ORIGINAL ARTICLE

# Positive response to galcanezumab following treatment failure to onabotulinumtoxinA in patients with migraine: *post hoc* analyses of three randomized double-blind studies

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**Background and purpose:** Humanized monoclonal antibody galcanezumab, which binds to calcitonin-gene-related peptide, has shown efficacy for episodic and chronic migraine prevention. These analyses evaluated galcanezumab response for migraine headache prevention in patients who previously failed onabotulinumtoxinA ('nonresponse' or 'inadequate response' or safety reasons).

**Methods:** *Post hoc* analyses included data from three double-blind, placebo-controlled, phase 3 episodic or chronic migraine studies; 2886 patients randomly received 120 or 240 mg galcanezumab or placebo. During double-blind periods the study drug was administered subcutaneously once a month for 6 months in EVOLVE-1 and -2 and for 3 months in REGAIN. The 120 mg groups received a 240 mg loading dose at month 1. Pooled analyses included 129 patients who failed onabotulinumtoxinA. Using mixed effect model repeat measurements, the least squares mean change from baseline in the number of migraine headache days (MHDs) was calculated for the first 3 months of treatment.

**Results:** For pooled analyses, significant decreases from baseline in the number of MHDs were observed for 120 mg (−3.91) and 240 mg (−5.27) galcanezumab overall versus placebo (−0.88) across 3-month time points for patients who failed onabotulinumtoxinA. Corresponding data for patients with chronic migraine showed significant decreases: 120 mg (−3.18) and 240 mg (−4.26) galcanezumab versus placebo (0.16). Significant reductions in the number of MHDs per month with acute medication use included 120 mg galcanezumab (−4.35) and 240 mg galcanezumab (−4.55) versus placebo (−0.83). Estimates of ≥50% response during months 1–3 were 9.4% for placebo, 41.3% for 120 mg galcanezumab and 47.5% for 240 mg galcanezumab.

**Conclusion:** Galcanezumab is an option for prevention of migraine in patients who have previously failed onabotulinumtoxinA preventive therapy.

## Introduction

Guidelines for migraine treatment recommend starting appropriate patients on preventive medications to reduce migraine attack frequency and severity [1]. Lack of effectiveness and intolerability often result in multiple medication switches, poor adherence or discontinuation [2–4]. A recent study in patients with episodic or chronic migraine reported that >75% of

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patients switched or discontinued their initial preventive treatment [5].

OnabotulinumtoxinA (onabotA) is approved by the US Food and Drug Administration for the prevention of headaches in adults with chronic migraine based on evidence from clinical trials and real-world studies [6–8]. Galcanezumab is a humanized monoclonal antibody that binds calcitonin-gene-related peptide (CGRP) ligand and is approved for migraine prevention in adults [9–11]. Phase 3 randomized controlled studies have demonstrated significantly greater reductions in the average number of monthly migraine headache days (MHDs) following monthly subcutaneous injections of galcanezumab for preventive treatment of episodic and chronic migraine [12–14].

Patients who do not respond to one preventive treatment or experience intolerable side effects might benefit from another preventive treatment. To explore this hypothesis, the benefit of galcanezumab for preventive treatment in patients who discontinued onabotA treatment was investigated.

## Methods

### Study design

The *post hoc* analyses included data from three double-blind, randomized, placebo-controlled phase 3 studies of similar design comparing galcanezumab versus placebo in patients with episodic migraine (NCT02614183; NCT02614196) [12,13] or chronic migraine (NCT02614261) [14]. Briefly, for each study, patients were randomized (2:1:1) to placebo, galcanezumab 120 mg or galcanezumab 240 mg. Study treatment was administered once monthly for 3–6 months during the double-blind period (subcutaneous injection via prefilled syringe). Patients received two subcutaneous injections of study treatment at each dosing visit. All patients randomized to galcanezumab received 240 mg as the first dose at month 1.

The studies were approved by independent ethics committees at each site and were conducted in accordance with the Declaration of Helsinki and internationally accepted standards of good clinical practice. All patients gave written informed consent before enrollment.

