month 2 and 52.8% (56/106; 30 mg) to 61.4% (43/70; 60 mg) experienced ≥50% reduction from baseline in MMDs in either month 2 or 3 (Fig. 4A). Among participants who did not have a ≥50% reduction in MMDs in month 1 or 2, 16.7% (10/60; 30 mg) to 37.2% (16/43; 60 mg) experienced a ≥50% reduction in MMDs in month 3 (Fig. 4B).

LTS trial

In the 52-week LTS trial, 84.7% (222/262) of participants treated with atogepant 60 mg who had an initial ≥50% response experienced sustained response throughout all subsequent quarters (quarters 2–4) (Fig. 5). Among those with an initial ≥75% response, 72.6% (119/164) continued to experience the same ≥75% response throughout the 52-week trial, and 90.8% (148/163) had a ≥50% response in all subsequent quarters (Fig. 6). Among those with an initial 100% response, 37.8% (17/45) continued to experience a 100% response throughout each subsequent quarter of the 52-week trial; 88.4% (38/43) had a ≥75% response, and 97.7% (42/43) had a ≥50% response in all subsequent quarters (Fig. 7).

Discussion

The 12-week results of the ADVANCE trial and the 52-week results of the LTS trial indicate that high proportions of participants with EM experience a meaningful reduction of ≥50% in MMDs in the first 4 weeks, and that those responses are usually sustained. In both ADVANCE and the LTS trial, most participants who had a ≥50% initial response continued to experience the response throughout their treatment period. For the 60 mg dose in the ADVANCE trial, 61.1% had at least a 50% reduction in MMDs over the first month and of those, 81.1% continued to experience that level of response through 3 months. These analyses highlight several factors that may contribute to clinical decision making, as well as patient counseling regarding both trialing and stopping treatment.

Table 1 Initial response subgroups and baseline monthly migraine days

	ADVANCE			LTS Trial
	10 mg	30 mg	60 mg	60 mg
N (mITT population)	214	223	222	521
Responses during initial period, ^a n/N1 (%)				
≥50% response subgroup	105/213 (49.3)	109/223 (48.9)	135/221 (61.1)	325/521 (62.4)
≥75% response subgroup	58/213 (27.2)	60/223 (26.9)	87/221 (39.4)	198/521 (38.0)
100% response subgroup	30/213 (14.1)	26/223 (11.7)	42/221 (19.0)	55/521 (10.6)
MMDs at baseline, mean (SD)	7.5 (2.5)	7.9 (2.3)	7.8 (2.3)	7.3 (2.6)

LTS, long-term safety; mITT, modified intent-to-treat; MMD, monthly migraine day

^aInitial period defined as 4 weeks for ADVANCE and 12 weeks for the LTS trial

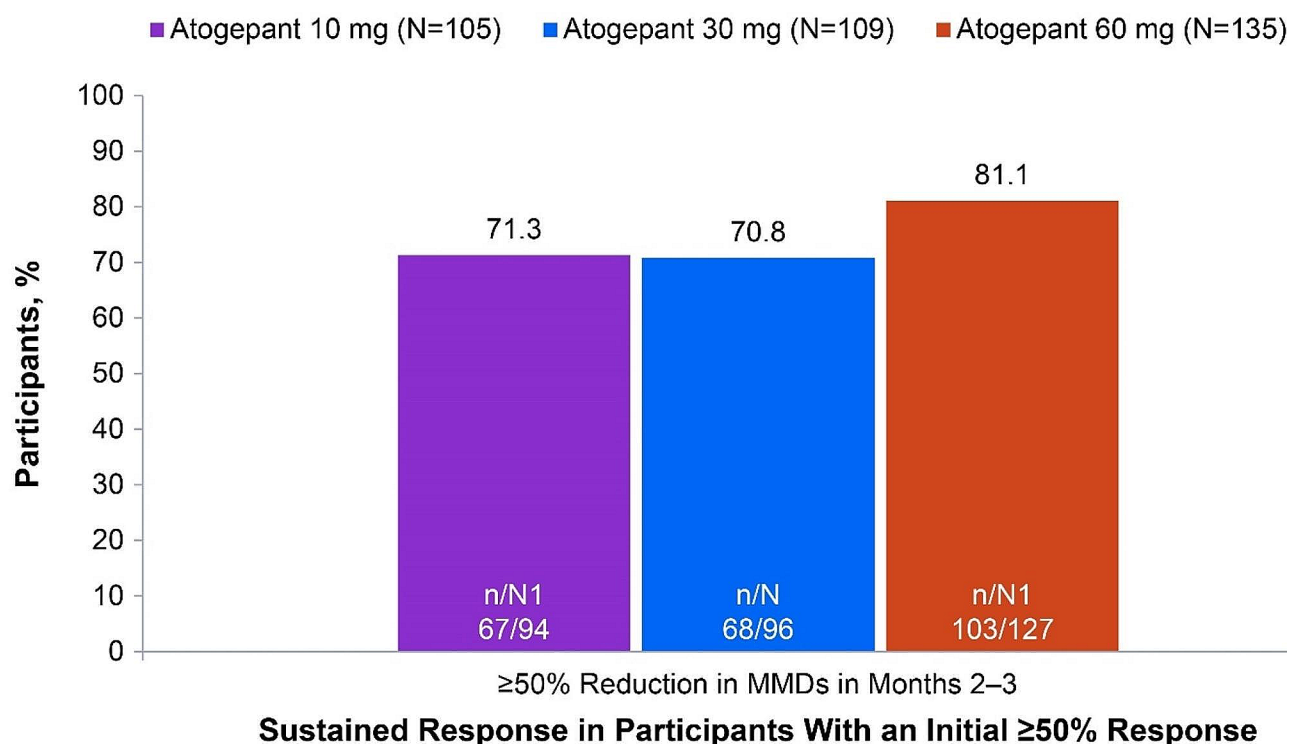


Fig. 1 Sustained Response in Both Months 2 and 3 Among Participants With a ≥50% Response in Month 1 (ADVANCE). MMDs, monthly migraine days; N, participants with a ≥50% reduction in MMDs in month 1; n, number of participants within a specific category; N1, number of participants available for analysis

