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ORIGINAL RESEARCH

Number Needed to Treat and Cost Per Responder Analysis of Anti-CGRP Monoclonal Antibodies for Migraine Prevention in Adults for Whom Prior Preventive Treatments have Failed

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ABSTRACT

Introduction: Four monoclonal antibodies (mAbs) targeting calcitonin gene-related peptide (CGRP) signaling are approved for migraine prevention and commonly prescribed/reimbursed after the failure of repurposed anti-migraine medications. Participants achieving clinical response [e.g., ≥ 50% monthly migraine days (MMDs) reduction] during an anti-CGRP mAb trial are likely to continue treatment. We calculated number needed to treat (NNT) and quarterly cost per responder (CPR) across four anti-CGRP mAbs.

Methods: Data were from randomized, double-blind, placebo-controlled phase 3b clinical trials that evaluated anti-CGRP mAbs (eptinezumab, fremanezumab, galcanezumab, erenumab) for migraine prevention in adults with episodic or chronic migraine for whom 2–4 prior preventive treatments have failed. NNT was calculated as 1 divided by absolute risk reduction (difference between active treatment and placebo in the proportion of participants with ≥ 50% or ≥ 75% MMD reduction over Weeks 1–12). CPR was calculated by multiplying NNT by the quarterly (3-month) drug acquisition CPR (£), based on the reimbursed list price in the United Kingdom (CPR could not be calculated for eptinezumab 300 mg). Statistical comparisons were not made.

Results: All anti-CGRP mAbs demonstrated higher rates of ≥ 50% and ≥ 75% MMD reduction than their respective placebo ($p < 0.05$). The NNT to achieve ≥ 50% MMD reduction ranged from 2.7 (eptinezumab 300 mg) to 6.0 (erenumab

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140 mg), and for ≥ 75%, 6.0 (eptinezumab 300 mg) to 16.2 (fremanezumab 675 mg/q). The cost per ≥ 50% responder ranged from £4647 (eptinezumab 100 mg) to £7009 (erenumab 140 mg), and for ≥ 75%, £9850 (eptinezumab 100 mg) to £21,862 (fremanezumab 675 mg/q). ***Conclusions***: These results show that, for most anti-CGRP mAbs, a low number of participants (< 10) with migraine need to be treated to achieve one person with a ≥ 50% or ≥ 75% reduction in MMDs over Weeks 1–12, with CPR ranging from £4647 (eptinezumab 100 mg) to £21,862 (fremanezumab 675 mg/q).

Keywords: Anti-CGRP; Eptinezumab; Cost per responder; Migraine; Number needed to treat

Key Summary Points

Why carry out this study?

Four monoclonal antibodies (mAbs) targeting calcitonin gene-related peptide (CGRP) signaling are approved for migraine prevention and are prescribed/reimbursed after failure of repurposed anti-migraine medications.

The number needed to treat (NNT) and cost per responder (CPR) were calculated for each anti-CGRP mAb based on phase 3b trials that included participants for whom 2–4 prior preventive treatments have failed. Given differences in trial design, all data were presented descriptively, with no formal indirect comparison made across treatments.

What was learned from this study?

Anti-CGRP mAbs are an effective preventive migraine treatment, as indicated by the high rates of ≥ 50% or ≥ 75% migraine responders.

The NNT to achieve ≥ 50% ranged from 2.7 for eptinezumab 300 mg to 6.0 for erenumab 140 mg, and the NNT to achieve ≥ 75% ranged from 6.0 for eptinezumab 300 mg to 16.2 for fremanezumab 675 mg/q.

The cost per ≥ 50% responder ranged from £4647 for eptinezumab 100 mg to £7009 for erenumab 140 mg, while the range of cost per ≥ 75% responder was £9850 for eptinezumab 100 mg to £21,862 for fremanezumab 675 mg/q. CPR was not calculated for eptinezumab 300 mg as it is not reimbursed in the UK as of the date of publication.

INTRODUCTION

Migraine is a chronic, disabling neurological disease that affects ~ 1 billion people worldwide [1]. Migraine is associated with substantial clinical and economic burden, both of which increase with disease severity [2, 3]. The path to adequate migraine treatment is not linear, and many people with migraine incur extra costs before receiving optimal therapy for symptom prevention and/or management [4–6]. In a cross-sectional survey across European countries, approximately 75% of respondents saw two or more specialists before receiving an accurate diagnosis [7]. Following diagnosis, a range of 7–67% respondents, depending on country of origin, reported seeking follow-up appointments at a specialized headache center [7]. In the United Kingdom (UK), the percentage of people with migraine receiving follow-up at a headache center was 23% [7]. Notably, 23% of the survey respondents indicated the need for effective treatment as a critical factor for improved quality of life [7]. A treatment is generally considered clinically meaningful if a patient experiences a ≥ 50% or ≥ 75% reduction in monthly migraine/headache days (i.e., ≥ 50% or ≥ 75% response) and/or the number needed to treat (NNT) is < 10 [8–13].

Monoclonal antibodies (mAbs) targeting calcitonin gene-related peptide (CGRP) are a class of migraine-specific preventive treatments that include eptinezumab, fremanezumab, galcanezumab, and erenumab [14]. Anti-CGRP mAbs are commonly prescribed/reimbursed only after failure of repurposed anti-migraine medications, limiting availability to people

living with migraine [15, 16]. Additional barriers to accessing anti-CGRP mAb therapies, as reported by people living with migraine in Europe, include a lack of healthcare coverage and not meeting the reimbursement criteria for use [7]. However, based on their demonstrated efficacy and safety, anti-CGRP mAbs have recently been recommended as first-line treatment options for migraine prevention by the European Headache Federation (EHF) and the American Headache Society (AHS) [9, 14].

Between 2018 and 2020, the use of anti-CGRP mAbs for migraine prophylaxis/prevention increased by an estimated 178%, despite being the most expensive treatment, compared with use of other migraine prophylaxis classes, including antidepressants, anticonvulsants, beta blockers, and angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers [17]. This may be due to the FDA and EMA approval of anti-CGRP mAbs in and around this time period [18–25], and/or because people living with migraine achieving clinical response [e.g., ≥ 50% reduction in monthly migraine days (MMDs)] during an anti-CGRP mAb trial are likely to continue treatment given continued access [26]. While oral medications (such as antidepressants, anticonvulsants, and beta blockers) are the most widely available and used treatments for migraine prevention, they are non-specific and are often associated with poor tolerability [15]. This frequently leads to discontinuation and inadequate disease management with these treatments, with a subsequent negative impact on the personal, social, and economic burden of migraine [15].

In contrast, migraine-specific anti-CGRP mAbs have a well-established efficacy and tolerability compared to repurposed anti-migraine medications, and have been shown to significantly reduce absenteeism and presenteeism in the workplace, the latter representing a large aspect of the migraine economic burden [15, 26, 27]. Additionally, some evidence suggests high levels of adherence and treatment persistence with anti-CGRP mAbs [28], and a decrease in outpatient acute and preventive migraine medication costs, although total costs with anti-CGRP mAbs were increased compared to standard of care [29]. Further, some anti-CGRP mAbs (eptinezumab, erenumab, fremanezumab, and galcanezumab) were found to be cost-effective for people with chronic migraine for whom three or more previous treatments failed [30–32]. Thus, the cost of treatment with anti-CGRP mAbs can be offset by their efficacy, high tolerability, and reduced personal and economic burden [15, 27–32].