### Patient selection

Study participants were adults (18–65 years) with at least a 1-year history of migraine. Patients had an episodic (EVOLVE-1 and -2) or chronic (REGAIN) migraine diagnosis as defined by the International Headache Society 2013 criteria [15]. During the EVOLVE-1 and -2 studies, no other preventive medications were allowed; stable doses of topiramate or propranolol were allowed in REGAIN. The primary key exclusion criterion for EVOLVE-1 and -2 was a history of failure to respond to three or more classes of migraine preventive treatments as defined by the American Academy of Neurology/American Headache Society treatment guidelines Level (A) and (B) evidence [1]. Botulinum toxin A and B treatment in the head or neck regions within 4 months prior to visit 2 was an exclusion criterion for both episodic migraine studies and the chronic migraine study.

In these analyses, failure with onabotA was self-reported by the patient, captured during medical history, and defined as cessation of drug for efficacy-related reasons ('nonresponse' or 'inadequate response') or safety reasons ('medical history event'). The total number of patients who failed onabotA treatment included only those who used onabotA more than 4 months prior to visit 2. In order to have a relatively large sample size, the 3-month double-blind period data from two episodic studies and one chronic migraine study were pooled.

### Outcome measures and statistical analyses

The primary outcome for these *post hoc* analyses was the overall mean change from baseline in the number of monthly MHDs during the first 3 months of the 6-month double-blind period for EVOLVE-1 and -2 and the entire 3-month double-blind period for REGAIN for all patients previously on onabotA and those who failed onabotA due to efficacy or safety reasons. In addition, the primary outcome was also evaluated exclusively for those patients with chronic migraine who participated in the REGAIN study. Additional outcomes included the following: the change from baseline in the number of MHDs with acute medication use for patients who failed onabotA; the change from baseline in the Migraine-Specific Quality of Life Questionnaire (MSQ) Role Function-Restrictive domain score version 2.1 [16] for onabotA failures; and the proportion of patients who had ≥50% decrease in the number of MHDs (50% responders) amongst onabotA failures.

The pooled analyses included intent-to-treat (ITT) patients who had received onabotA prior to randomization of the three studies and a subset of patients who had failed onabotA. Continuous repeated measures including change in MHDs, change in MHDs with acute medication use and change in MSQ Role Function-Restrictive at months 1, 2 and 3 were

analyzed using the mixed effect model repeated measures analysis method. The least squares mean change from baseline averaged over the 3-month double-blind period was estimated from the mixed effect model repeated measures method (denoted as overall mean change). The categorical repeated measures of 50% response rate at months 1, 2 and 3 were analyzed using a generalized linear mixed model. The overall proportion of patients with at least 50% response over 3 months for each treatment was estimated using inverse logit transformation of the least squares means estimate of the main effect of treatment.

## Results

In these *post hoc* analyses, 129 patients were onabotA failures ($n = 11$ EVOLVE-1, $n = 20$ EVOLVE-2, $n = 98$ REGAIN) and were included in the *post hoc* analyses that follow. However, as a sensitivity analysis, the primary efficacy measure of change from baseline in the number of MHDs was also analyzed for the 200 patients ($n = 17$ EVOLVE-1, $n = 43$ EVOLVE-2, $n = 140$ REGAIN) who received onabotA prior to each of the three studies. Demographic and baseline medical characteristics of onabotA failures are summarized in Table 1. Most patients in each treatment group previously had been prescribed three or more preventive medications prior to the administration of onabotA (Table S1).

For ITT onabotA failures, mean number of days from the last dose of onabotA to the first dose of galcanezumab was 569.6, 543.8 and 699.3 days for the 120 mg, 240 mg and placebo groups, respectively. The percentage of onabotA failures who received onabotA for ≥12 months was 55.6% for placebo versus 64.0% for galcanezumab 120 mg and 43.8% for galcanezumab 240 mg. For patients previously on onabotA, the mean number of days from the last dose of onabotA to the first dose of galcanezumab was 516.5, 534.1 and 599.0 for the 120 mg, 240 mg and placebo groups, respectively. The percentage of patients who received onabotA for ≥12 months was 49.0% for placebo versus 60.5% for galcanezumab 120 mg and 47.2% for galcanezumab 240 mg.