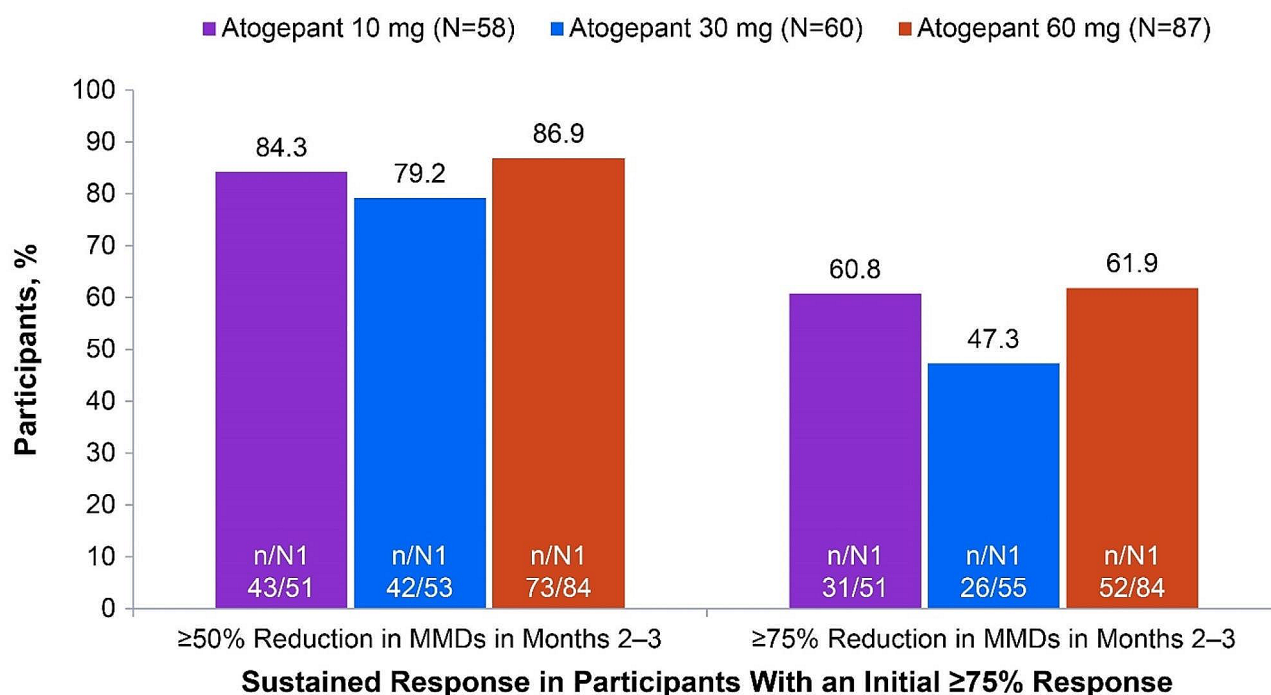


Fig. 2 Sustained Response of ≥50% in Both Months 2 and 3 Among Participants With a ≥75% Response in Month 1 (ADVANCE). MMDs, monthly migraine days; N, participants with a ≥75% reduction in MMDs in month 1; n, number of participants within a specific category; N1, number of participants available for analysis

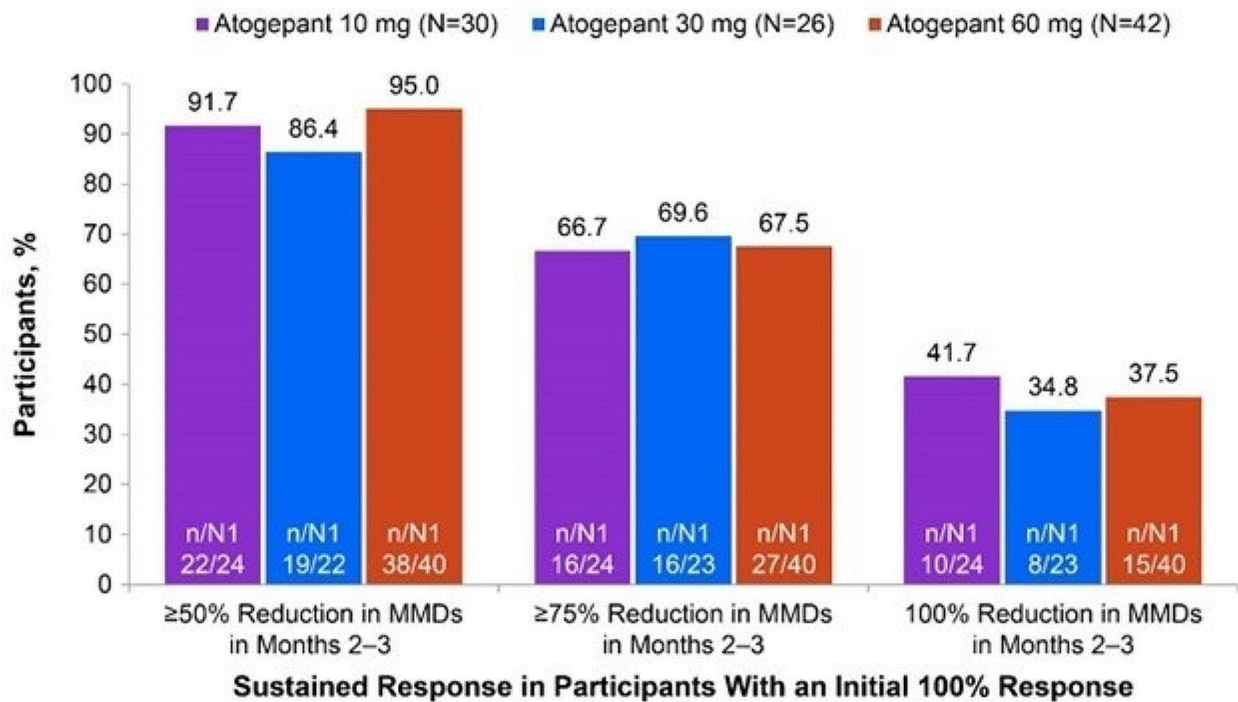


Fig. 3 Sustained Response of $\geq 50\%$ in Both Months 2 and 3 Among Participants With a 100% Response in Month 1 (ADVANCE). MMDs, monthly migraine days; N, participants with a 100% reduction in MMDs in month 1; n, number of participants within a specific category; N1, number of participants available for analysis

