Neurol Ther (2024) 13:339–353
https://doi.org/10.1007/s40120-023-00575-5

ORIGINAL RESEARCH

Eptinezumab Demonstrated Efficacy Regardless of Prior Preventive Migraine Treatment Failure Type: Post Hoc Analyses of the DELIVER Study

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Received: October 27, 2023 / Accepted: December 20, 2023 / Published online: January 18, 2024

ABSTRACT

Introduction: In the DELIVER study, eptinezumab reduced monthly migraine days (MMDs) more than placebo in patients with 2–4 prior preventive migraine treatment failures. This post hoc analysis evaluated the efficacy of eptinezumab across the 24-week placebo-controlled period of the DELIVER study in subgroups defined by prior treatment failure type.

Methods: DELIVER (NCT04418765) randomized adults with migraine to eptinezumab 100 mg, 300 mg, or placebo, administered intravenously every 12 weeks. Changes from baseline in MMDs and percentages of patients with ≥ 50% reduction from baseline in MMDs (≥ 50% migraine responder rates [MRRs]) were summarized in subgroups of patients defined by prior treatment failure type. Subgroups were not mutually exclusive and included patients for whom topiramate, beta blockers (metoprolol, propranolol), amitriptyline, and/or flunarizine had failed.

Results: Across Weeks 1–12 in all subgroups, patients treated with eptinezumab experienced greater reductions from baseline in MMDs than

Prior Presentation: Pozo-Rosich P, Ashina M, Tepper S, et al. Eptinezumab demonstrated efficacy regardless of prior preventive migraine treatment failure: Post hoc DELIVER analyses. *Cephalalgia*. 2023;43(1_suppl):227. doi:https://doi.org/10.1177/03331024231189112. Presented at: IHC 2023; September 14–17, 2023.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40120-023-00575-5.

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those receiving placebo (reductions ranged from 4.5–5.5 vs 1.6–2.4, respectively), with larger reductions over Weeks 13–24. Similarly, ≥ 50% MRRs were consistently higher with eptinezumab than placebo and increased following a second infusion.
Conclusion: In all subgroups, regardless of prior preventive treatment failure type, eptinezumab demonstrated greater reductions in MMDs and higher MRRs compared with placebo.
Trial Registration: ClinicalTrials.gov (Identifier: NCT04418765).

Keywords: Anti-CGRP; Eptinezumab; Migraine; Preventive treatment

Key Summary Points

Why carry out this study?

In patients with migraine, failure of multiple preventive therapies is often required before receiving anti-calcitonin gene-related peptide monoclonal antibody treatment (e.g., eptinezumab); however, guidelines for how many and which therapies must fail vary by country and payor

This study evaluated the efficacy of eptinezumab versus placebo across 24 weeks of treatment in the DELIVER study in patients with migraine and 2–4 prior preventive treatment failures and in subgroups defined by type of prior treatment failure (topiramate, metoprolol/propranolol, amitriptyline, and/or flunarizine)

What was learned from the study?

Regardless of prior preventive treatment failure type, treatment with eptinezumab resulted in greater reduction in monthly migraine days (MMDs) than placebo across 24 weeks of treatment in all subgroups

A larger proportion of patients treated with eptinezumab than with placebo experienced ≥ 50% MMD reduction across all subgroups

Given the differences in preventive migraine treatment guidelines, it is important that the efficacy of eptinezumab does not appear to be impacted by the type or prior preventive medicine that led to treatment failure

INTRODUCTION

Migraine is a prevalent neurological disease [1] that is burdensome and costly [2] to individuals, disabling their participation in society [3]. An unmet need existed for treatment that provides sustained migraine prevention to reduce migraine-related burden, particularly because discontinuation of traditional oral preventive treatments due to lack of efficacy, tolerability, and poor adherence is common [4]. The newer class of monoclonal antibodies (mAbs) targeting calcitonin gene-related peptide (CGRP) provides an additional option in the preventive migraine armamentarium to potentially address this unmet need.

Preventive migraine treatment regulations and guidelines can vary by country and payor; thus, patients with migraine may each have an individualized migraine treatment journey prior to finding effective treatment. In Spain, the Ministry of Health and Spanish Agency of Medicines and Medical Devices reimburses anti-CGRP mAbs to patients who have ≥ 8 headache days per month and who have not responded to three or more preventive treatments (one of which must be onabotulinumtoxinA in the case of chronic migraine) [5–7]. In the UK, the National Institute for Health and Care Excellence recommends at least three preventive migraine treatment failures (i.e., beta blockers, antidepressants, and/or antiepileptics) prior to prescribing an anti-CGRP mAb [8–11]. The French National Authority for Health recommends at least two prior preventive treatment failures, with beta blockers (propranolol and metoprolol) and antiepileptics (topiramate) recommended for first- and second-line treatments, respectively [12, 13]. The Danish Medicines Council recommends anti-CGRP

mAbs for use in chronic migraine if at least one antihypertensive and one antiepileptic medication have failed for a patient [14]. The Canadian Agency for Drugs and Technologies in Health recommends at least two prior preventive treatment failures as well, with more treatment types mentioned as potential preventive treatment options (i.e., beta blockers, tricyclic antidepressants, verapamil or flunarizine, sodium valproate, topiramate, or gabapentin) despite a lack of clinical evidence [15, 16]. In the US, the Institute for Clinical and Economic Review provides guidance of at least two preventive migraine treatment failures from two different classes prior to prescribing anti-CGRP mAbs, with botulinum toxin A as the first-line treatment for chronic migraine and antiepileptics (divalproex sodium, sodium valproate, topiramate) or beta blockers (metoprolol, propranolol, timolol) as the first-line treatment for episodic migraine [17]. Due to the multiple potential lines of therapy before reaching anti-CGRP treatment in current guidelines, it is important to demonstrate consistent effect of anti-CGRP treatment regardless of prior preventive treatment failure type.

Eptinezumab is the most recent anti-CGRP mAb to be indicated for the preventive treatment of migraine in adults in the US, Europe, and other regions [18, 19]. Multiple large-scale phase 3 clinical trials established the efficacy and safety of eptinezumab for migraine prevention, including its rapid and sustained migraine-preventive effects [20–25]. One of these trials, DELIVER, evaluated the efficacy and safety of eptinezumab in patients with 2–4 prior preventive migraine treatment failures [25]. The primary data from the 24-week placebo-controlled period of DELIVER demonstrated reductions in migraine frequency and severity with eptinezumab compared with placebo in this difficult-to-treat population. This post hoc analysis evaluated the efficacy of eptinezumab versus placebo across 24 weeks of treatment in DELIVER subgroups defined by type of prior treatment failure.