Failure due to efficacy with onabotA for the ITT population was reported as nonresponse for 28.0% of galcanezumab 120 mg, 28.1% of galcanezumab 240 mg and 47.2% of placebo patients. Corresponding efficacy data due to an inadequate response to onabotA were reported for 72.0%, 68.8% and 52.8% of patients, respectively. Safety events associated with onabotA failure were reported for 0%, 3.1% and 1.4% of patients, respectively.

### Change from baseline in number of monthly MHDs

For patients who failed onabotA, significant overall decreases from baseline in number of MHDs were observed for 120 mg (−3.91) and 240 mg (−5.27) galcanezumab across 3-month time points versus placebo (−0.88). Compared with placebo, significant decreases from baseline in the number of monthly MHDs were observed for galcanezumab at all time points for ITT patients previously on onabotA (all $P$ values versus placebo ≤0.03; Fig. 1) and for ITT patients who failed onabotA (all $P$ values versus placebo ≤0.03; Fig. 2).

For the subset of patients with chronic migraine who failed onabotA ($n = 98$), significant overall

**Table 1** Demographic and baseline medical characteristics of onabotA failures

| | EVOLVE-1 ($n = 11$) | EVOLVE-2 ($n = 20$) | REGAIN ($n = 98$) |
|---|---|---|---|
| Mean age, years (SD) | 46.5 (10.8) | 44.3 (9.5) | 47.5 (10.5) |
| Female, *n* (%) | 11 (100.0) | 18 (90.0) | 84 (85.7) |
| White, *n* (%) | 10 (90.9) | 12 (60.0) | 89 (90.8) |
| Geographic region, *n* (%) | | | |
| North America | 11 (100.0) | 5 (25.0) | 43 (43.9) |
| Europe | 0 (0) | 9 (45.0) | 51 (52.0) |
| Other | 0 (0) | 6 (30.0) | 4 (4.1) |
| Mean duration of migraine diagnosis, years (SD) | 26.2 (18.1) | 26.7 (14.9) | 26.6 (13.9) |
| Mean number of monthly MHDs, days (SD) | 9.6 (2.9) | 10.2 (3.0) | 19.6 (4.6) |
| Mean number of monthly MHDs with acute medication use, days (SD) | 8.6 (3.2) | 8.1 (4.3) | 16.6 (6.4) |
| Migraine Disability Assessment, mean total score (SD) | 45.2 (29.4) | 47.5 (42.6) | 69.0 (62.5) |
| Failed ≥2 preventives in past 5 years, *n* (%) | 7 (63.6) | 13 (65.0) | 83 (84.7) |
| MSQ Role Function-Restrictive score, mean (SD)[a] | 42.1 (17.1) | 44.7 (13.8) | 36.7 (17.4) |

MHDs, migraine headache days; MSQ, Migraine-Specific Quality of Life Questionnaire; onabotA, onabotulinumtoxinA. [a]The MSQ Role Function-Restrictive domain measures the functional impact of migraine on work or daily activities, relationship with family and friends, leisure time, productivity, concentration, energy and tiredness. Scoring for the MSQ Role Function-Restrictive domain ranges from 0 to 100, with higher scores indicating better functioning (i.e. patients experience fewer restrictions on the performance of day-to-day activities).

decreases from baseline in number of MHDs were observed for 120 mg (−3.18) and 240 mg (−4.26) galcanezumab across 3-month time points versus placebo (0.16; each $P$ value < 0.04). Both doses of galcanezumab led to significant decreases from baseline in the number of monthly MHDs at all time points compared to placebo (all $P$ values versus placebo <0.03) except for the 120 mg dose at month 1.

### Change from baseline in the number of MHDs with acute medication use

Patients in both galcanezumab dose groups reported significant decreases versus placebo in the number of MHDs per month with acute medication use across months 1, 2 and 3 for ITT patients previously on onabotA (all $P$ values versus placebo ≤0.01; Fig. 3). Overall, there was a reduction in the mean number of MHDs per month with acute medication use of −4.35 [95% confidence interval (CI) −6.66, −2.03] for galcanezumab 120 mg, −4.55 (95% CI −6.68, −2.43) for galcanezumab 240 mg, and −0.83 (95% CI −2.45, 0.79) for placebo.