Understanding the costs per anti-CGRP mAb treatment responder and absolute effect measure (as assessed by the NNT) of these treatments would better place their clinical effectiveness in an economic context [33, 34]. In the United States (US), for example, treatment costs per person with migraine can average in the tens of thousands of dollars annually and increase with additional previous treatments that fail [35]. The objective of this analysis was to present the NNT and cost per responder (CPR) for anti-CGRP mAbs amongst people with migraine for whom previous oral preventive treatments failed.

METHODS

Data Sources

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. As such, no direct ethical approval or informed consent was required. Data were collected from published randomized, double-blind, placebo-controlled, phase 3b clinical trials that evaluated the safety and efficacy of an anti-CGRP mAb for migraine prevention in adults with episodic migraine (EM) or chronic migraine (CM) for whom 2–4 prior preventive treatments have failed. Trials in this analysis were DELIVER (eptinezumab) [36], FOCUS (fremanezumab) [37], CONQUER (galcanezumab) [38], and LIBERTY (erenumab) [39].

Key aspects of each trial's design and patient population are summarized in Table 1 [36–39]. The DELIVER, FOCUS, and CONQUER trials included participants with EM or CM. The LIBERTY trial included participants with EM only, with or without aura. In DELIVER, participants

Table 1 Summary of anti-CGRP mAb phase 3b clinical trials included in analysis

	DELIVER[36] eptinezumab	FOCUS[37] fremanezumab	CONQUER[38] galcanezumab	LIBERTY[39] erenumab
Trial design	Phase 3b, randomized clinical trial comprising: • 24-week, double-blind, placebo-controlled period • 48-week, dose-blinded, extension period	Phase 3b, randomized clinical trial comprising: • 12-week, double-blind, placebo-controlled period • 12-week, dose-blinded, extension period	Phase 3b, randomized clinical trial comprising: • 12-week, double-blind, placebo-controlled period	Phase 3b, randomized trial comprising: • 12-week, double-blind, placebo-controlled period • 156-week, open-label, extension period
Migraine population	Adults with CM or EM and 2–4 prior preventive treatment failures	Adults with CM or EM and 2–4 prior preventive treatment failures	Adults with CM or EM and 2–4 prior preventive treatment failures	Adults with EM and 2–4 prior preventive treatment failures
Region(s)	• North America (United States) • Europe (Poland, Czech Republic, Georgia, Bulgaria, Slovakia, Spain, France, Germany, United Kingdom, Hungary, Belgium, Finland, Denmark, Russia, Italy, and Sweden)	• North America (United States) • Europe (Belgium, Czech Republic, Denmark, Finland, France, Germany, Italy, Netherlands, Poland, Spain, Sweden, Switzerland, United Kingdom)	• North America (United States and Canada) • Europe (United Kingdom, Hungary, Belgium, France, Spain, Czech Republic, Germany, Netherlands) • Asia (Japan and South Korea)	• Europe (Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Norway, Netherlands, Spain, Sweden, Switzerland, United Kingdom) • Australia
Trial arms	• Eptinezumab 100 mg (n = 299) • Eptinezumab 300 mg (n = 293) • Placebo (n = 298)	• Fremanezumab 225 mg/month (n = 283) • Fremanezumab 675 mg/quarter (n = 276) • Placebo (n = 279)	• Galcanezumab 120 mg (n = 232) • Placebo (n = 230)	• Erenumab 140 mg (n = 121) • Placebo (n = 125)
Mode of administration	Quarterly intravenous infusion	Monthly subcutaneous injection or quarterly subcutaneous injection[a]	Monthly subcutaneous injection[b]	Monthly subcutaneous injection

Table 1 continued

	DELIVER[36] eptinezumab	FOCUS[37] fremanezumab	CONQUER[38] galcanezumab	LIBERTY[39] erenumab
Assessment of ≥ 50% MRR	• Secondary trial outcome • Analyzed over Weeks 1–12	• Secondary trial outcome • Analyzed over Weeks 1–12	• Secondary trial outcome • Analyzed over Weeks 1–12	• Primary trial outcome • Analyzed assessed over Weeks 9–12
Assessment of ≥ 75% MRR	• Secondary trial outcome • Analyzed over Weeks 1–12	• Prespecified exploratory trial outcome • Analyzed over Weeks 1–12	• Secondary trial outcome • Analyzed over Weeks 1–12	• Secondary trial outcome • Analyzed over Weeks 9–12
Sex, % male (*n*/*N*)[c]	• 10% (90/890)	• 16% (138/838)	• 14% (65/462)	• 19% (46/246)
Mean age (years)[d]	• 43.1–44.6	• 45.8–46.8	• 45.7–45.9	• 44.2–44.6
Mean MMDs at baseline[c]	• 13.7–13.9	• 14.1–14.3	• 13.0–13.4	• 9.2–9.3
Mean MHDs at baseline[c]	• 14.4–14.5	• 12.4–12.8 (of at least moderate severity)	• 14.8–15.3	• 10.1
Number of prior preventive treatment failures, % (*n*/*N*)[d]	• Two: 62% (550/890) • Three: 31% (277/890) • Four: 7% (60/890)	• Two: 50% (415/838) • Three: 32% (265/838) • Four: 18% (153/838)	• Two: 58% (269/462) • Three: 30% (139/462) • Four: 10% (46/462)	• Two: 39% (95/246) • Three: 38% (93/246) • Four: 23% (56/246)

CGRP calcitonin gene-related peptide, *CM* chronic migraine, *EM* episodic migraine, *mAb* monoclonal antibody, *MHDs* monthly headache days, *MMDs* monthly migraine days, *MRR* migraine responder rates

[a]In the FOCUS trial, fremanezumab was administered quarterly at a dose of 675 mg (mg/q) or monthly at a dose of 225 mg (mg/m) in participants with episodic migraine, or monthly with a loading dose of 675 mg followed by 225 mg/m in participants with chronic migraine

[b]In the CONQUER trial, participants were administered galcanezumab 120 mg per month (with a 240-mg loading dose administered as two 120-mg injections) for 3 months

[c]Data represent % (*n*/*N*) of participants summed across all arms in the trial. Percentage values may not sum to 100% due to rounding

[d]Data represent the range of mean values (years, MMDs, or MHDs) reported across all arms in the trial

were randomized to treatment with intravenous (IV) eptinezumab 100 mg, eptinezumab 300 mg, or placebo, administered every 12 weeks [36]. In FOCUS, participants were randomized to quarterly fremanezumab (675 mg in Month 1, followed by placebo for Months 2 and 3), monthly fremanezumab (225 mg in EM and 675 mg in CM in Month 1, and 225 mg in both migraine subgroups in Months 2 and 3), or placebo (monthly), administered subcutaneously [37]. In CONQUER, participants were randomized to monthly subcutaneous administration of galcanezumab 120 mg (with a loading dose of 240 mg) or placebo [38]. In LIBERTY, participants were randomized to either erenumab 140 mg or placebo, administered subcutaneously [39]. All trials included a 12-week, randomized, double-blind, placebo-controlled period during which efficacy outcomes of interest were analyzed.