METHODS

Study Design

The DELIVER study was a multicenter, parallel-group, double-blind, randomized, placebo-controlled phase 3b clinical study conducted at 96 locations across Europe and the US. The detailed protocol, statistical analysis plan, and patient disposition flow chart have been published [25].

The DELIVER study was conducted in accordance with the standards of Good Clinical Practice as defined by the International Conference on Harmonisation and all applicable federal and local regulations. All study documentation was approved by the local review board at each of the 96 study sites across Europe and the US or by a central institutional review board or ethics committee (Supplementary Materials Appendix 1). All patients provided written informed consent prior to any study procedures. The DELIVER trial is registered on ClinicalTrials.gov (NCT04418765) and EudraCT (2019-004497-25).

Patients

Detailed inclusion and exclusion criteria have been published [25, 26], with key criteria summarized here. Eligible patients, aged 18–75 years, were required to have a history of migraine as defined by International Classification of Headache Disorders (3rd edition) diagnostic criteria for $\geq$ 12 months before screening and onset at or before 50 years of age. Patients had to have documented evidence (medical record or physician confirmation) of 2–4 prior preventive treatment failures due to inadequate efficacy, tolerability, or contraindications within the past 10 years. Prior failure could be with propranolol or metoprolol, topiramate, amitriptyline, flunarizine, candesartan, valproate or divalproex, or botulinum toxins A/B (if taken for chronic migraine). At least one failure had to be due to inadequate efficacy with one of the following medications: propranolol or metoprolol, topiramate, amitriptyline, flunarizine, or candesartan. Patients were

ineligible if they had a treatment failure on a previous treatment targeting the CGRP pathway or had a treatment failure on valproate/divalproex or onabotulinumtoxinA and the treatment was not the most recent preventive medication prior to study inclusion.

Randomization and Treatment

DELIVER randomized adults with migraine to receive eptinezumab 100 mg, 300 mg, or placebo via intravenous infusion at baseline (Day 0) and Week 12. Blinded personnel administered infusions over a period of 30 (up to 45) min.

Data Collection and Outcomes

Patients completed a daily electronic diary, which captured headache episodes, migraine attacks, and headache characteristics, including severity, length, and intake of acute medication. Patients attended four physical visits (screening, baseline, and end of Weeks 12 and 24) and four phone contact visits (end of Weeks 4, 8, 16, and 20). The primary efficacy endpoint in the DELIVER study was the change from baseline in the number of monthly migraine days (MMDs) following the first infusion (Weeks 1–12) [25]. A migraine day was defined using International Headache Society criteria [27]. This post hoc analysis summarizes the changes from baseline in MMDs and the percentages of patients experiencing $\geq$ 50% reduction in MMDs (i.e., $\geq$ 50% migraine responder rates [MRRs]) in subgroups of patients based on prior treatment type.

Statistical Analyses

Sample size and power estimation were not conducted for this post hoc analysis. Data were analyzed for the following subpopulations of patients with treatment failures on: topiramate, beta blockers (metoprolol or propranolol), amitriptyline, and/or flunarizine. Due to the low number of patients, subgroups defined by prior failure on candesartan, valproate or divalproex, and/or botulinum toxin were not analyzed. Patients may have had prior failures across multiple types of treatment; therefore, subgroups are not mutually exclusive.

The estimated mean changes from baseline in MMDs are from a mixed model for repeated measures that included effects for 4-week periods from Weeks 1–4 to 21–24, country, stratification factor (monthly headache days [MHDs] at baseline: $\leq 14/ > 14$), and treatment as factors; baseline MMD score as a continuous covariate; treatment-by-month interaction; baseline score-by-month interaction; and stratum-by-month interaction. Restricted maximum likelihood estimation was used. The $\geq$ 50% MRRs were analyzed using logistic regression. The model included baseline MMDs as a continuous covariate and treatment and stratification (MHDs at baseline: $\leq 14/ > 14$) as factors. *P*-values (two sided) were not controlled for multiplicity and thus are descriptive.

All statistical analyses were conducted using SAS software (SAS Institute, Inc., Cary, NC, USA) v9.4 or later.

RESULTS

The full analysis set comprised 890 patients (eptinezumab 100 mg, $n = 299$; eptinezumab 300 mg, $n = 293$; placebo, $n = 298$). There were 633 (71.1%) patients for whom topiramate had previously failed, 538 (60.4%) for whom beta blockers failed, 508 (57.1%) for whom amitriptyline failed, and 333 (37.4%) for whom flunarizine failed. Demographics by subgroup are reported in Table 1. Patients were predominantly female ($\sim$ 90%), with a mean age of $\sim$ 44 years and 13.7–14.2 mean MMDs at baseline. Rates of comorbid psychiatric (12–14%), vascular/cardiac (11–15%), and nervous system (3–5%) disorders were similar across groups.

Reductions in MMDs were greater with eptinezumab than with placebo in all subgroups (Table 2). Differences from placebo in change from baseline were similar across subgroups. In patients treated with eptinezumab across subgroups, larger differences from placebo in change from baseline were consistently observed following a second infusion (Weeks