### Change from baseline in Migraine-Specific Quality of Life Questionnaire Role Function-Restrictive scores

For patients who were onabotA failures, those administered galcanezumab 120 or 240 mg had significantly improved MSQ Role Function-Restrictive scores overall and at months 1, 2 and 3 versus placebo ($P$ values versus placebo ≤0.03), except for the galcanezumab 120 mg dose at month 1 (Fig. 4).

### Estimated proportion of 50% responders for MHDs

The proportion of onabotA failure patients achieving at least a 50% response rate (i.e. ≥50% reduction from baseline in the number of MHDs per month) was significantly greater in patients treated with galcanezumab 120 or 240 mg versus placebo across months 1, 2 and 3 (all $P$ values versus placebo ≤0.02;

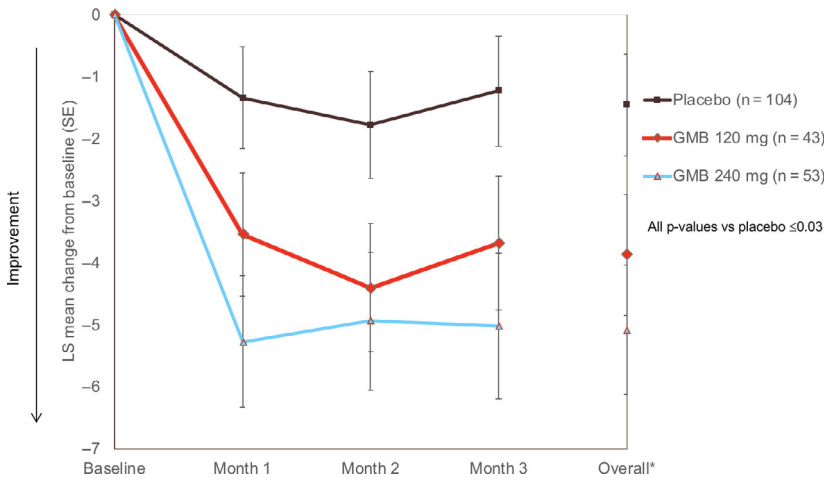


**Figure 1** Change from baseline in number of MHDs: previously on onabotA. GMB, galcanezumab; LS, least squares; MHDs, migraine headache days; OnabotA, onabotulinumtoxinA; SE, standard error. *Overall represents the average over months 1 to 3. [Colour figure can be viewed at wileyonlinelibrary.com]

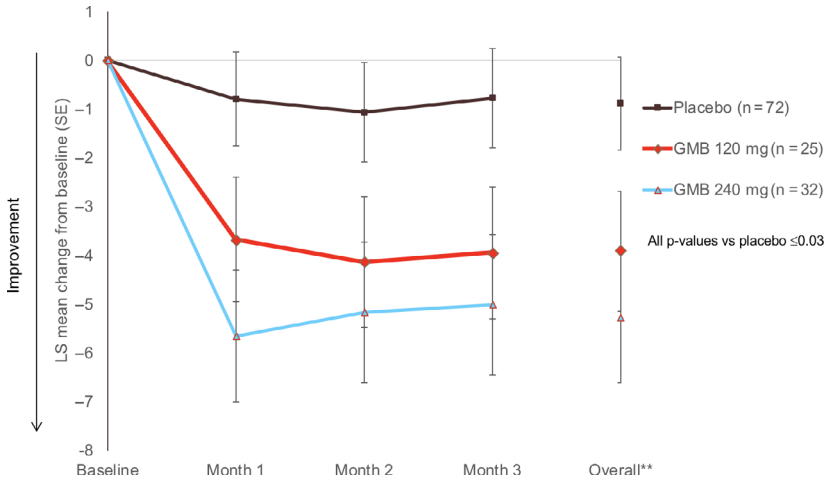


**Figure 2** Change from baseline in number of MHDs: onabotA failures*. GMB, galcanezumab; LS, least squares; MHDs, migraine headache days; OnabotA, onabotulinumtoxinA; SE, standard error. *Failure defined as lack of efficacy or safety/tolerability issues. **Overall represents the average over months 1 to 3. [Colour figure can be viewed at wileyonlinelibrary.com]