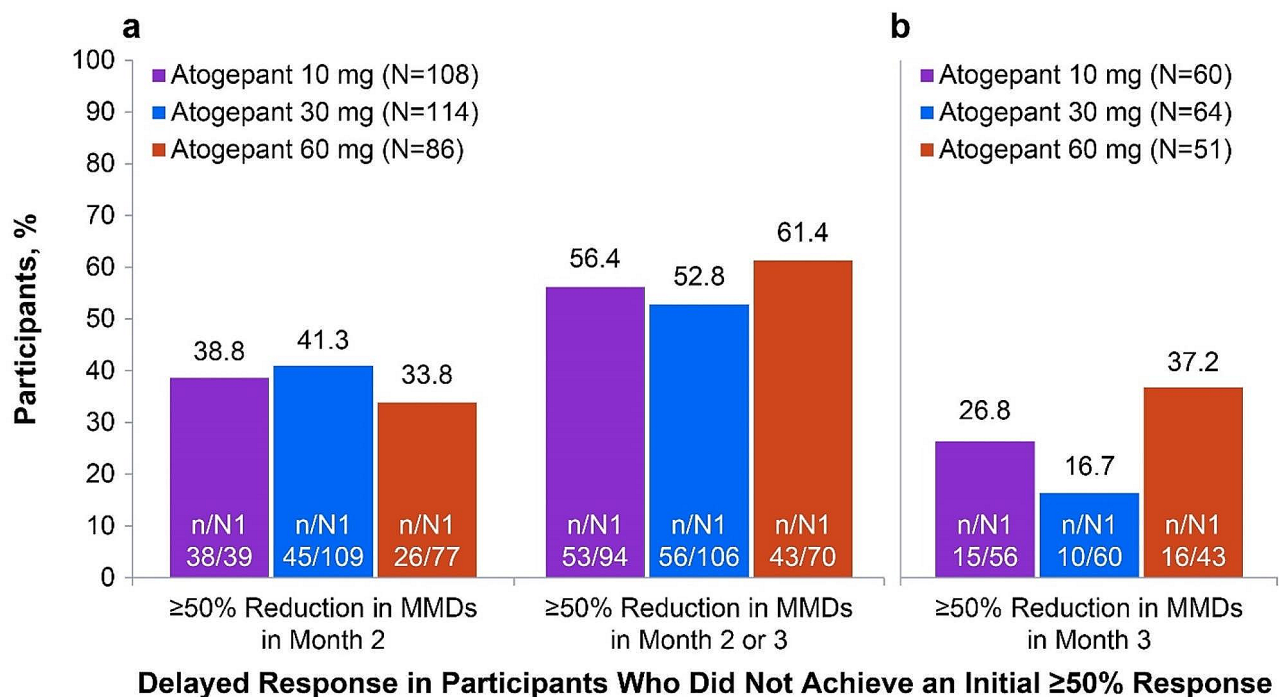


Fig. 4 Delayed Response of $\geq 50\%$ Among Participants Without a $\geq 50\%$ Response in Month 1 (a) and Months 1 and 2 (b) (ADVANCE). MMDs, monthly migraine days; N, total number of participants included in the modified intent-to-treat population; n, number of participants not achieving response; N1, total number of participants with determinable data