Table 1 Demographic characteristics, by prior preventive treatment failure type

	Topiramate (*N* = 633)	Beta blockers (*N* = 538)	Amitriptyline (*N* = 508)	Flunarizine (*N* = 333)
Sex, *n* (%)				
Female	562 (88.8)	488 (90.7)	458 (90.2)	303 (91.0)
Male	71 (11.2)	50 (9.3)	50 (9.8)	30 (9.0)
Age (years), mean (SD)	43.8 (10.7)	43.7 (10.6)	44.0 (10.7)	44.3 (10.8)
Country, *n* (%)				
Poland	163 (25.8)	163 (30.3)	90 (17.7)	170 (51.1)
Czech Republic	207 (32.7)	102 (19.0)	130 (25.6)	22 (6.6)
Georgia	87 (13.7)	140 (26.0)	158 (31.1)	65 (19.5)
East Europe[†]	76 (12.0)	49 (9.1)	41 (8.1)	39 (11.7)
South Europe[†]	69 (10.9)	52 (9.7)	55 (10.8)	26 (7.8)
West Europe[†]	26 (4.1)	28 (5.2)	29 (5.7)	11 (3.3)
USA	5 (0.8)	4 (0.7)	5 (1.0)	0
Comorbid disorders, *n* (%)				
Psychiatric	91 (14.4)	68 (12.6)	64 (12.6)	41 (12.3)
Vascular/cardiac	98 (15.5)	83 (15.4)	69 (13.6)	35 (10.5)
Nervous system	31 (4.9)	27 (5.0)	16 (3.1)	18 (5.4)
Age at current migraine diagnosis (years), mean (SD)	28.7 (12.4)	29.7 (12.3)	30.4 (12.5)	30.4 (11.9)
MMDs at baseline, mean (SD)	13.8 (5.7)	13.7 (5.6)	14.2 (5.5)	13.8 (5.6)
Migraine diagnosis, *n* (%)[‡]				
Chronic migraine	291 (46.0)	240 (44.6)	247 (48.6)	153 (45.9)
Episodic migraine	341 (53.9)	298 (55.4)	260 (51.2)	180 (54.1)
Not applicable	1 (0.2)	0	1 (0.2)	0
MOH diagnosis, *n* (%)[§]	81 (12.8)	72 (13.4)	66 (13.0)	46 (13.8)
Prior treatment failures[¶]				
2	357 (56.4)	288 (53.5)	259 (51.0)	175 (52.6)
3	218 (34.4)	194 (36.1)	199 (39.2)	113 (33.9)
4	57 (9.0)	56 (10.4)	49 (9.6)	45 (13.5)

MHDs monthly headache days, *MMDs* monthly migraine days, *MOH* medication-overuse headache, *SD* standard deviation

[†]East Europe includes Bulgaria, Hungary, Russia, and Slovakia; West Europe includes Germany, Denmark, Finland, and Sweden; South Europe includes Belgium, Spain, France, UK, and Italy

[‡]Based on number of MMDs and MHDs derived using definitions and rules for missing data as specified in the statistical analysis plan

[§]Per International Classification of Headache Disorders, 3rd edition, criteria

[¶]Two patients had fewer than two previous preventive treatment failures and represent protocol deviations: one patient receiving eptinezumab 300 mg had one previous failure on amitriptyline, and one patient receiving placebo had one previous failure on topiramate

Table 2 Change from baseline in monthly migraine days over 12-week intervals, by prior preventive treatment failure type

	Eptinezumab 100 mg	Eptinezumab 300 mg	Placebo
Topiramate			
Weeks 1–12, *n*	207	217	209
LS mean (SD)	− 4.8 (0.44)	− 5.5 (0.43)	− 2.3 (0.43)
Δ placebo, LS mean (95% CI)	− 2.5 (− 3.4, − 1.7)	− 3.3 (− 4.1, − 2.4)	
P-value vs placebo†	< 0.0001	< 0.0001	
Weeks 13–24, *n*	199	213	209
LS mean (SD)	− 5.4 (0.47)	− 6.2 (0.45)	− 2.4 (0.46)
Δ placebo, LS mean (95% CI)	− 3.0 (− 3.9, − 2.0)	− 3.8 (− 4.7, − 2.8)	
P-value vs placebo†	< 0.0001	< 0.0001	
Beta blockers			
Weeks 1–12, *n*	183	164	191
LS mean (SD)	− 4.5 (0.55)	− 5.0 (0.56)	− 1.6 (0.54)
Δ placebo, LS mean (95% CI)	− 2.9 (− 3.8, − 2.0)	− 3.4 (− 4.3, − 2.5)	
P-value vs placebo†	< 0.0001	< 0.0001	
Weeks 13–24, *n*	174	162	189
LS mean (SD)	− 5.0 (0.57)	− 5.9 (0.58)	− 2.0 (0.56)
Δ placebo, LS mean (95% CI)	− 3.0 (− 4.0, − 2.0)	− 3.9 (− 4.9, − 2.9)	
P-value vs placebo†	< 0.0001	< 0.0001	
Amitriptyline			
Weeks 1–12, *n*	159	174	175
LS mean (SD)	− 4.7 (0.51)	− 5.0 (0.48)	− 1.8 (0.50)
Δ placebo, LS mean (95% CI)	− 3.0 (− 3.9, − 2.0)	− 3.2 (− 4.2, − 2.3)	
P-value vs placebo†	< 0.0001	< 0.0001	
Weeks 13–24, *n*	153	169	172
LS mean (SD)	− 5.6 (0.54)	− 6.0 (0.51)	− 2.2 (0.53)
Δ placebo, LS mean (95% CI)	− 3.3 (− 4.4, − 2.3)	− 3.8 (− 4.8, − 2.8)	
P-value vs placebo†	< 0.0001	< 0.0001	
Flunarizine			
Weeks 1–12, *n*	123	101	109
LS mean (SD)	− 5.0 (0.73)	− 5.5 (0.76)	− 2.4 (0.78)
Δ placebo, LS mean (95% CI)	− 2.6 (− 3.7, − 1.4)	− 3.0 (− 4.2, − 1.8)	
P-value vs placebo†	< 0.0001	< 0.0001	

Table 2 continued

	Eptinezumab100 mg	Eptinezumab300 mg	Placebo
Weeks 13–24, *n*	121	97	109
LS mean (SD)	− 5.6 (0.75)	− 6.0 (0.78)	− 2.6 (0.79)
Δ placebo, LS mean (95% CI)	− 3.0 (− 4.2, − 1.8)	− 3.4 (− 4.7, − 2.1)	
P-value vs placebo[†]	< 0.0001	< 0.0001	

The estimated LS means and 95% confidence intervals are from a mixed model for repeated measures with month, country, stratification factor (monthly headache days at baseline: ≤ 14/ > 14), and treatment as factors, baseline score as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction
Δ, difference from [placebo], *CI* confidence interval, *LS* least squares, *SD* standard deviation
[†]Post hoc; not controlled for multiplicity