The ≥ 50% and ≥ 75% migraine responder rates (MRRs), defined as the percentage of participants with ≥ 50% or ≥ 75% reduction from baseline in MMD, respectively, were the efficacy outcomes of interest and sourced from primary reports [36–39]. Thresholds of ≥ 50% and ≥ 75% for MRRs were used because they were consistently reported across studies, and because they are considered clinically meaningful outcomes in both clinical trials and real-world settings, with a ≥ 50% response commonly required for continued treatment under reimbursement policies, and a ≥ 75% response considered a more optimal outcome associated with higher treatment satisfaction and improved quality of life [8–11, 40–44]. The ≥ 50% MRR was a primary efficacy endpoint in LIBERTY, a key secondary efficacy endpoint in DELIVER and CONQUER, and a secondary endpoint in FOCUS. The 75% MRR was a key secondary efficacy endpoint in DELIVER and CONQUER, a secondary endpoint in LIBERTY, and a prespecified exploratory endpoint in FOCUS. MRRs were assessed over Weeks 1–12 in all trials except for LIBERTY, in which MRRs were assessed over Weeks 9–12, which was the most comparable timepoint.

MRRs account for within-trial changes from baseline in MMDs, which helps reduce the influence of between-trial differences in baseline MMD levels when comparing treatment effects across trials. However, no formal treatment comparisons (e.g., network meta-analysis or statistical modelling) were conducted. MRRs and subsequent analyses were not adjusted to account for differences between trials that may impact comparisons—e.g., migraine population, timing of MRR analysis, number of treatment arms, route/frequency of administration for trial medication, and distribution of number of prior treatment failures (Table 1)—thus, the results here are intended as a descriptive side-by-side presentation rather than a formal direct comparison.

Outcomes and Analysis Methods

The NNT is an efficacy measure that estimates the number of people who need to be treated to prevent or achieve a desired outcome for one person [45–47]. The lower the NNT, the more effective the treatment [48]. If an NNT value is < 10, this is generally considered a useful indicator that a treatment is likely to provide a meaningful clinical benefit to patients [13, 49, 50]. In this analysis, NNT was calculated as 1 divided by absolute risk reduction (ARR), where ARR was the difference in MRR between active and placebo treatment groups [45]. Calculated values are rounded upward to the nearest integer values in the text and presented as the calculated value in the figures. Here, we calculated the NNT for two desired outcomes, the absolute difference in ≥ 50% or ≥ 75% MRR, between each anti-CGRP mAb treatment group versus their respective trial placebo.

The cost per ≥ 50% responder or ≥ 75% responder was calculated for each anti-CGRP mAb (using the quarterly UK list price from 2023) by multiplying the quarterly costs per year per responder (£) of UK drug acquisition costs by the NNT estimates for ≥ 50% or ≥ 75% MRR, respectively [40–43]. CPR was only calculated for drug doses that were recommended for reimbursement on the National Health Service by the National Institute for Health and Care Excellence (NICE)

in the UK and refers to costs for a 12-week period of treatment [40–43]. The CPR for eptinezumab 300 mg was not calculated in this analysis as this dose is not reimbursed in the UK at the time of publication.

RESULTS

Migraine Responder Rates

All anti-CGRP mAbs demonstrated a larger percentage of participants with ≥ 50% and ≥ 75% MRR than their respective placebo group ($p < 0.05$ for each anti-CGRP mAb vs. the respective placebo) [36–39]. In DELIVER, 42% of participants treated with eptinezumab 100 mg and 49% treated with eptinezumab 300 mg had a ≥ 50% reduction in MMDs, compared with 13% of the placebo group (Fig. 1). In FOCUS, 34% of participants treated with fremanezumab 225 mg/month or 675 mg/quarter had a ≥ 50% MMD reduction versus 9% of those receiving placebo (Fig. 1). Of those treated with galcanezumab 120 mg in CONQUER, 38% had a ≥ 50% reduction in MMDs, compared with 13% of the placebo group (Fig. 1). Finally, in LIBERTY, 30% of participants treated with erenumab 140 mg had a ≥ 50% MMD reduction versus 14% of participants receiving placebo (Fig. 1).

Eptinezumab 100 mg and 300 mg resulted in 16% and 19% of participants, respectively, with a ≥ 75% reduction in MMDs compared to 2% of those receiving placebo (Fig. 2). The percentage of participants with ≥ 75% reduction in MMDs was 12% and 8% with fremanezumab 225 mg/month and 675 mg/quarter, respectively, compared to 2% with placebo (Fig. 2). With galcanezumab 120 mg, 15% of participants had a ≥ 75% reduction in MMDs versus 3% of the placebo group (Fig. 2). Of those treated with erenumab 140 mg versus placebo, 12% versus 4%, respectively, had a ≥ 75% reduction in MMDs (Fig. 2).

Number Needed to Treat

Fewer participants needed to be treated with eptinezumab to achieve clinical response (≥ 50% or ≥ 75% MRR) compared to other anti-CGRP mAbs [36–39]. For the ≥ 50% reduction in MMDs, the NNT values were 3 (calculated value: 2.7) for eptinezumab 300 mg and 4 (3.4) for eptinezumab 100 mg, 4 (3.9 for each) for both fremanezumab doses, 5 (4.1) for galcanezumab 120 mg, and 6 (6.0) for erenumab 140 mg (Fig. 3; Table S1).

For ≥ 75% reduction in MMDs, the NNT values were 6 (6.0) for eptinezumab 300 mg and 8 (7.3) for eptinezumab 100 mg, 10 (9.8) for fremanezumab 225 mg/month and 17 (16.2) for fremanezumab 675 mg/quarter, 9 (8.9) for galcanezumab 120 mg, and 13 (12.9) for erenumab 140 mg (Fig. 4; Table S2).

Cost Per Responder

The CPR was calculated for anti-CGRP mAb therapies that are recommended by NICE and reimbursed in the UK [40–43]; thus, the CPR for eptinezumab 300 mg could not be calculated. Using the published quarterly list price from 2023, the cost per ≥ 50% MRR ranged from £4,647 with eptinezumab 100 mg to £7009 with erenumab 140 mg (Fig. 5; Table S1). The cost per ≥ 75% responder ranged from £9850 with eptinezumab 100 mg to £21,862 with fremanezumab 675 mg/quarter (Fig. 6; Table S2). As the CPR is determined by multiplying the quarterly price and NNT, this high cost per ≥ 75% responder associated with fremanezumab is likely related to the high NNT value, given the similar quarterly prices.