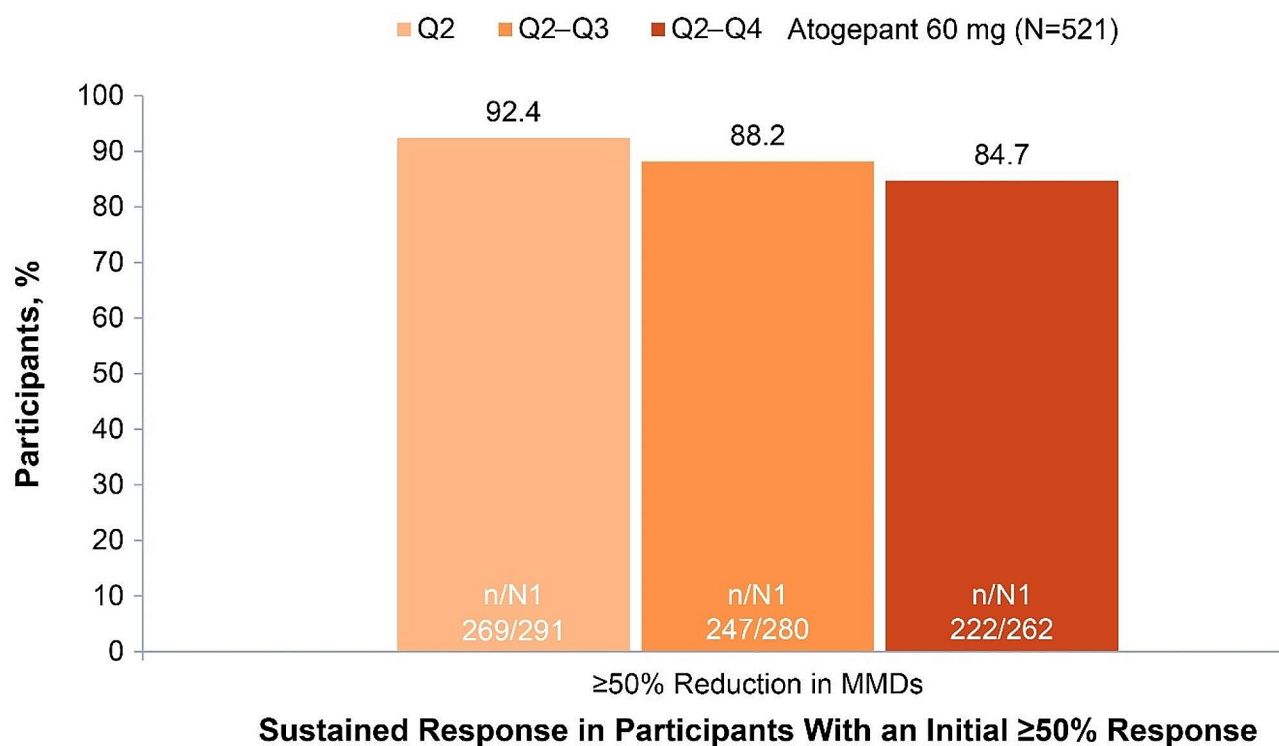


Fig. 5 Sustained Response Over 52 Weeks Among Participants With a ≥50% Response in Q1 (52-Week Trial). MMDs, monthly migraine days; N, participants included in the modified intent-to-treat population; n, number of Q1 with initial response who had sustained response in Q2, Q2-Q3, or Q2-Q4; N1, number of Q1 with initial response from participants with determinable data at Q2, Q2-Q3, or Q2-Q4; Q, quarter

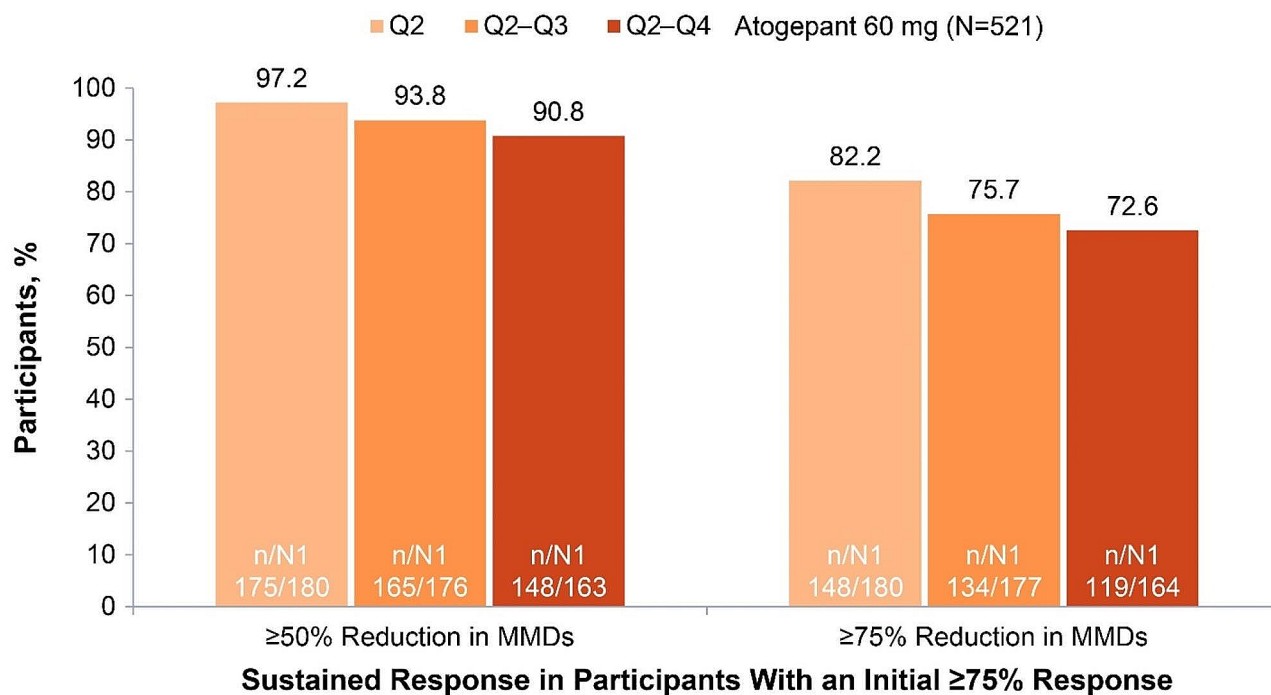


Fig. 6 Sustained Response of ≥50% Over 52 Weeks Among Participants With a ≥75% Response in Q1 (52-Week Trial). MMDs, monthly migraine days; N, participants included in the modified intent-to-treat population; n, number of Q1 with initial response who had sustained response in Q2, Q2-Q3, or Q2-Q4; N1, number of Q1 with initial response from participants with determinable data at Q2, Q2-Q3, or Q2-Q4; Q, quarter