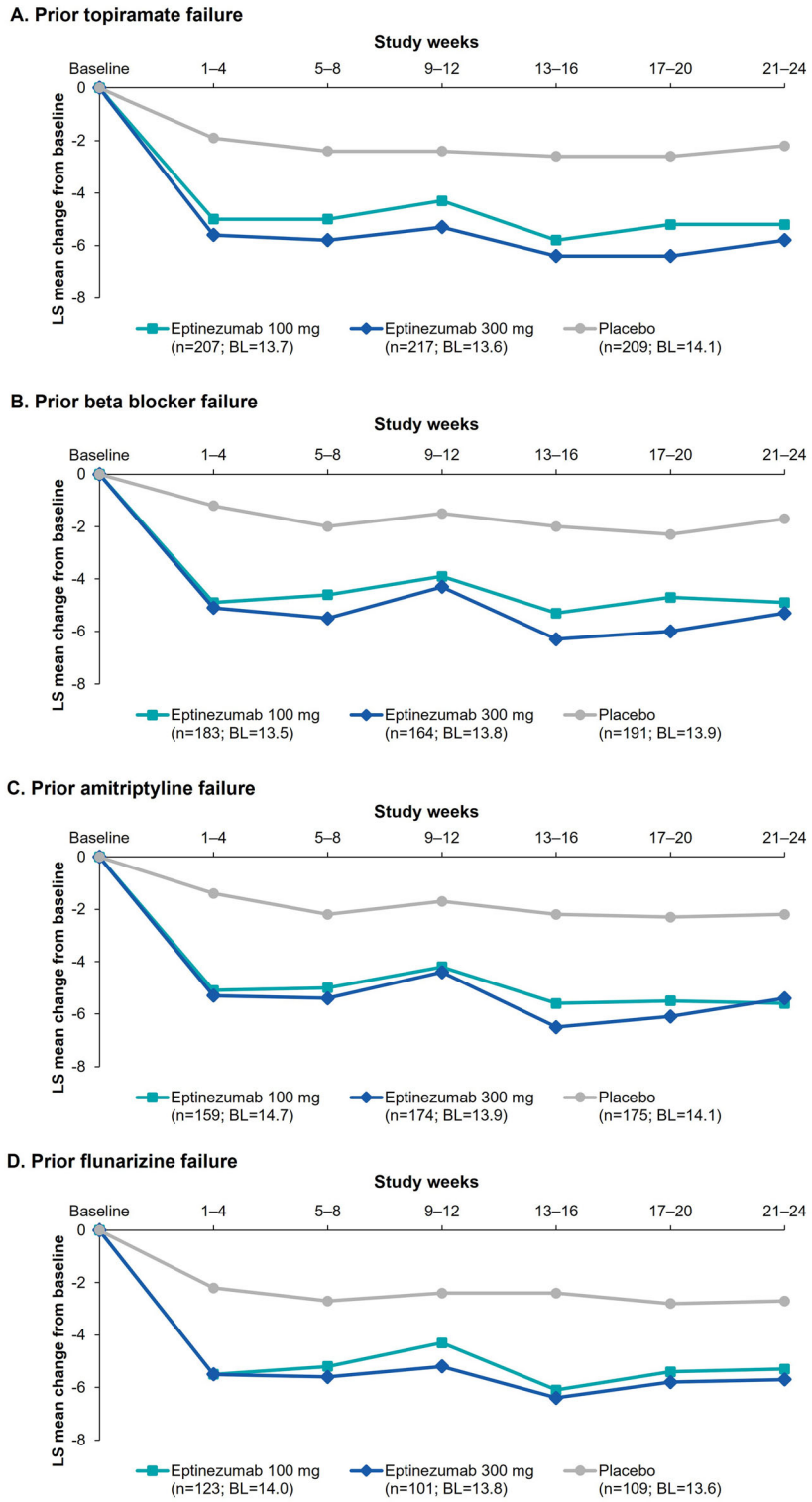
13–24). Greater reductions in MMDs were observed with eptinezumab versus placebo as early as Weeks 1–4 (Fig. 1), with the effect sustained or further improved through the duration of the 24-week treatment period.

Across all subgroups over Weeks 1–12, more than one-third of patients treated with eptinezumab 100 mg and approximately half of patients treated with eptinezumab 300 mg achieved ≥ 50% migraine response compared with < 15% of patients who received placebo (Fig. 2). The proportion of patients achieving ≥ 50% migraine response increased following a second infusion, with more than half of all patients treated with eptinezumab achieving ≥ 50% reduction in MMDs over Weeks 13–24. Similar ≥ 50% MRRs were observed across prior failure subgroups. Across subgroups and time points, both eptinezumab doses had a 3.2–9.4-fold odds of ≥ 50% response compared with placebo (Table 3).

DISCUSSION

Given the differences in preventive migraine treatment regulations and guidelines as described earlier, and that eptinezumab is currently a later-line preventive option in many regions, it is important to understand whether the efficacy of eptinezumab is impacted by failure of earlier-line preventive therapies. In this post hoc analysis of patients with migraine and 2–4 prior preventive migraine treatment failures, eptinezumab reduced MMDs more and resulted in larger ≥ 50% MRRs than placebo regardless of the type of prior treatment failure (i.e., topiramate, beta blockers, amitriptyline, and flunarizine). The efficacy of eptinezumab was further improved with a second dose, as evidenced by larger differences from placebo in change in MMDs and higher rates of ≥ 50% migraine response across all subgroups. Patients who received placebo had a lower treatment effect, as seen in the full analysis set [25] compared to the PROMISE-1 [20] and PROMISE-2 [22] studies, which did not differ between subgroups and which did not substantially improve following a second placebo infusion. Psychiatric, vascular/cardiac, and nervous system disorders were similar across subgroups, suggesting no influence of comorbidities on prior treatment failure type. Together, these results provide post hoc evidence that the efficacy of eptinezumab is not meaningfully affected by the type of treatment that had failed prior to eptinezumab initiation, and that efficacy is sustained across 6 months of treatment.