DISCUSSION

Anti-CGRP mAbs are an effective treatment option for migraine prevention, including for people living with migraine for whom previous therapies failed. In the identified trials of anti-CGRP mAbs in adults with EM or CM for whom 2–4 prior preventive treatments have failed,

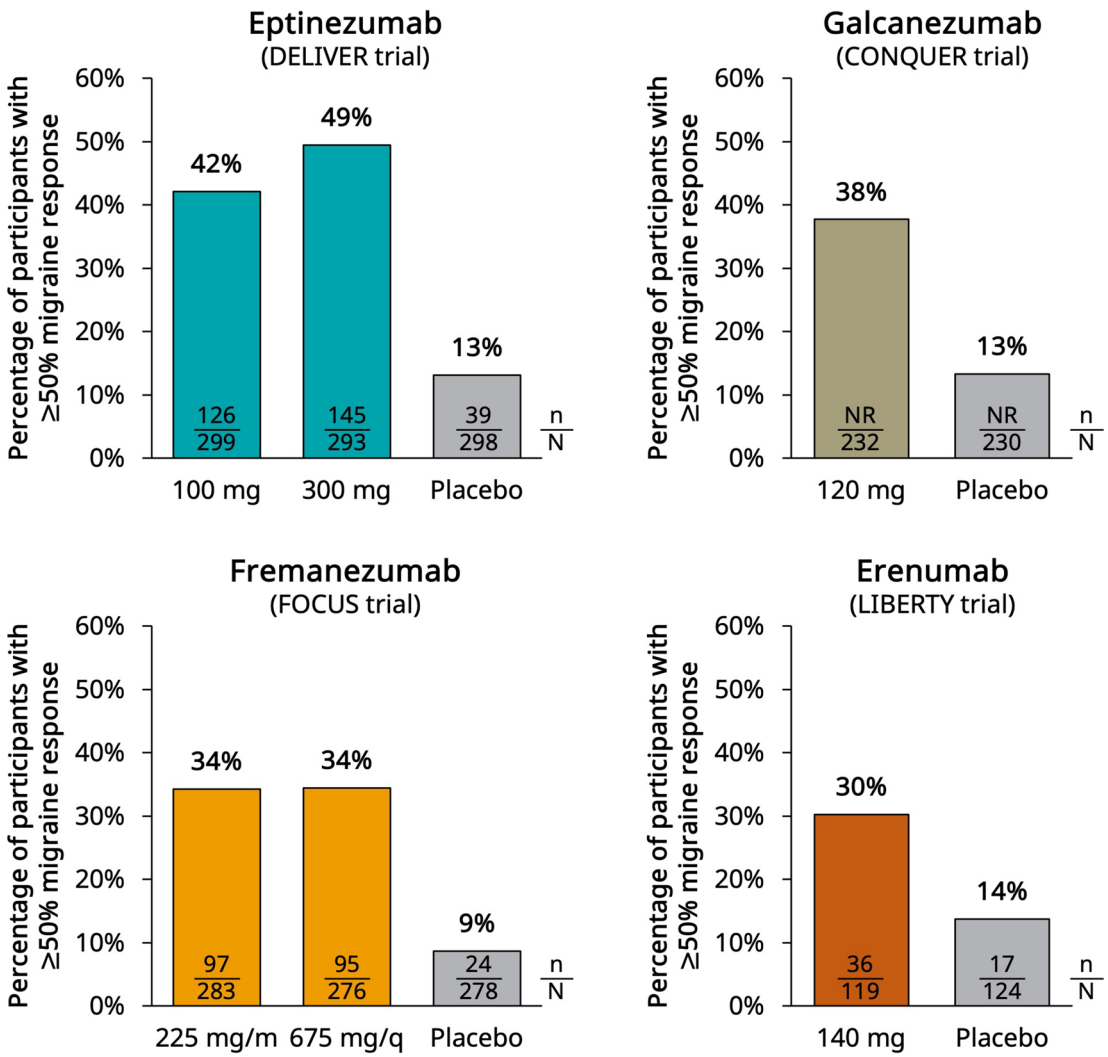

Fig. 1 Migraine responder rates (MRRs) ≥ 50% over Weeks 1–12 or Weeks 9–12 for each anti-CGRP mAb in participants with EM or CM for whom 2–4 prior treatments had failed. MRRs were assessed over Weeks 1–12 in all trials except for LIBERTY, in which they were assessed over Weeks 9–12, the most comparable timepoint; $p < 0.05$ for each anti-CGRP mAb versus each respective placebo. *CGRP* calcitonin gene-related peptide, *CM* chronic migraine, *EM* episodic migraine, *m* month, *mAb* monoclonal antibody, *mg* milligram, *MMD* monthly migraine day, *n* number of participants with ≥ 50% reduction in monthly migraine days, *N* number of participants randomized to indicated trial arm, *NR* value not reported in primary publication, *PBO* placebo, *q* quarter

there was a greater percentage of participants achieving ≥ 50% and ≥ 75% MRRs with any anti-CGRP mAb therapy versus the trial's placebo group [36–39]. This evidence of efficacy of the anti-CGRP mAb class of preventive treatment is supported by recent elevation to first-line therapies for migraine prevention by the EHF and AHS [9, 14].

The NNT values reported here are mostly consistent with previously published NNT values for anti-CGRP mAb treatments in the prevention of migraine [51–53]. In the PROMISE-1 trial for eptinezumab in participants with EM [54], NNT estimates to achieve a ≥ 50% MRR over Weeks 1–12 were 4 for both the eptinezumab 100 mg and 300 mg, with the 75% MRR not reported