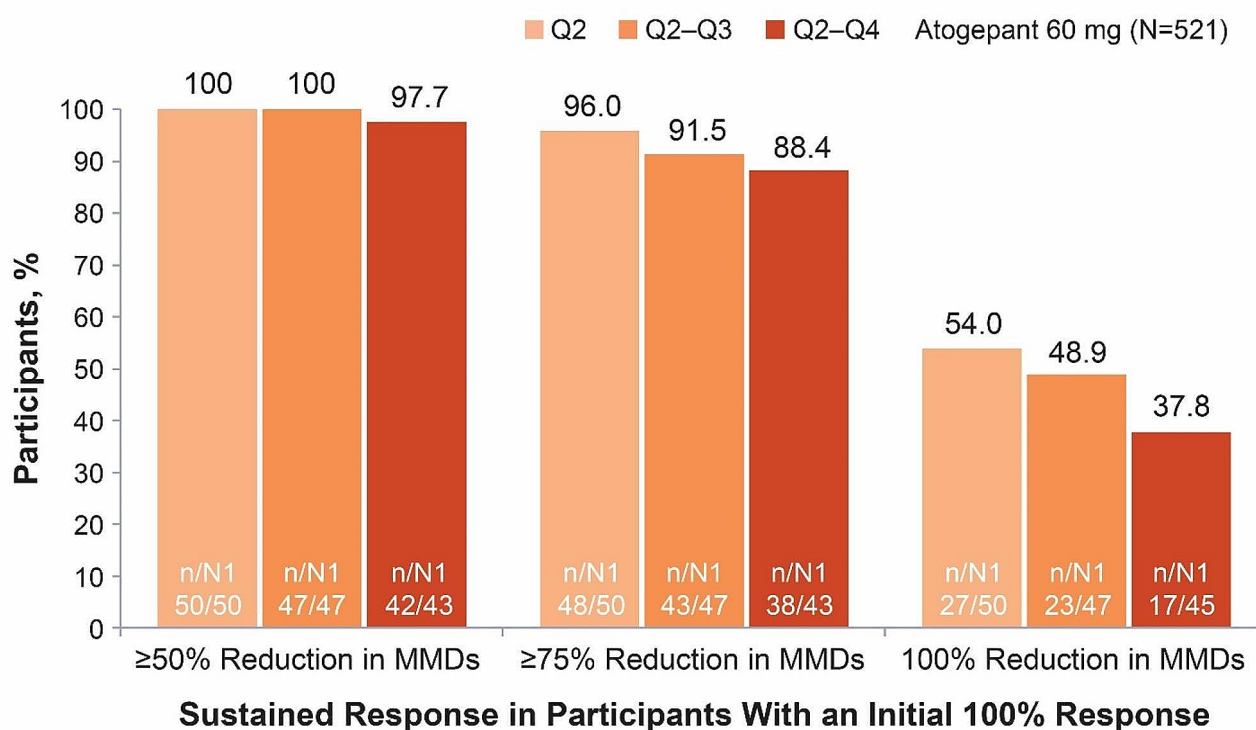


Fig. 7 Sustained Response of $\geq 50\%$ Over 52 Weeks Among Participants With a 100% Response in Q1 (52-Week Trial). MMDs, monthly migraine days; N, participants included in the modified intent-to-treat population; n, number of Q1 with initial response who had sustained response in Q2, Q2-Q3, or Q2-Q4; N1, number of Q1 with initial response from participants with determinable data at Q2, Q2-Q3, or Q2-Q4; Q, quarter

Guidelines from the American Headache Society (AHS) outline parameters for giving a chosen preventive migraine treatment regimen an adequate trial before discontinuing. For injectable CGRP pathway-targeted monoclonal antibodies, it is recommended that clinical benefit be assessed after 3 months of a monthly treatment and after 6 months of a quarterly treatment [11]. For an oral generic preventive treatment, it is recommended that the medication be trialed for a minimum of 8 weeks at the target therapeutic dose before determining a lack of effectiveness [11]. Recent discussion of European guidelines by the European Headache Federation (EHF) suggested that, based on excellent tolerability data, if there is no other reason to stop treatment, the use of CGRP-targeted monoclonal antibodies should only be stopped when MMDs decrease to 4 or less; however, further studies are needed to investigate the long-term effects of discontinuation [23]. Although neither guideline directly references adequate trial or discontinuation recommendations for oral small-molecule CGRP receptor antagonists (gepants) [11, 24], both emphasize the improved tolerability of CGRP-targeted preventive migraine therapies over traditional nonspecific oral therapies (e.g., beta-blockers, calcium-channel blockers, and anti-depressants) [11, 23, 25]. Moreover, the most recently updated AHS position statement

now recommends CGRP-targeted therapies, including gepants, as first-line treatment options for the preventive treatment of migraine, stating that the cumulative evidence for their efficacy, safety, and tolerability is significantly greater than that for any established migraine preventive therapy [25]. Our present data demonstrate both subsequent and sustained responses associated with atogepant, suggesting that sustained clinical benefits may be achieved with continued use of atogepant.

Considerations for long-term migraine treatment include potential delayed treatment effect, sustained treatment effect over 1 year with minimal diminishing, and dose-dependent effect. Findings suggest that those with migraine may benefit from atogepant treatment even if they do not have a response in the first month. Among ADVANCE study participants who did not experience a $\geq 50\%$ reduction from baseline in MMDs with atogepant 60 mg in the first month, 61.4% proceeded to experience at least a 50% reduction in MMDs in month 2 or 3. In the LTS study, 62.4% experienced at least a 50% reduction in MMDs over the first quarter and 92.4% continued to experience that level of response through the second quarter. Additionally, in the LTS trial, over 90% of participants who experienced a $\geq 75\%$ or 100% initial response had a $\geq 50\%$ response in each subsequent quarter. Furthermore, relatively few participants who

experienced a $\geq 50\%$ initial response experienced $< 25\%$ response by the end of the ADVANCE (5.3–5.5%) or LTS (2.3%) trial. Results from the ADVANCE trial also suggest dose response effects on sustained benefits of atogepant treatment. At each level of response ($\geq 50\%$, $\geq 75\%$, and 100%), the proportions of participants who had sustained response were highest in the groups that received atogepant 60 mg (Table 1).

Our post hoc analyses build on earlier findings and demonstrate that when an initial response to atogepant is experienced, these benefits are often sustained with continued treatment. In clinical trials and in practice, a $\geq 50\%$ reduction from baseline in MMDs is considered to be a clinically meaningful response to preventive treatment for episodic migraine [26]. In a pivotal trial for atogepant, 52–62% of participants who received atogepant experienced $\geq 50\%$ reduction in MMDs across the full 12-week double-blind treatment period [19]. A secondary analysis of ADVANCE demonstrated that a $\geq 50\%$ reduction in MMDs with atogepant treatment occurred as early as the first 4 weeks and increased over time [27]. Furthermore, a separate analysis found that a significantly higher percentage of atogepant- vs. placebo-treated participants reported being migraine free on day 1 after treatment initiation (atogepant: 85.9–89.2%; placebo: 74.8%), reflecting a relatively rapid onset of action for atogepant [28]. Conventional oral preventive treatments often require titration periods to determine the appropriate dosage, whereas atogepant has demonstrated both early onset and sustained efficacy for the preventive treatment of migraine. Together, our findings may alter clinical decision making for the preventive treatment of migraine.