These results are similar to a post hoc analysis of galcanezumab in a similar population [28], suggesting that across anti-CGRP mAbs, the type of prior treatment failure does not substantially alter the efficacy of anti-CGRP treatment. The post hoc galcanezumab analysis used the CONQUER study population of patients with migraine and 2–4 prior preventive treatment failures, and analysis subgroups for topiramate, amitriptyline, propranolol,


A. Prior topiramate failure
Study weeks
Baseline
1–4
5–8
9–12
13–16
17–20
21–24
0
-2
-4
-6
-8
LS mean change from baseline
Eptinezumab 100 mg (n=207; BL=13.7)
Eptinezumab 300 mg (n=217; BL=13.6)
Placebo (n=209; BL=14.1)
B. Prior beta blocker failure
Study weeks
Baseline
1–4
5–8
9–12
13–16
17–20
21–24
0
-2
-4
-6
-8
LS mean change from baseline
Eptinezumab 100 mg (n=183; BL=13.5)
Eptinezumab 300 mg (n=164; BL=13.8)
Placebo (n=191; BL=13.9)
C. Prior amitriptyline failure
Study weeks
Baseline
1–4
5–8
9–12
13–16
17–20
21–24
0
-2
-4
-6
-8
LS mean change from baseline
Eptinezumab 100 mg (n=159; BL=14.7)
Eptinezumab 300 mg (n=174; BL=13.9)
Placebo (n=175; BL=14.1)
D. Prior flunarizine failure
Study weeks
Baseline
1–4
5–8
9–12
13–16
17–20
21–24
0
-2
-4
-6
-8
LS mean change from baseline
Eptinezumab 100 mg (n=123; BL=14.0)
Eptinezumab 300 mg (n=101; BL=13.8)
Placebo (n=109; BL=13.6)

◀ **Fig. 1** Change from baseline in monthly migraine days over 4-week intervals, by prior preventive treatment failure type. The estimated LS means are from a mixed model repeated measure with month, country, stratification factor (monthly headache days at baseline: ≤ 14/ > 14), and treatment as factors, baseline score as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction. *BL* baseline [mean monthly migraine days], *LS* least squares

metoprolol, valproate or divalproex, and onabotulinumtoxinA [28]; across prior failures, the effect with galcanezumab did not differ substantially. While studies with erenumab (LIBERTY) and fremanezumab (FOCUS) have demonstrated efficacy in patients with 2–4 prior treatment failures, the analyses did not evaluate efficacy across individual prior treatment types [29, 30].

The types of medications that must fail before patients may begin treatment with anti-CGRPs belong to different pharmacological classes, and they often show little efficacy and poor tolerability in treatment of migraine [4, 31, 32]. In a study conducted prior to the approval of anti-CGRP mAbs in 2021, discontinuation of these preventive treatments was common [33]. In the 2013 International Burden of Migraine Study, 41% of patients with chronic migraine discontinued one or more preventive medications [4]. The most common reasons for discontinuation were lack of efficacy (39–48%, depending on treatment class) and side effects (34–53%) [4]. In 2021, the ATTAIN study reported that 28.2% of patients discontinued their preventive medication (antidepressants, antihypertensives, antiepileptics, anticonvulsants, botulinum toxin A/B) without consulting their health care provider within the 6-month follow-up period [33].

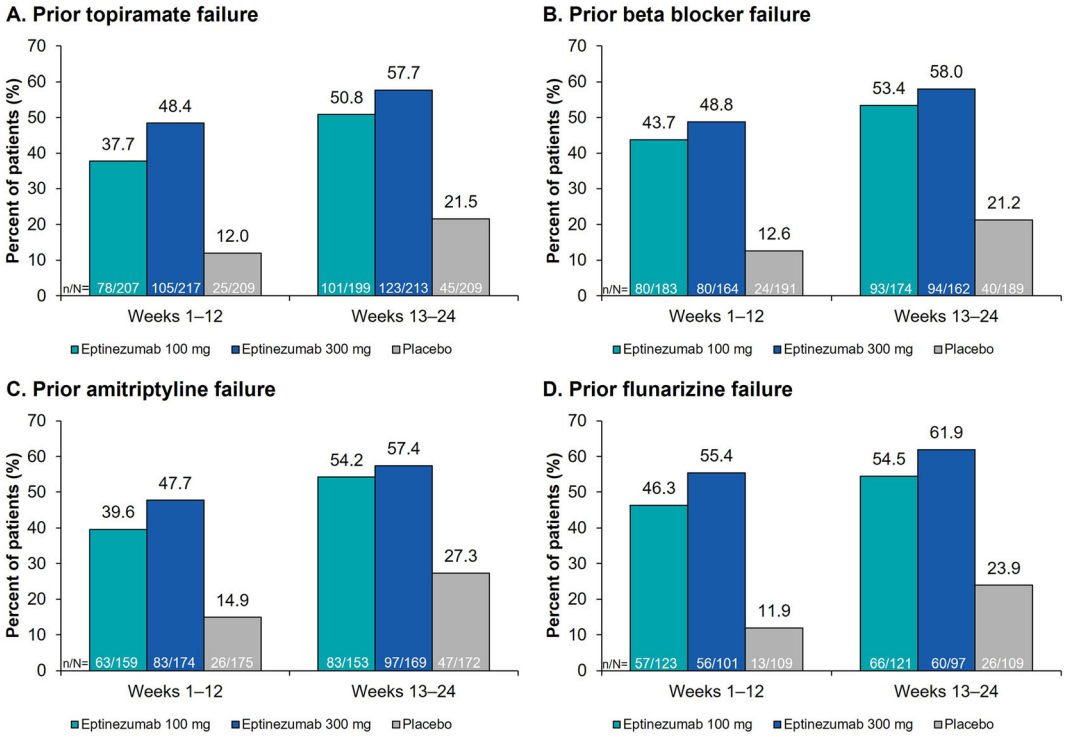


Fig. 2 Migraine responder rates of ≥ 50% over 12-week intervals, by prior preventive treatment failure type. The ≥ 50% response threshold is calculated as the average percentage change in monthly migraine days

Table 3 Odds ratios of ≥ 50% migraine response over 12-week intervals, by prior preventive treatment failure type