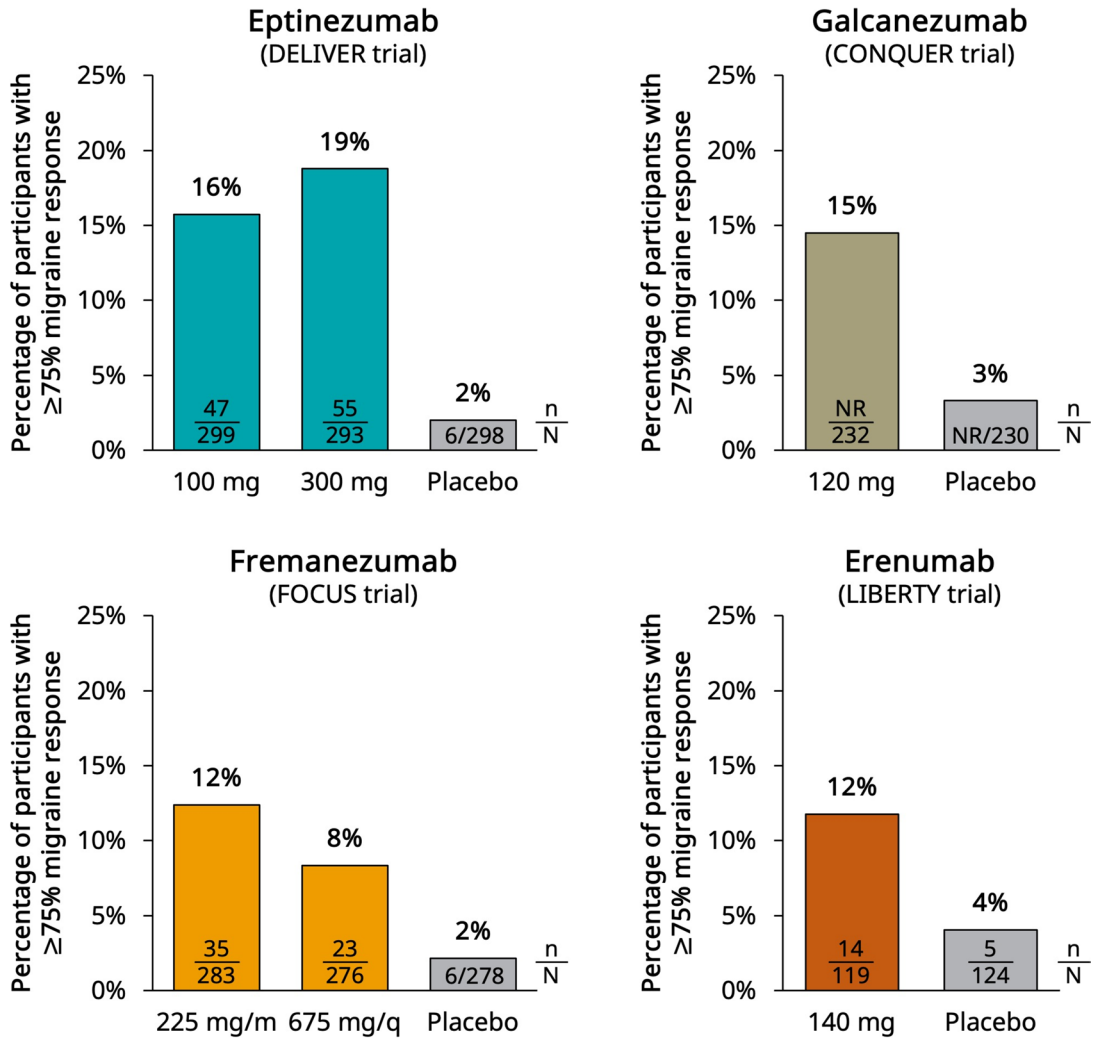

Fig. 2 Migraine responder rates (MRRs) ≥ 75% over Weeks 1–12 or Weeks 9–12 for each anti-CGRP mAb in participants with EM or CM for whom 2–4 prior treatments had failed. MRRs were assessed over Weeks 1–12 in all trials except for LIBERTY, in which they were assessed over Weeks 9–12, the most comparable timepoint; $p < 0.05$ for each anti-CGRP mAb versus each respective placebo. *CGRP* calcitonin gene-related peptide, *CM* chronic migraine, *EM* episodic migraine, *m* month, *mAb* monoclonal antibody, *mg* milligram, *MMD* monthly migraine day, *n* number of participants with ≥ 75% reduction in monthly migraine days, *N* number of participants randomized to indicated trial arm, *NR* value not reported in primary publication, *PBO* placebo, *q* quarter

[55]. In the PROMISE-2 trial in participants with CM [56], over Weeks 1–12, the NNT values were 6 and 5 for ≥ 50% MRR and 9 and 6 for a ≥ 75% MRR for eptinezumab 100 mg and 300 mg, respectively [55]. The NNT to achieve a ≥ 50% or a ≥ 75% response over 3 months for fremanezumab in participants with high-frequency EM were 3 and 6 for 225 mg/month, respectively, and 4 and 13 for 675 mg/month, respectively [55]. For participants with CM, the NNT values were 17 and 25 for fremanezumab 675 mg/quarter, respectively [55]. For galcanezumab, NNT estimates to achieve a ≥ 50% or a ≥ 75% MRR over 3–6 months ranging from 4 to 23 have been reported based on data from four phase 3, randomized, double-blind, placebo-controlled

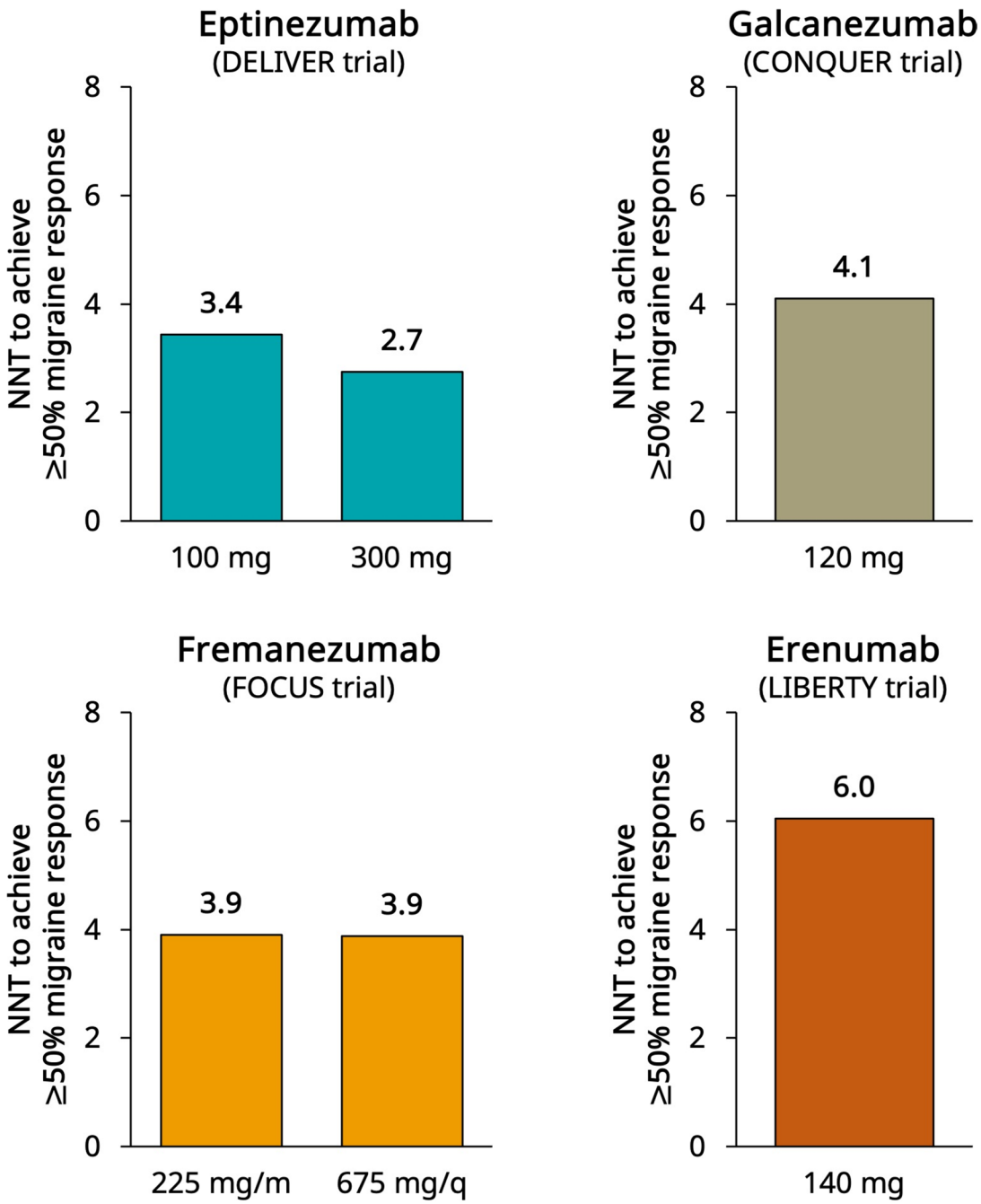

Fig. 3 Number needed to treat (*NNT*) to achieve one person with ≥ 50% migraine response over Weeks 1–12 or Weeks 9–12 for each anti-CGRP mAb in participants with EM or CM for whom 2–4 prior treatments had failed. *CGRP* calcitonin gene-related peptide, *CM* chronic migraine, *EM* episodic migraine, *m* month, *mAb* monoclonal antibody, *mg* milligram, *q* quarter