Analyses of injectable monoclonal antibodies that target the CGRP pathway for the treatment of EM have also evaluated duration of treatment responses [29, 30]. The STRIVE study demonstrated sustained efficacy in treating EM by showing that the majority of erenumab-treated participants who experienced a $\geq 50\%$ reduction in MMDs during the last 3 months of the 24-week double-blind treatment period also had this response in the last 3 months of the 52-week dose-blind active treatment phase [29]. Results from the PROMISE-1 and PROMISE-2 studies demonstrated the sustained efficacy of intravenous eptinezumab through the analysis of cumulative months in which participants had a $\geq 50\%$ reduction in MMDs [30, 31]. Additionally, a post hoc analysis of data from study participants with EM who received galcanezumab biweekly showed sustained response over 3 months and delayed response in a portion of them who did not have a response at month 1 but did see a $\geq 50\%$ reduction in MMDs in months 2 or 3 [32].

A potential limitation of these post hoc analyses is the lack of a placebo control group. The efficacy of atogepant compared with placebo has previously been established

using change from baseline in MMDs and response rates [17]. Our goal here was to evaluate the persistence of response. Additionally, both ADVANCE and the LTS trial were conducted in individuals with EM, which may limit the generalizability of the results to those with chronic migraine. However, results from a post hoc analysis of the PROGRESS trial demonstrated that most participants with chronic migraine who experienced an initial $\geq 30\%$ or $\geq 50\%$ MMD response had sustained the response throughout the 12-week trial [33]. An additional limitation of this analysis is that the proportion of participants who experienced a delayed treatment response was evaluated only for the ADVANCE trial. These topics should be further explored in future analyses.

Conclusion

In the ADVANCE trial, $> 70\%$ of participants who experienced an initial $\geq 50\%$ response at month 1 continued to experience this response throughout the 12-week treatment period, and $> 50\%$ of participants who did not experience a $\geq 50\%$ response in month 1 proceeded to experience a $\geq 50\%$ response in months 2 and 3. In the LTS trial, approximately 85% of participants who experienced a $\geq 50\%$ initial response at quarter 1 continued to experience this response throughout the 52-week trial. Additionally, of participants who experienced a $\geq 75\%$ or 100% initial response, $> 90\%$ had a $\geq 50\%$ response in subsequent quarters. The results of these sustained response analyses demonstrate that, in the subgroup who experience an initial treatment response with atogepant, the majority have a sustained response for up to a year. These findings may provide additional support for decision making in clinical practice.

Abbreviations

AHS	American Headache Society
CGRP	Calcitonin gene-related peptide
EM	Episodic migraine
CM	Chronic migraine
LTS	Long-term safety
mITT	Modified intent-to-treat
MMD	Monthly migraine day
SC	Standard care

Acknowledgements

AbbVie and the authors thank all the trial investigators and the individuals who participated in these clinical trials. Medical writing support was provided by Peloton Advantage, LLC, an OPEN Health company, and was funded by AbbVie.

Author contributions

Study design: RBL, MF, NC. Study investigator: RBL. Collection and assembly of data: YL, NC, BD. Data analysis: YL, NC, BD. Data interpretation: All authors. Manuscript preparation: RBL, NC, BD. Manuscript review and revisions: All authors. Final approval of manuscript: All authors.

Funding

AbbVie funded this trial and contributed to the study design, the collection, analysis, and interpretation of data, and the review and approval of the final version for publication. All authors had access to relevant data and

participated in the drafting, review, and approval of this publication. No honoraria or payments were made for authorship.

Data availability

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 (SAP), and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the US 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."

Declarations

Ethics approval and consent to participate

The ADVANCE and LTS trials were approved by an institutional review board or independent ethics committee and registered at ClinicalTrials.gov: NCT03777059 (ADVANCE) and NCT03700320 (LTS trial). For each trial, participants provided written informed consent. All study conduct was in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice.

Consent for publication

Not applicable.

Competing interests

RBL has received research support from the National Headache Foundation, the National Institutes of Health, and the US Food and Drug Administration. He serves as consultant for, advisory board member of, or has received honoraria or research support from AbbVie/Allergan, Amgen, Biohaven, Dr. Reddy's Laboratories (Promius), electroCore, Eli Lilly, GlaxoSmithKline, Lundbeck, Merck, Novartis, Teva, Vector, and Vedanta Research. He receives royalties from *Wolff's Headache*, 8th edition (Oxford University Press, 2009), and Informa. He holds stock/options in Biohaven and Manistee. SJN has served as consultant for AbbVie, Eli Lilly, Lundbeck, Pfizer, Theranica, and Tonix. She has received honoraria for work in education or publishing from American Academy of Neurology, American Headache Society, Diamond Headache Clinic Research and Educational Foundation, MedLink Neurology, MJH Life Sciences, NACCME, Springer, WebMD/Medscape, and Wolters Kluwer. PP-R has received, in the last 3 years, personal fees for advisory boards and speaker panels from AbbVie, Amgen, Chiesi, Eli Lilly, Lundbeck, Medscape, Novartis, Pfizer, and Teva, and for serving on the scientific advisory board of Lilly Foundation Spain and Gadea Science Foundation. She is the principal investigator for clinical trials sponsored by AbbVie, Amgen, Biohaven, Eli Lilly, Lundbeck, Novartis, and Teva. Her group has received grants from AbbVie, Era-Net Neuron, European Commission, Instituto Carlos III, International Headache Society, MINECO, Novartis, FEDER RIS3CAT, and Teva. She serves as an associate editor for *Cephalalgia*, *Headache*, *Neurologia*, *The Journal of Headache and Pain*, and *Revista de Neurologia*. She is the Honorary Secretary of the International Headache Society. She does not hold any stock or options. TB has participated in advisory boards for AbbVie, Biohaven, and Theranica. She is a clinical trial investigator for Lundbeck. PM has received research funding from AbbVie, Amgen, Biogen, Biohaven, EMD Serono, Lundbeck, Novartis, and Teva, and has received personal compensation for advisory boards and/or speakers bureaus for AbbVie, Aeon, Amgen, Biohaven, Lilly, Lundbeck, Revance, and Teva. MF was an employee of AbbVie at the time of study conduct and may hold AbbVie stock. DWD reports the following conflicts: Consulting: Amgen, Atria, CapiThera Ltd., Cerecin, Ceruvia Lifesciences LLC, CoolTech, Ctrl M, Allergan, AbbVie, Biohaven, Escient, GlaxoSmithKline, Halion, Lundbeck, Eli Lilly, Novartis, Impel, Satsuma, Theranica, WL Gore, Genentech, Nocira, Perfood, Praxis, AYYA Biosciences, Revance, Pfizer. Honoraria: American Academy of Neurology, Headache Cooperative of the Pacific, Headache Cooperative of New England, Canadian Headache Society, MF Med Ed Research, Biopharm Communications, CEA Group Holding Company (Clinical Education Alliance