	Eptinezumab 100 mg	Eptinezumab 300 mg	Placebo
Topiramate			
Weeks 1–12			
≥ 50% MRR, *n*/*N* (%)	78/207 (37.7)	105/217 (48.4)	25/209 (12.0)
OR vs placebo (95% CI)	4.5 (2.7, 7.5)	6.9 (4.3, 11.6)	
P-value vs placebo†	< 0.0001	< 0.0001	
Weeks 13–24			
≥ 50% MRR, *n*/*N* (%)	101/199 (50.8)	123/213 (57.7)	45/209 (21.5)
OR vs placebo (95% CI)	3.8 (2.5, 5.8)	5.0 (3.3, 7.7)	
P-value vs placebo†	< 0.0001	< 0.0001	
Beta blockers			
Weeks 1–12			
≥ 50% MRR, *n*/*N* (%)	80/183 (43.7)	80/164 (48.8)	24/191 (12.6)
OR vs placebo (95% CI)	5.4 (3.3, 9.2)	6.7 (4.0, 11.5)	
P-value vs placebo†	< 0.0001	< 0.0001	
Weeks 13–24			
≥ 50% MRR, *n*/*N* (%)	93/174 (53.4)	94/162 (58.0)	40/189 (21.2)
OR vs placebo (95% CI)	4.2 (2.7, 6.8)	5.2 (3.3, 8.5)	
P-value vs placebo†	< 0.0001	< 0.0001	
Amitriptyline			
Weeks 1–12			
≥ 50% MRR, *n*/*N* (%)	63/159 (39.6)	83/174 (47.7)	26/175 (14.9)
OR vs placebo (95% CI)	3.9 (2.3, 6.7)	5.3 (3.2, 9.0)	
P-value vs placebo†	< 0.0001	< 0.0001	
Weeks 13–24			
≥ 50% MRR, *n*/*N* (%)	83/153 (54.2)	97/169 (57.4)	47/172 (27.3)
OR vs placebo (95% CI)	3.2 (2.0, 5.2)	3.6 (2.3, 5.7)	
P-value vs placebo†	< 0.0001	< 0.0001	

Table 3 continued

	Eptinezumab 100 mg	Eptinezumab 300 mg	Placebo
Flunarizine			
Weeks 1–12			
≥ 50% MRR, *n*/*N* (%)	57/123 (46.3)	56/101 (55.4)	13/109 (11.9)
OR vs placebo (95% CI)	6.5 (3.4, 13.3)	9.4 (4.8, 19.7)	
P-value vs placebo[†]	< 0.0001	< 0.0001	
Weeks 13–24			
≥ 50% MRR, *n*/*N* (%)	66/121 (54.5)	60/97 (61.9)	26/109 (23.9)
OR vs placebo (95% CI)	4.0 (2.3, 7.2)	5.3 (2.9, 9.9)	
P-value vs placebo[†]	< 0.0001	< 0.0001	

The comparison between treatment groups to placebo is based on a logistic regression model including baseline monthly migraine days as a continuous covariate, and treatment and stratification factor (monthly headache days at baseline: ≤ 14/ > 14) as factors

CI confidence interval, *MRR* migraine responder rate, *OR* odds ratio

[†]Post hoc; not controlled for multiplicity

Prior to anti-CGRP mAbs, no other preventive medications were developed specifically for the preventive treatment of migraine. One potential reason for high discontinuation with traditional oral preventive treatments is that these medications were developed for conditions other than migraine (e.g., onabotulinumtoxinA for pain [34], amitriptyline for depression [35]). The benefits of eptinezumab, regardless of prior preventive medication type that led to treatment failure, together with the lack of rationale and limited efficacy and tolerability of traditional preventive migraine treatments warrant further discussion that the landscape of treatment sequence could be modified and updated.

Limitations

These results are subject to the limitations inherent in post hoc analyses; however, the findings are strengthened by being post hoc analyses of predefined endpoints using predefined methodology. The population of DELIVER comprised predominantly white and female participants, which may limit generalizability to the full migraine population. Because of the range of prior preventive treatment types and prescribing possibilities, dosage and duration of prior preventive medication were considered outside the scope of this manuscript. Additionally, the prior treatment failure subgroups are not mutually exclusive. Subgroups that are independent of each other (i.e., where patients fall into only one category) may lead to different efficacy of anti-CGRP treatment. Analyses did not account for differential lines of therapy within treatment types (i.e., various combinations of prior failures) or time since failure. Candesartan, valproate/divalproex, and onabotulinumtoxinA groups were too small to justify analysis. Patients for whom onabotulinumtoxinA was not the most recent failure were excluded, which may have impacted the inclusion rate. The DELIVER study included a small number of patients with four prior preventive treatment failures (eptinezumab 100 mg, $n = 19$; eptinezumab 300 mg, $n = 14$; placebo, $n = 27$); therefore, differences across number of prior treatment failures were not analyzed [25]. Given regional variations in procedures and treatment sequence requirements as well as differences in access to preventive treatment,

this study may be limited in generalizability to the general migraine population with multiple treatment failures.

CONCLUSIONS

Regardless of prior preventive treatment failure type, treatment with eptinezumab demonstrated greater reductions in migraine frequency and increases in magnitude of response compared with placebo across all subgroups, with reductions sustained through the 24-week treatment period. Differences from placebo in change from baseline increased following a second infusion with both eptinezumab doses across all subgroups, suggesting that a second dose may provide additional benefit.

ACKNOWLEDGEMENTS

The authors thank the participants of the DELIVER study.

Medical Writing, Editorial, and Other Assistance. The authors thank Emily Bolen and Nicole Coolbaugh, CMPP, of The Medicine Group (New Hope, PA, USA), for providing medical writing support and assistance with manuscript preparation in accordance with Good Publication Practice guidelines, which was funded by H. Lundbeck A/S (Copenhagen, Denmark).

Author Contributions. All authors had full access to the study data and take responsibility for the integrity of the data and the accuracy of the data analysis. Patricia Pozo-Rosich, Messoud Ashina, Stewart J. Tepper, Mette Krog Josiassen, and Bjørn Sperling contributed to the conception or design of the study. Sidsel Jensen, Line Pickering Boserup, Mette Krog Josiassen, and Bjørn Sperling contributed to obtaining funding. Patricia Pozo-Rosich and Messoud Ashina were study investigators, contributing to the acquisition of data. Sidsel Jensen and Mette Krog Josiassen conducted statistical analyses, and all authors contributed to the interpretation of data. All authors were involved in drafting the manuscript, and all authors critically revised the manuscript for important intellectual content. All authors provided final approval of the manuscript content for submission and had final responsibility for the decision to submit for publication.

Funding. The study was sponsored and funded by H. Lundbeck A/S, including medical writing support for the development of the manuscript. In collaboration with the academic authors, the sponsor participated in the design and conduct of the study and in the collection, management, analysis, and interpretation of the data. The preparation, review, and approval of the manuscript was undertaken by all authors and by a professional medical writer and editor funded by the sponsor. All authors and H. Lundbeck A/S prepared, reviewed, and approved the final version of the manuscript and made the decision to submit the manuscript for publication. The sponsor did not have the right to veto publication or to control the decision regarding to which journal the manuscript was submitted. H Lundbeck A/S funded publication, including the journal's Rapid Service Fee.