studies examining the safety and efficacy of 120-mg or 240-mg doses in adults with migraine [12]. Finally, for erenumab (140 mg), NNT values ranging from 4 to 10 have been reported over 3–6 months [57]. An NNT value of < 10 is generally considered a useful predictor regarding

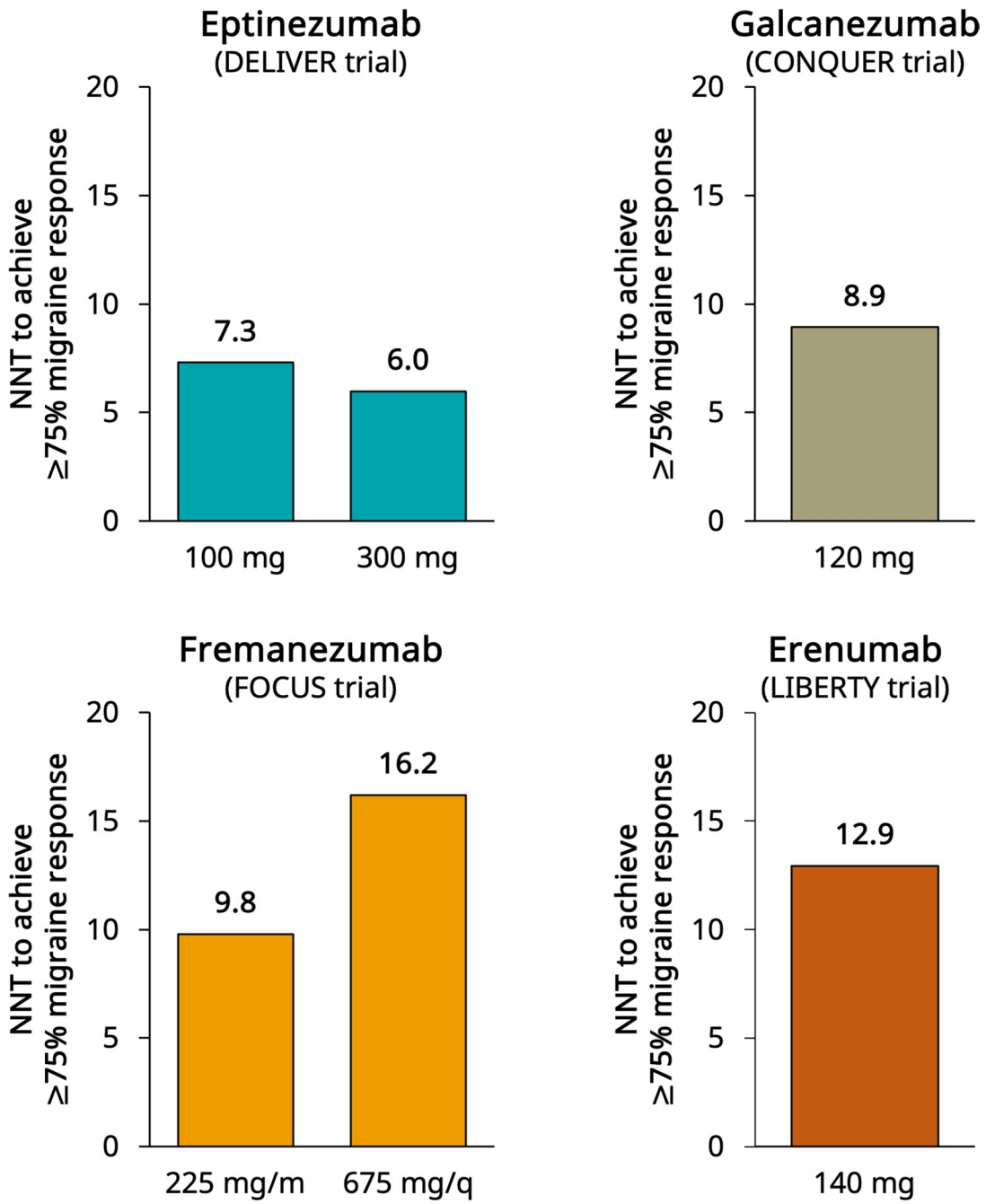

Fig. 4 Number needed to treat (*NNT*) to achieve one person with ≥ 75% migraine response over Weeks 1–12 or Weeks 9–12 for each anti-CGRP mAb in participants with EM or CM for whom 2–4 prior treatments had failed. *CGRP* calcitonin gene-related peptide, *CM* chronic migraine, *EM* episodic migraine, *m* month, *mAb* monoclonal antibody, *mg* milligram, *q* quarter

whether a treatment is likely to have a meaningful clinical benefit for patients [49]. These data suggest that a low NNT (< 10) is a consistent finding across studies evaluating anti-CGRP mAbs, including for people living with migraine for whom prior treatment(s) had failed [12, 49,