LLC), Teva (speaking), Amgen Japan (speaking), Eli Lilly Canada (speaking), Lundbeck (speaking), Pfizer (speaking), Vector Psychometric Group, Clinical Care Solutions, CME Outfitters, Curry Rockefeller Group, DeepBench, Global Access Meetings, KLJ Associates, Academy for Continued Healthcare Learning, Majallin LLC, Medlogix Communications, Medica Communications LLC, MJH Lifesciences, Miller Medical Communications, WebMD Health/Medscape, Wolters Kluwer, Oxford University Press, Cambridge University Press. Non-profit board membership: American Brain Foundation, American Migraine Foundation, ONE Neurology, Precon Health Foundation, Global Patient Advocacy Coalition, Atria Health Collaborative, Atria Academy of Science and Medicine, Arizona Brain Injury Alliance, Domestic Violence HOPE Foundation/Panfila, CSF Leak Foundation. Research support: Department of Defense, National Institutes of Health, Henry Jackson Foundation, Sperling Foundation, American Migraine Foundation, Patient-Centered Outcomes Research Institute (PCORI). Stock options/shareholder/patents/board of directors: Ctrl M (options), Aural Analytics (options), Axon Therapeutics (board/options), ExSano (options), Palion (options), Keimon Medical (options), Man and Science, Healint (options), Theranica (options), Second Opinion/Mobile Health (options), Epien (options), Nocira (options), Matterhorn (shares), Ontologics (shares), King-Devick Technologies (options/board), Precon Health (options/board), ScotiLyfe (board), EigenLyfe (options/board), AYYA Biosciences (options), Axon Therapeutics (options/board), Cephalgia Group (options/board), Atria Health (options/employee). Patent 17189376.1-1466v: Title: Onabotulinum Toxin Dosage Regimen for Chronic Migraine Prophylaxis (non-royalty bearing). Patent application submitted: Synaquest® (Precon Health). YL, NC, and BD are employees of AbbVie and may hold AbbVie stock.

Data sharing 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 (SAP), and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the US 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."

Author details

¹Albert Einstein College of Medicine, Bronx, NY, USA

²Thomas Jefferson University, Philadelphia, PA, USA

³Headache Unit, Department of Neurology, Vall d'Hebron University Hospital, Barcelona, Spain

⁴Headache Research Group, Vall d'Hebron Institute of Research, Universitat Autònoma de Barcelona, Barcelona, Spain

⁵Department of Neurology, Yale University School of Medicine, New Haven, CT, USA

⁶New England Institute for Neurology & Headache, Stamford, CT, USA

⁷AbbVie, North Chicago, IL, USA

⁸Mayo Clinic, Phoenix, AZ, USA

⁹Atria Academy of Science and Medicine, New York, NY, USA

Received: 28 March 2024 / Accepted: 30 April 2024

Published online: 21 May 2024

References

1. Headache Classification Committee of the International Headache Society (2018) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia* 38:1-211
2. (2016) Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the global burden of Disease Study 2015. *Lancet* 388:1545–1602