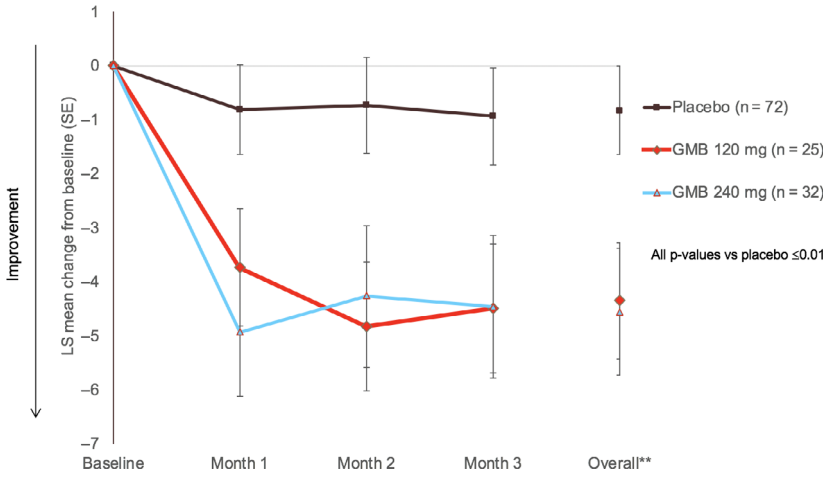


**Figure 3** Change from baseline in number of MHDs with acute medications used to treat migraine: onabotA failures*. GMB, galcanezumab; LS, least squares; MHDs, migraine headache days; OnabotA, onabotulinumtoxinA; SE, standard error. *Failure defined as lack of efficacy or safety/tolerability issues. **Overall represents the average over months 1 to 3. [Colour figure can be viewed at wileyonlinelibrary.com]

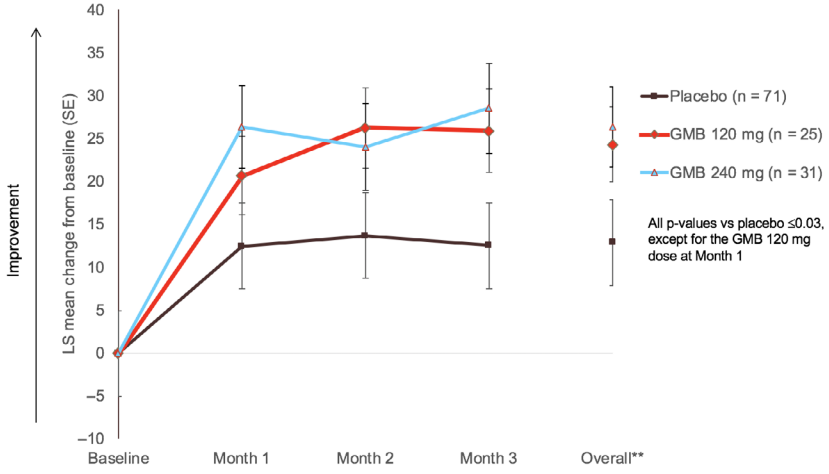


**Figure 4** Change from baseline in the Migraine-Specific Quality of Life Questionnaire Role Function-Restrictive domain score: onabotA failures*. GMB, galcanezumab; LS, least squares; OnabotA, onabotulinumtoxinA; SE, standard error. *Failure defined as lack of efficacy or safety/tolerability issues. **Overall represents the average over months 1 to 3. [Colour figure can be viewed at wileyonlinelibrary.com]

Fig. 5). Overall, estimates of ≥50% response during months 1, 2 and 3 were 41.3% (95% CI 20.1%, 66.3%) for galcanezumab 120 mg, 47.5% (95% CI 25.2%, 70.7%) for galcanezumab 240 mg and 9.4% (95% CI 4.0%, 20.8%) for placebo.