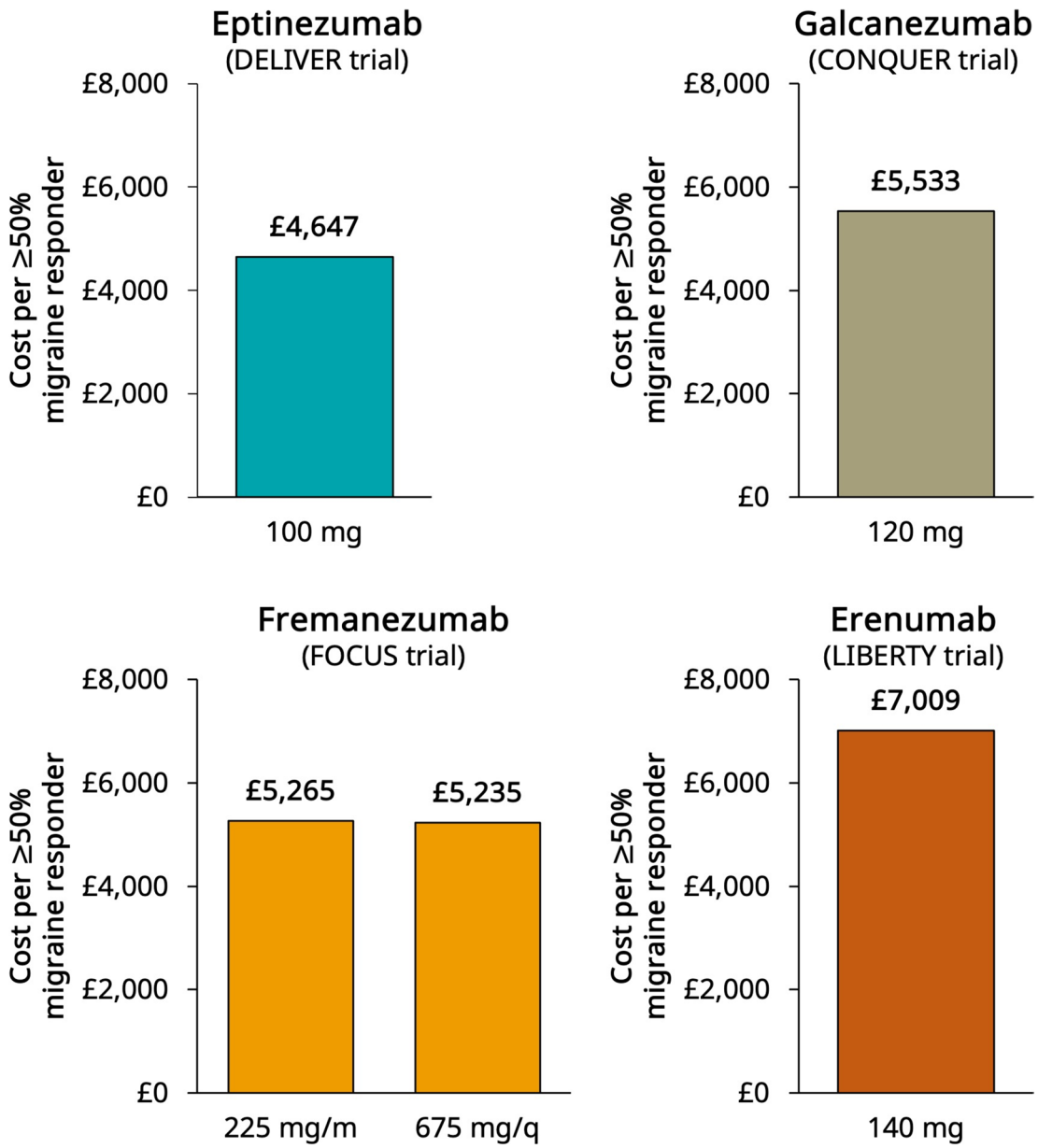

Fig. 5 Quarterly cost per ≥ 50% migraine responder for each anti-CGRP mAb in participants with EM or CM for whom 2–4 prior treatments had failed. Costs per responder were calculated based on 2023 quarterly list prices for drug doses reimbursed in the UK. As of the date of publication, eptinezumab 300 mg is not reimbursed in the UK and was thus not included in this analysis. *CGRP* calcitonin gene-related peptide, *CM* chronic migraine, *EM* episodic migraine, *m* month, *mAb* monoclonal antibody, *mg* milligram, *q* quarter, *UK* United Kingdom

51, 54–57]. In a benefit–risk analysis of data from phase 3 randomized-controlled trials for all anti-CGRP mAbs and other migraine preventive drugs, including topiramate, propranolol, and onabotulinumtoxinA, in participants with CM or EM, the NNT to achieve ≥ 50% MRR suggested greater efficacy of anti-CGRP mAbs over other migraine prophylactics [51].

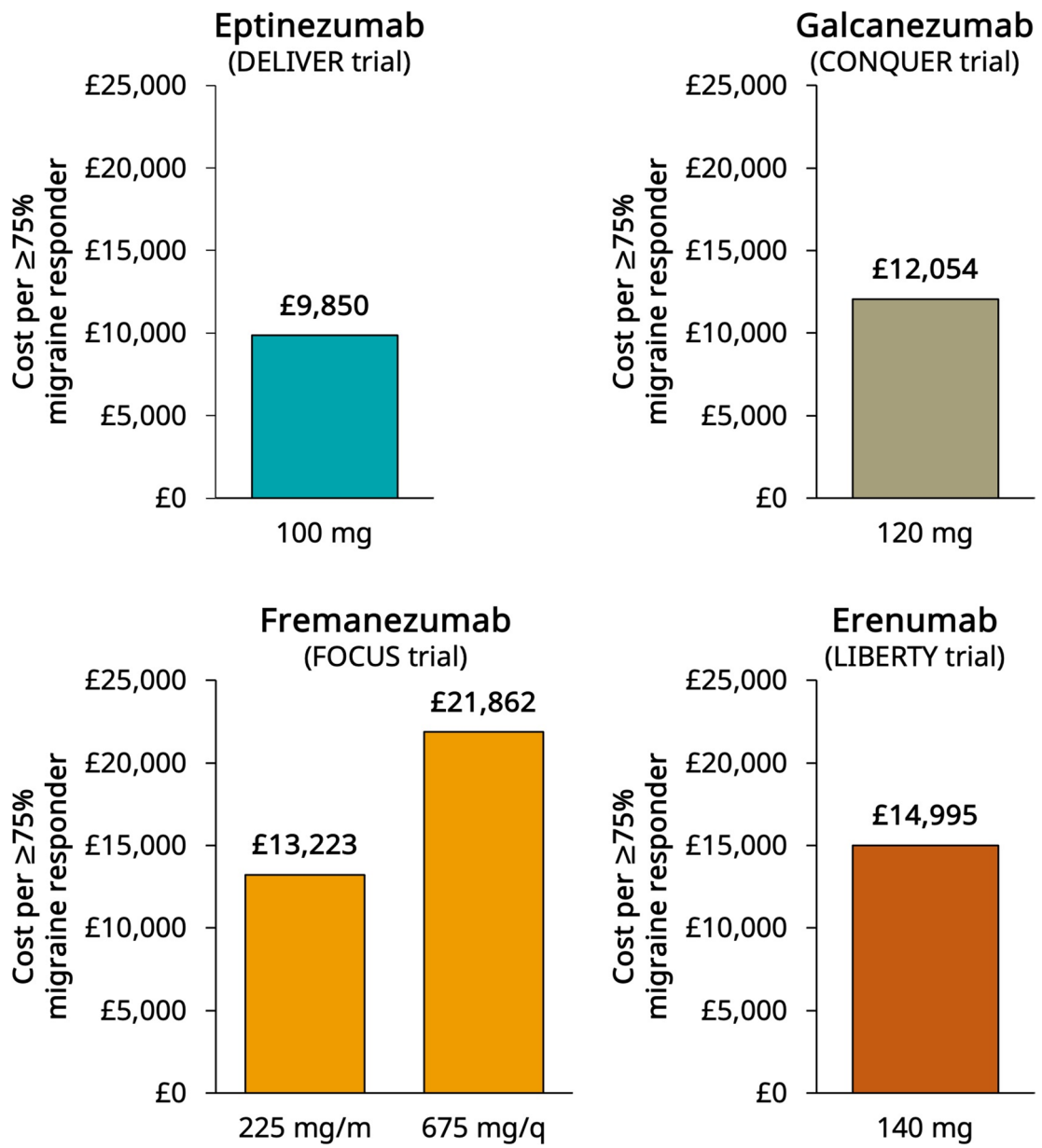

Fig. 6 Quarterly cost per ≥ 75% migraine responder for each anti-CGRP mAb in participants with EM or CM for whom 2–4 prior treatments had failed. Costs per responder were calculated based on the 2023 quarterly list price for drug doses reimbursed in the UK. As of the date of publication, eptinezumab 300 mg is not reimbursed in the UK and was thus not included in this analysis. *CGRP* calcitonin-related gene peptide, *CM* chronic migraine, *EM* episodic migraine, *m* month, *mAb* monoclonal antibody, *mg* milligram, *q* quarter, *UK* United Kingdom