Data Availability. In accordance with EFPIA's and PhRMA's "Principles for Responsible Clinical Trial Data Sharing" guidelines, Lundbeck is committed to responsible sharing of clinical trial data in a manner that is consistent with safeguarding the privacy of patients, respecting the integrity of national regulatory systems, and protecting the intellectual property of the sponsor. The protection of intellectual property ensures continued research and innovation in the pharmaceutical industry. Deidentified data are available to those whose request has been reviewed and approved through an application submitted to https://www.lundbeck.com/global/our-science/clinical-data-sharing.

Declarations

Conflicts of Interest. Patricia Pozo-Rosich reports honoraria as a consultant and participation in the last 3 years in advisory boards for AbbVie, Amgen, Biohaven, Chiesi, Eli Lilly,

Lundbeck, Medscape, Novartis, Pfizer, and Teva Pharmaceuticals; institutional research support from AbbVie, AGAUR, EraNet NEURON, Instituto Investigación Carlos III, International Headache Society, La Caixa Foundation, Novartis, PERIS, RIS3CAT FEDER, and Teva Pharmaceuticals; being a principle investigator for over 50 clinical trials (phases II, III, and IV) for the treatment of migraine and other headaches; education projects with AbbVie, Almirall, Chiesi, Eli Lilly, Lundbeck, Medlink, Medscape, Neurodiem, Novartis, and Teva Pharmaceuticals; participation in the Scientific Advisory Board of Migraine Research Foundation & Lilly Foundation Spain and Honorary Secretary of the International Headache Society; and being an associate editor for *Cephalalgia*, *Headache*, *The Journal of Headache and Pain*, *Neurologia*, and *Frontiers of Neurology*, director for headache section of *Revista de Neurologia*, and editorial advisor for headache section of *Revista de Neurologia*. Messoud Ashina has received personal fees from AbbVie, Amgen, Eli Lilly, GlaxoSmithKline, Lundbeck, Novartis, Pfizer, and Teva Pharmaceuticals during the conduct of the study; has received research support from Lundbeck Foundation, Novo Nordisk Foundation, and Novartis; and has served as associate editor of *Cephalalgia*, associate editor of *The Journal of Headache and Pain*, and associate editor of *Brain*. Stewart J. Tepper reports research funding from Abbvie, Aeon, Axsome, Cassava, Cognition, Eli Lilly, Inhibikase, Lundbeck, Neurolief, Pfizer, PrecisionMed, Suven, and UCB. He acts as a Consultant and/or on Advisory Boards (honoraria) with Aeon, Abbvie, Alphasights, Amgen, Aruene, Atheneum, Axsome Therapeutics, Becker Pharmaceutical Consulting, ClearView Healthcare Partners, ClickTherapeutics, CoolTech, CRG, Decision Resources, Defined Health, DRG, Eli Lilly, ExpertConnect, FCB Health, Fenix, GLG, Guidepoint Global, Health Advances, Health Science Communications, HMP Communications, Impel, Initiatior Pharma, InteractiveForums, Keyquest, Ki Health Partners, Krog and Partners, Lundbeck, M3 Global Research, Magnolia Innovation, MJH Holdings, Miravo Healthcare, Neurofront Therapeutics, Neurolief, Novartis, P Value Communications, Pain Insights, Palion Medical, Pfizer, Pulmatrix, Putnam Associates, Rehaler, SAI MedPartners, Satsuma, Scilex, Slingshot Insights, Spherix Global Insights, Strategy Inc, Synapse Medical Communication, System Analytic, Taylor and Francis, Tegus, Teva, Theranica, Trinity Partners, Unity HA, Vial, and XOC. He received salary from Dartmouth-Hitchcock Medical Center, Thomas Jefferson University, and Ki Health Partners. He serves on the Speakers Bureau for AbbVie, Eli Lilly, Pfizer, Scilex, and Teva. He received certified Continuing Medical Education CME honoraria from the American Academy of Neurology, American Headache Society, Annenberg Center for Health Sciences, Catamount Medical Education, Diamond Headache Clinic, Forefront Collaborative, Haymarket Medical Education, HMP Global, Medical Education Speakers Network, Medical Learning Institute Peerview, Migraine Association of Ireland, Miller Medical Education, National Association for Continuing Education, North American Center for CME, The Ohio State University, Physicians' Education Resource, PlatformQ Education, Primed, Vindico Medical Education, and WebMD/Medscape. Sidsel Jensen, Line Pickering Boserup, Mette Krog Josiassen, and Bjørn Sperling are full-time employees of H. Lundbeck A/S. Sidsel Jensen, Mette Krog Josiassen, and Bjørn Sperling own stock in Lundbeck or one of its subsidiary companies.

Ethical Approval. The study was conducted in accordance with standards of Good Clinical Practice as defined by the International Conference on Harmonisation and all applicable federal and local regulations. The local review board or a central institutional review board/ethics committee approved all study documentation at each of the 96 study sites across Europe and the US (Supplementary Materials Appendix 1). All patients provided written informed consent prior to study participation. DELIVER is registered on ClinicalTrials.gov (NCT04418765) and EudraCT (2019–004497-25).

REFERENCES

1. Ashina M. Migraine. N Engl J Med. 2020;383(19):1866–76.

2. Messali A, Sanderson JC, Blumenfeld AM, Goadsby PJ, Buse DC, Varon SF, et al. Direct and indirect costs of chronic and episodic migraine in the United States: a web-based survey. Headache. 2016;56(2):306–22.

3. Ashina M, Katsarava Z, Do TP, Buse DC, Pozo-Rosich P, Özge A, et al. Migraine: epidemiology and systems of care. Lancet. 2021;397(10283):1485–95.

4. Blumenfeld AM, Bloudek LM, Becker WJ, Buse DC, Varon SF, Maglinte GA, et al. 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. 2013;53(4):644–55.

5. Spanish Ministry of Health Positioning Report: Fremanezumab Therapeutics in Migraine Prophylaxis 2020. Available from: https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/IPT_11-2020-fremanezumab-Ajovy.pdf.