## Discussion

These *post hoc* analyses in adult patients diagnosed with episodic or chronic migraine demonstrated that galcanezumab given as preventive treatment had a beneficial effect for the subgroup who had previously failed onabotA treatment. Overall, galcanezumab administered in monthly injectable doses of 120 or 240 mg provided significant reductions from baseline in the number of monthly MHDs versus placebo, which was consistent with findings from the primary studies [12–14]. Other key observations for the onabotA failure subgroup were significant reductions in the number of MHDs per month with acute medication use, significant improved MSQ Role Function-Restrictive scores, and significantly more patients achieving at least a 50% reduction from baseline in the number of MHDs per month versus placebo. Both doses of galcanezumab appeared to be equally effective during the 3-month observation period for all outcomes.

Notably, the majority of patients in these analyses were enrolled in the REGAIN study and thus had chronic migraine. Because onabotA is approved by the Food and Drug Administration for prevention of chronic migraine, patients with chronic migraine are more likely than patients with episodic migraine to try onabotA as preventive migraine therapy. In our analysis that included only patients with chronic migraine who failed onabotA, both doses of galcanezumab provided significant reductions from baseline in the number of monthly MHDs versus placebo across the 3-month time points. Because patients with chronic migraine are perceived to have more severe disease

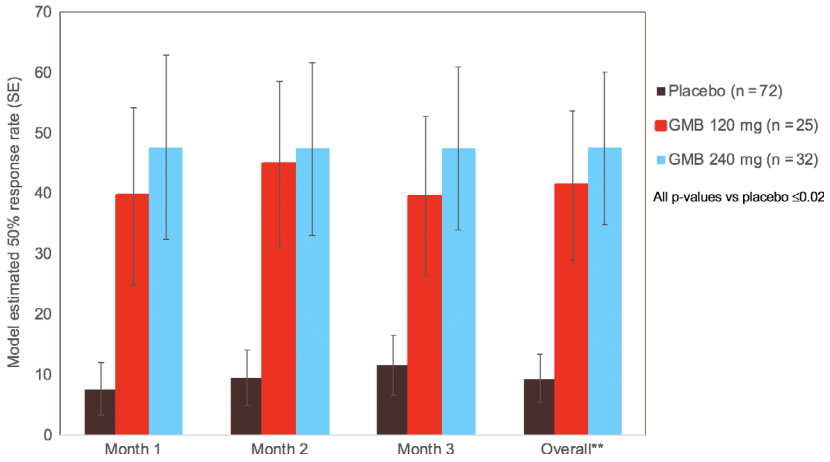


**Figure 5** Estimated proportion of 50% responders for MHDs: onabotA failures*. GMB, galcanezumab; MHDs, migraine headache days; SE, standard error. *Failure defined as lack of efficacy or safety/tolerability issues. **Overall represents the average over months 1 to 3. [Colour figure can be viewed at wiley onlinelibrary.com]

and are impacted more by their disease, the efficacy of galcanezumab as a preventive migraine medication is noteworthy. Furthermore, it appears that the patients in this analysis had low placebo effects, which may help to explain the significant differences between galcanezumab and placebo. It is also possible that patients with chronic migraine who received prior preventive migraine therapy are less likely to show a placebo effect.

Use of acute medications to treat migraine attacks is common and is often utilized by patients prescribed preventive migraine medications. In one study in a large administrative US healthcare claims database, the majority of patients who initiated preventive migraine medications also utilized acute treatments (81%) [17]. Preventive therapies that can demonstrate reduction in acute medication use have the potential to reduce costs from acute medication use and potential complications from extended frequent use of acute medication. Our observation that administration of preventive migraine treatment with galcanezumab significantly reduced the need for acute medications is clinically relevant to the patient and clinician, especially amongst the subpopulation of patients who failed onabotA treatment.