The choice of an anti-CGRP mAb for migraine prevention should consider both clinical effectiveness and economic factors to optimize treatment outcomes [26]. Evaluating the CPR provides insights into the economic implications of anti-CGRP mAb treatments, with potential cost savings depending on the specific drug and its pricing.

Limitations

The results of this study must be interpreted cautiously. Although the trials include comparable populations and participants who are currently considered eligible for reimbursable real-world treatment with an anti-CGRP mAb, key differences in their design preclude statistical comparison between trial outcomes—e.g., migraine population (both EM and CM or CM only), timing of MRR analysis (Weeks 1–12 or Weeks 9–12), number of treatment arms (2 or 3), route/frequency of administration for trial medication (monthly or quarterly; subcutaneously or IV), and distribution of number of prior treatment failures (Table 1) [36–39]. Indeed, while NNT is considered an intuitive measure to understand the efficacy of an intervention, the treatment-specific odds ratios derived from a meta-analysis or directly taken from an individual study must be applied to the same reference response probability to understand the efficacy of an intervention [58]. Importantly, it was not the goal of this work to make formal statistical comparisons between efficacy outcomes from each trial, but instead to present the calculated NNT and CPR for the four anti-CGRP mAb therapies side-by-side descriptively.

In the LIBERTY trial, only participants with EM were included, and MRRs were reported for Weeks 9–12 only, as this was the only comparable time point [39]. In all other trials, participants with EM or CM were included and MRRs were analyzed over Weeks 1–12 [36–38]. The CPR analyses presented here are based solely on drug doses that are approved for use and reimbursed in the UK using the quarterly list prices (Table S3); thus, the CPR for eptinezumab 300 mg could not be calculated. Eptinezumab 300 mg was included in MRR and NNT analyses as it is approved and reimbursed in other countries (e.g., the US) [36]. Additionally, the CPR analyses do not include infusion center costs for eptinezumab nor the loading dose for galcanezumab, and it is possible that these elements may contribute to a higher real-world CPR. Further costs, such as costs associated with the first administration of subcutaneous drugs (e.g., administration by a health care provider in a facility), have also not been included and costs related to people unable to self-administer subcutaneous treatments were not accounted for within this study. NNT was calculated based on clinical trial data which may present lower NNT values as better results are often observed in real-world studies [59–61]. Finally, in the UK, the reimbursed population consists of people for whom ≥ 3 prior treatments failed, which were not analyzed here. It is also important to note that the calculations for CPR in this study used the UK list price for each anti-CGRP mAb, but the real-world CPR may be lower due to confidential discounts available in the UK. However, when taking into account administration costs, dosage, price per dose, and commercial arrangements for all treatments, the total cost associated with eptinezumab 100 mg every 12 weeks has been reported to be similar to, or lower than, that with erenumab (140 mg 4-weekly), fremanezumab (225 mg monthly or 675 mg 3-monthly), or galcanezumab (120 mg monthly after a 240-mg initial loading dose) [40–43].

Although safety is another important consideration in the selection of preventive migraine treatment, number needed to harm (NNH) was not analyzed here; however, all anti-CGRP mAbs have demonstrated comparable safety profiles to placebo, with no serious safety concerns [36–39, 62]. Based on post-marketing surveillance and pooled analyses of clinical trial data, adverse advents associated with anti-CGRP mAbs include hypertension and severe constipation (erenumab 140 mg), increased risk of infections [particularly eptinezumab at higher doses (NNH = 24) and galcanezumab at clinically used doses (NNH = 77)], and injection-site reactions (galcanezumab 120 mg, erenumab 140 mg, and monthly/quarterly fremanezumab) [63–66].

CONCLUSION

This analysis of participants with either EM or CM for whom 2–4 prior preventive treatments have failed identified that, for a large majority of the anti-CGRP mAbs, a low number of participants (< 10) is needed to be treated in order to achieve one person with a ≥ 50%

or ≥ 75% reduction in MMDs over Weeks 1–12, with the CPR ranging from £4647 with eptinezumab 100 mg (the only dose analyzed for CPR in this study since eptinezumab 300 mg is not reimbursed in the UK as of the date of publication) to £21,862 with fremanezumab 675 mg/q. Given differences in trial design between the anti-CGRP mAb clinical trials, these descriptive side-by-side analyses cannot be used for indirect comparison.

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Declarations

Conflict of Interest. Dimos D. Mitsikostas has received consulting fees from AstraZeneca, Bristol Mayers Squibb, Eli Lilly, Lundbeck, Novartis, Pfizer, Roche, and Teva; payment or honoraria for presentations from Allergan/AbbVie, AstraZeneca, Bristol Mayers Squibb, Eli Lilly, Genesis Pharma, Lundbeck, Merck, Novartis, Roche, and Teva; support for attending meetings or travel from Allergan/AbbVie, Eli Lilly, Genesis Pharma, Lundbeck, Novartis, and Teva; has performed clinical trials as Principal Investigator for Amgen, Eli Lily, Lundbeck, Novartis, and Pfizer; is the member of the Management Group of Headache Scientific Panel and of Coordinating Panel for Functional Disorder at European Academy of Neurology; and is the president of Hellenic Headache Society. Susanne F. Awad, Rikke Kongerslev, Line Pickering Boserup, and Ravinder Phul are full-time employees of H. Lundbeck A/S or one of its subsidiary companies. Xin Ying Lee was a full-time employee of H. Lundbeck A/S during data analysis and initial manuscript stages. She is currently an employee of Novo Nordisk, which was not involved in nor has competing interest with this study. Simona Sacco has received grants or contracts from Novartis and Uriach; has received consulting fees and payment or honoraria for presentations from Abbot, Allergan/AbbVie, AstraZeneca, Eli Lilly, Lundbeck, Novartis, Novo Nordisk, and Pfizer; support for attending meetings or travel from Eli Lilly, Lundbeck, Novartis, and Teva; equipment or services from Allergan/AbbVie and Novo Nordisk; is the second vice-president for European Headache Federation;

and is the president-elect for European Stroke Organization.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. As such, no direct ethical approval or informed consent was required.

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