6. Spanish Ministry of Health Positioning Report: Erenumab Therapeutics in Migraine Prophylaxis 2019. Available from: https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/IPT-erenumab-Aimovig.pdf.

7. Spanish Ministry of Health Positioning Report: Galcanezumab Therapeutics in Migraine Prophylaxis 2019. Available from: https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/IPT-galcanezumab-Emgality.pdf.

8. NICE Recommendations: Eptinezumab. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10677.

9. NICE Recommendations: Erenumab. Available from: https://www.nice.org.uk/guidance/TA682/chapter/1-Recommendations.

10. NICE Recommendations: Fremanezumab. Available from: https://www.nice.org.uk/guidance/TA764/chapter/1-Recommendations.

11. NICE Recommendations: Galcanezumab. Available from: https://www.nice.org.uk/guidance/TA659/chapter/1-Recommendations

12. French National Authority for Health—Opinions on Drugs: Galcanezumab (Emgality) 2020. Available from: https://www.has-sante.fr/jcms/p_3191463/en/emgality.

13. French National Authority for Health— Opinions on Drugs: Fremanezumab (Ajovy) 2022. Available from: https://www.has-sante.fr/jcms/p_3367543/en/ajovy-fremanezumab.

14. The Danish Medicines Council's drug recommendation in the case of medicinal products for chronic migraine–inclusion criteria for initiation, follow-up and discontinuation. Medicinradet. 2022;1.3.

15. CADTH Reimbursement Review: Erenumab (Aimovig) 2021. Available from: https://www.cadth.ca/erenumab.

16. CADTH Reimbursement review: fremanezumab (Ajovy) 2021. Available from: https://www.cadth.ca/fremanezumab.

17. ICER Calcitonin Gene-Related Peptide (CGRP) Inhibitors as preventive treatments for patients with episodic or chronic migraine: effectiveness and value final evidence report 2018. Available from: https://icer.org/wp-content/uploads/2020/10/ICER_Migraine_Final_Evidence_Report_070318-1.pdf.

18. (2022) Vyepti [package insert]. Bothell, WA, Lundbeck Seattle BioPharmaceuticals, Inc. 2022.

19. Emergency Medicines Agency Summary of Opinion: Vyepti 2022.

20. Ashina M, Saper J, Cady R, Schaeffler BA, Biondi DM, Hirman J, et al. Eptinezumab in episodic migraine: a randomized, double-blind, placebo-

controlled study (PROMISE-1). Cephalalgia. 2020;40(3):241–54.

21. Smith TR, Spierings ELH, Cady R, Hirman J, Schaeffler B, Shen V, et al. Safety and tolerability of eptinezumab in patients with migraine: a pooled analysis of 5 clinical trials. J Headache Pain. 2021;22(1):16.

22. Lipton RB, Goadsby PJ, Smith J, Schaeffler BA, Biondi DM, Hirman J, et al. Efficacy and safety of eptinezumab in patients with chronic migraine: PROMISE-2. Neurology. 2020;94(13):e1365–77.

23. Silberstein S, Diamond M, Hindiyeh NA, Biondi DM, Cady R, Hirman J, et al. 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. 2020;21(1):120.

24. Kudrow D, Cady RK, Allan B, Pederson SM, Hirman J, Mehta LR, et al. Long-term safety and tolerability of eptinezumab in patients with chronic migraine: a 2-year, open-label, phase 3 trial. BMC Neurol. 2021;21(1):126.

25. Ashina M, Lanteri-Minet M, Pozo-Rosich P, Ettrup A, Christoffersen CL, Josiassen MK, et al. Safety and efficacy of eptinezumab for migraine prevention in patients with two-to-four previous preventive treatment failures (DELIVER): a multi-arm, randomised, double-blind, placebo-controlled, phase 3b trial. Lancet Neurol. 2022;21(7):597–607.

26. Ashina M, Lanteri-Minet M, Ettrup A, Christoffersen CL, Josiassen MK, Phul R, et al. Efficacy and safety of eptinezumab for migraine prevention in patients with prior preventive treatment failures: subgroup analysis of the randomized, placebo-controlled DELIVER study. Cephalalgia. 2023;43(5): 3331024231170807.

27. Tassorelli C, Diener HC, Dodick DW, Silberstein SD, Lipton RB, Ashina M, et al. Guidelines of the International Headache Society for controlled trials of preventive treatment of chronic migraine in adults. Cephalalgia. 2018;38(5):815–32.

28. Kuruppu DK, Tobin J, Dong Y, Aurora SK, Yunes-Medina L, Green AL. Efficacy of galcanezumab in patients with migraine who did not benefit from commonly prescribed preventive treatments. BMC Neurol. 2021;21(1):175.

29. Ferrari MD, Reuter U, Goadsby PJ, Paiva da Silva Lima G, Mondal S, Wen S, et al. Two-year efficacy and safety of erenumab in participants with episodic migraine and 2–4 prior preventive treatment failures: results from the LIBERTY study. J Neurol Neurosurg Psychiatry. 2022;93(3):254–62.

30. Pazdera L, Cohen JM, Ning X, Campos VR, Yang R, Pozo-Rosich P. Fremanezumab for the preventive treatment of migraine: subgroup analysis by number of prior preventive treatments with inadequate response. Cephalalgia. 2021;41(10):1075–88.

31. Lipton RB, Silberstein SD. Episodic and chronic migraine headache: breaking down barriers to optimal treatment and prevention. Headache. 2015;55(Suppl 2):103–22.

32. Hepp Z, Dodick DW, Varon SF, Gillard P, Hansen RN, Devine EB. Adherence to oral migraine-preventive medications among patients with chronic migraine. Cephalalgia. 2015;35(6):478–88.

33. Kawata AK, Shah N, Poon JL, Shaffer S, Sapra S, Wilcox TK, et al. Understanding the migraine treatment landscape prior to the introduction of calcitonin gene-related peptide inhibitors: results from the Assessment of TolerabiliTy and Effectiveness in MigrAINe Patients using Preventive Treatment (ATTAIN) study. Headache. 2021;61(3): 438–54.

34. Do TP, Hvedstrup J, Schytz HW. Botulinum toxin: a review of the mode of action in migraine. Acta Neurol Scand. 2018;137(5):442–51.

35. Guaiana G, Barbui C, Hotopf M. Amitriptyline for depression. Cochrane Database Syst Rev. 2007;18(3): CD004186.