The positive benefit of galcanezumab in onabotA failures was further supported by the improved health-related quality of life relative to baseline for the MSQ Role Function-Restrictive domain, which measures the effect of migraine on daily social and work-related activities [16]. Although no significant difference was found between the two doses of galcanezumab, the overall 3-month improvement in the MSQ Role Function-Restrictive score was 2-fold greater for galcanezumab versus placebo with average increases in scores of 24–26 points (on a 100-point scale).

Finally, the estimated proportion of patients who were 50% responders over the 3-month observation period was approximately 4-fold greater for galcanezumab-treated patients versus placebo recipients.

The results of these *post hoc* analyses of galcanezumab in patients with episodic or chronic migraine with prior preventive onabotA failure are consistent with the results of two STRIVE subgroup studies of erenumab that included patients who had failed ≥1 or ≥2 prior preventive treatments due to lack of efficacy and/or intolerability [18,19]. Preliminary findings in erenumab-treated patients (140 mg dose) with episodic migraine who had failed at least one previous preventive drug class demonstrated greater placebo-adjusted treatment differences in the treatment failure subgroups versus the overall population [18]. Similar findings were observed, with greater clinical benefits observed for the erenumab 140 mg dose amongst patients with chronic migraine after monthly erenumab injections versus placebo in patients with prior treatment failures (≥1, ≥2 and ≥3) [19].

Patients who have at least four attacks per month of any severity are advised to receive preventive treatment; additionally, patients having two or more migraine attacks per month with severe impairment or requiring bed rest would probably benefit from preventive migraine medication [20]. Effective and well-tolerated preventive migraine medications are likely to reduce disability and time lost from work/social events, and may encourage adherence. Physicians are encouraged to work with patients to better identify their needs and expectations and to educate patients with migraine about the advantages of preventive migraine medications.

There are several limitations and strengths that need to be considered when interpreting the findings presented herein. Enrolled patients were primarily middle-aged, white, females; and restrictions in the inclusion criteria may limit the generalizability of our findings. Patients with serious and unstable medical

conditions were excluded, as were patients who had demonstrated significant treatment resistance to multiple previous migraine preventive medications. It is possible that patients who had chronic migraine became episodic after trying onabotA and were then enrolled into the EVOLVE studies; longitudinal data prior to prescreening were not available. The 3-month duration for these *post hoc* analyses, whilst sufficient to demonstrate efficacy, may not be long enough to demonstrate the ultimate effects of the treatment. Although the effect of galcanezumab for patients who failed onabotA in other patient populations requires further investigation due to the small sample size, the *post hoc* analyses performed herein were robust. Also, onabotA failure (efficacy or safety reasons) was based on patient recall that was captured during the patient medical history. Finally, our analyses did not compare the efficacy of galcanezumab to onabotA and were not intended to suggest that galcanezumab replace onabotA therapy in the treatment algorithm of chronic migraine. However, our analyses explore if galcanezumab is an alternative for patients who have had an inadequate response or are intolerant to onabotA.

## Conclusion

These *post hoc* analyses demonstrated the efficacy of galcanezumab, a humanized monoclonal antibody that binds CGRP and prevents its biological activity without blocking the CGRP receptor, in patients with episodic or chronic migraine who experienced prior onabotA preventive treatment failure. These data may be useful to clinicians who are treating patients who have failed onabotA preventive treatment for migraine.

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## Disclosure of conflict of interest

All authors are employees and minor stockholders of Eli Lilly and Company or Lilly USA, LLC, except Dr Ailani, who is on the speakers' bureau and has served as a consultant for Alder, Amgen, Allergan, Eli Lilly and Company, Promius, Electrocore and Teva; is on the speaker's bureau for Avanir; has served as a consultant for Impel and AlphaSights; and is a section editor for *Current Pain and Headache Reports (Uncommon Headache Syndromes)*, and Dr Nagy, who provides research support for Alder, ATI, Allergan, Eli Lilly and Company and Teva; is on the advisory board for Alder, Amgen, Eli Lilly and Company, Pernix, Supernus, Teva and Upsher-Smith; is a consultant for Xenon, Zosano and Impel; and is on the speakers' bureau for Amgen, Avanir, Electrocore and Teva.

## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Prior preventive medications amongst onabotA failures.

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