3. (2018) Global, regional, and national burden of migraine and tension-type headache, 1990–2016: a systematic analysis for the global burden of Disease Study 2016. *Lancet Neurol* 17:954–976
4. Steiner TJ, Stovner LJ, Jensen R, Uluduz D, Katsarava Z (2020) Migraine remains second among the world's causes of disability, and first among young women: findings from GBD2019. *J Headache Pain* 21:137
5. Buse DC, Yurgakh MS, Lee LK, Bell J, Cohen JM, Lipton RB (2020) Burden of illness among people with migraine and ≥ 4 monthly headache days while using acute and/or preventive prescription medications for migraine. *J Manag Care Spec Pharm* 26:1334–1343
6. Buse DC, Fanning KM, Reed ML, Murray S, Dumas PK, Adams AM et al (2019) Life with migraine: effects on relationships, career, and finances from the Chronic Migraine Epidemiology and Outcomes (CaMEO) study. *Headache* 59:1286–1299
7. Lipton RB, Munjal S, Alam A, Buse DC, Fanning KM, Reed ML et al (2018) Migraine in America Symptoms and Treatment (MAST) study: baseline study methods, treatment patterns, and gender differences. *Headache* 58:1408–1426
8. Buse DC, Reed ML, Fanning KM, Bostic R, Dodick DW, Schwedt TJ et al (2020) Comorbid and co-occurring conditions in migraine and associated risk of increasing headache pain intensity and headache frequency: results of the Migraine in America Symptoms and Treatment (MAST) study. *J Headache Pain* 21:23
9. Miller S, Matharu MS (2014) Migraine is underdiagnosed and undertreated. *Practitioner* 258:19–24
10. Torres-Ferrús M, Quintana M, Fernandez-Morales J, Alvarez-Sabin J, Pozo-Rosich P (2017) When does chronic migraine strike? A clinical comparison of migraine according to the headache days suffered per month. *Cephalalgia* 37:104–113
11. Ailani J, Burch RC, Robbins MS (2021) The American Headache Society consensus statement: update on integrating new migraine treatments into clinical practice. *Headache* 61:1021–1039
12. Hepp Z, Dodick DW, Varon SF, Gillard P, Hansen RN, Devine EB (2015) Adherence to oral migraine-preventive medications among patients with chronic migraine. *Cephalalgia* 35:478–488
13. Hepp Z, Bloudek LM, Varon SF (2014) Systematic review of migraine prophylaxis adherence and persistence. *J Manag Care Pharm* 20:22–33
14. Blumenfeld AM, Bloudek LM, Becker WJ, Buse DC, Varon SF, Maglinte GA et al (2013) Patterns of use and reasons for discontinuation of prophylactic medications for episodic migraine and chronic migraine: results from the second International Burden of Migraine Study (IBMS-II). *Headache* 53:644–655
15. Ford JH, Jackson J, Milligan G, Cotton S, Ahl J, Aurora SK (2017) A real-world analysis of migraine: a cross-sectional study of disease burden and treatment patterns. *Headache* 57:1532–1544
16. Qulipta [package insert] (2023) AbbVie
17. Ailani J, Lipton RB, Goadsby PJ, Guo H, Miceli R, Severt L et al (2021) Atogepant for the preventive treatment of migraine. *N Engl J Med* 385:695–706
18. Ashina M, Tepper SJ, Reuter U, Blumenfeld AM, Hutchinson S, Xia J et al (2023) Once-daily oral atogepant for the long-term preventive treatment of migraine: findings from a multicenter, randomized, open-label, phase 3 trial. *Headache* 63:79–88
19. Goadsby PJ, Dodick DW, Ailani J, Trugman JM, Finnegan M, Lu K et al (2020) Safety, tolerability, and efficacy of orally administered atogepant for the prevention of episodic migraine in adults: a double-blind, randomised phase 2b/3 trial. *Lancet Neurol* 19:727–737
20. Klein BC, Miceli R, Severt L, McAllister P, Mechtler L, McVige J et al (2023) Safety and tolerability results of atogepant for the preventive treatment of episodic migraine from a 40-week, open-label multicenter extension of the phase 3 ADVANCE trial. *Cephalalgia* 43:3331024221128250
21. US Food and Drug Administration. Migraine: developing drugs for preventive treatment. Guidance for Industry: US Food and Drug Administration (2023) [June 2023]. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/migraine-developing-drugs-preventive-treatment>
22. Buse DC, Reed ML, Fanning KM, Dabruzzo BL, Lipton RB (2022) Characterizing preventive treatment gaps in migraine: interim results from the CaMEO-International study United States sample [abstract IOR-05]. *Headache* 62(suppl 1):60–61
23. Al-Hassany L, Lyons HS, Boucherie DM, Farham F, Lange KS, Marscholke K et al (2023) The sense of stopping migraine prophylaxis. *J Headache Pain* 24:9
24. Sacco S, Amin FM, Ashina M, Bendtsen L, Deligianni CI, Gil-Gouveia R et al (2022) European Headache Federation guideline on the use of monoclonal antibodies targeting the calcitonin gene related peptide pathway for migraine prevention – 2022 update. *J Headache Pain* 23:67
25. Charles AC, Digre KB, Goadsby PJ, Robbins MS, Hershey A (2024) Calcitonin gene-related peptide-targeting therapies are a first-line option for the prevention of migraine: an American Headache Society position statement update. *Headache* 64:333–341
26. Tfelt-Hansen P, Pascual J, Ramadan N, Dahlof C, D'Amico D, Diener HC et al (2012) Guidelines for controlled trials of drugs in migraine: third edition. A guide for investigators. *Cephalalgia* 32:6–38
27. Lipton RB, Pozo-Rosich P, Blumenfeld AM, Dodick DW, McAllister P, Li Y et al (2022) Rates of response to atogepant for migraine prophylaxis among adults: a secondary analysis of a randomized clinical trial. *JAMA Netw Open* 5:e2215499
28. Schwedt TJ, Lipton RB, Ailani J, Silberstein SD, Tassorelli C, Guo H et al (2022) Time course of efficacy of atogepant for the preventive treatment of migraine: results from the randomized, double-blind ADVANCE trial. *Cephalalgia* 42:3–11
29. Goadsby PJ, Reuter U, Hallström Y, Broessner G, Bonner JH, Zhang F et al (2020) One-year sustained efficacy of erenumab in episodic migraine: results of the STRIVE study. *Neurology* 95:e469–e479
30. Smith TR, Janelidze M, Chakhava G, Cady R, Hirman J, Allan B et al (2020) Eptinezumab for the prevention of episodic migraine: sustained effect through 1 year of treatment in the PROMISE-1 study. *Clin Ther* 42:2254–2265e2253
31. Silberstein S, Diamond M, Hindiyeh NA, Biondi DM, Cady R, Hirman J et al (2020) Eptinezumab for the prevention of chronic migraine: efficacy and safety through 24 weeks of treatment in the phase 3 PROMISE-2 (Prevention of migraine via intravenous ALD403 safety and efficacy-2) study. *J Headache Pain* 21:120
32. Goadsby PJ, Dodick DW, Martinez JM, Ferguson MB, Oakes TM, Zhang Q et al (2019) Onset of efficacy and duration of response of galcanezumab for the prevention of episodic migraine: a post-hoc analysis. *J Neurol Neurosurg Psychiatry* 90:939–944
33. Lipton R, Chalermpananupap N, Nahas-Geiger S, Pozo-Rosich P, McAllister P, Tatsuoka Y et al (2023) Sustained and subsequent response to atogepant among individuals with chronic migraine: post hoc analysis of the PROGRESS trial [abstract P-180]. *Headache* 63(suppl 1):168–169

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.