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Two-year efficacy and safety of erenumab in participants with episodic migraine and 2–4 prior preventive treatment failures: results from the LIBERTY study

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ABSTRACT

Objective To evaluate individual and group long-term efficacy and safety of erenumab in individuals with episodic migraine (EM) for whom 2–4 prior preventatives had failed.

Methods Participants completing the 12-week double-blind treatment phase (DBTP) of the LIBERTY study could continue into an open-label extension phase (OLEP) receiving erenumab 140 mg monthly for up to 3 years. Main outcomes assessed at week 112 were: ≥50%, ≥75% and 100% reduction in monthly migraine days (MMD) as group responder rate and individual responder rates, MMD change from baseline, safety and tolerability.

Results Overall 240/246 (97.6%) entered the OLEP (118 continuing erenumab, 122 switching from placebo). In total 181/240 (75.4%) reached 112 weeks, 24.6% discontinued, mainly due to lack of efficacy (44.0%), participant decision (37.0%) and adverse events (AEs; 12.0%). The ≥50% responder rate was 57.2% (99/173) at 112 weeks. Of ≥50% responders at the end of the DBTP, 36/52 (69.2%) remained responders at ≥50% and 22/52 (42.3%) at >80% of visits. Of the non-responders at the end of the DBTP, 60/185 (32.4%) converted to ≥50% responders in at least half the visits and 24/185 (13.0%) converted to ≥50% responders in >80% of visits. Change from baseline at 112 weeks in mean (SD) MMD was −4.2 (5.0) days. Common AEs (≥10%) were nasopharyngitis, influenza and back pain.

Conclusions Efficacy was sustained over 112 weeks in individuals with difficult-to-treat EM for whom 2–4 prior migraine preventives had failed. Erenumab treatment was safe and well tolerated, in-line with previous studies.

Trial registration number NCT03096834

INTRODUCTION

Migraine is a common, highly disabling, episodic or chronic neurovascular headache disorder that remains undertreated.[1 2] Although treatments for acute attack have greatly improved over the last decades, they provide full relief in fewer than half of patients.[3] The current non-calcitonin gene-related peptide (CGRP) oral preventive medicines were not designed for migraine, do not provide improvement for many patients, and are associated with poor tolerability.[3] Adherence is also consequently poor.[4]

Erenumab is a fully human, potent, selective monoclonal antibody that targets and blocks the canonical CGRP receptor.[5] Clinical trials have demonstrated the preventive efficacy and good tolerability of erenumab in episodic migraine (EM)[6–8] and chronic migraine (CM).[9–11] The long-term efficacy, tolerability and safety of erenumab in patients for whom <2 prior migraine prophylactic medications had failed over 1 year in EM[7] and CM,[11] and over 5 years in EM[12] have been reported. Post hoc analysis suggests that erenumab may also be effective in individuals with difficult-to-treat migraine for whom multiple preventive treatments have failed.[13–15] The 12-week randomised, double-blind, placebo-controlled LIBERTY study confirmed the efficacy and safety of monthly erenumab 140 mg in individuals with EM for whom 2–4 prior preventive treatments had failed.[16] Subsequent follow-up demonstrated that efficacy was maintained throughout the first year of the open label extension phase (OLEP).[17] Efficacy of erenumab on the functional outcomes at 12 Weeks have been published previously.[18] This study addresses the interim results of the 2-year efficacy, safety and tolerability follow-up in 240 LIBERTY participants who completed the placebo-controlled, double-blind treatment phase (DBTP) and entered an ongoing 3-year OLEP with monthly erenumab 140 mg. The data were presented in an abstract form at the 62nd Annual Scientific Meeting of the American Headache Society.[19]

METHODS

Study design

LIBERTY (NCT03096834) was a multicentre, randomised, double-blind, placebo-controlled, parallel-group, phase 3b study conducted across Europe and Australia in participants with EM for whom 2–4 prior preventive treatments had failed.

The study design and other details of LIBERTY study have been reported previously.[16–18] In brief, the study was conducted in five phases: screening (2 weeks), baseline period (4 weeks), a DBTP (12 weeks), an ongoing OLEP (156 weeks) and a safety follow-up (12 weeks). The DBTP baseline is referred to as 'baseline' in this manuscript. Participants were

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initially randomised (1:1) to subcutaneous erenumab 140 mg (given as two 70 mg injections) or placebo once every 4 weeks for 12 weeks. Participants completing the DBTP could enrol in an ongoing 3-year OLEP, in which all participants received erenumab 140 mg monotherapy. Other preventive comedications were not permitted.

Study participants

Inclusion and exclusion criteria for the study have been described previously.[16–18] Adults ≤65 years of age with a documented history of migraine (with or without aura) according to the International Classification of Headache Disorders third Edition (beta version)[20] for ≥12 months, a diagnosis of EM (4–14 migraine days per month) over the past 3 months and <15 days/month of headache symptoms could enrol in this study. Other prerequisites for inclusion were[1] failed 2–4 prior prophylactic treatments with amitriptyline, candesartan, flunarizine, lisinopril, propranolol or metoprolol, topiramate, valproate or divalproex, venlafaxine or other locally approved preventives[2]; failed one treatment and failed or considered unsuitable for a secondary preventive treatment with propranolol or metoprolol, topiramate or flunarizine; and[3] failed or considered unsuitable for treatment with valproate or divalproex.[16–18]

'Efficacy failure' was defined as having no meaningful reduction in headache frequency after administration of the respective medication for an adequate period at therapeutic doses based on the investigator's assessment within the last 5 years prior to screening. 'Tolerability failure' was documented as discontinuation due to adverse events (AEs) at any time. 'Not suitable' was defined as unsuitable for treatment due to contraindications or precautions or other medically relevant reasons, as confirmed by the treating doctor.[16–18]

Participants were excluded if they met the following criteria: at least 50 years of age at migraine onset, history of cluster headache or hemiplegic migraine headache, hypersensitivity or previous exposure to erenumab, previous treatment with products targeting the CGRP pathway or botulinum toxin A treatment in the head or neck region within the 4 months before initiation/during the baseline phase. Participants who were pregnant or nursing, history of seizure; major psychiatric disorders, active chronic pain syndrome, current diagnosis of ECG abnormalities, hepatic disease, malignancy within the last 5 years or a history of cerebrovascular or cardiovascular disease/surgery within the year prior to screening, and those with medication overuse for any indication in the month before/during the baseline phase were also excluded.[16–18] Detailed inclusion/exclusion criteria have been provided in online supplemental appendix 2.

Outcome measures

Efficacy outcomes assessed at Week 112 of the OLEP included the proportion of participants achieving ≥50%, ≥75% and 100% reduction from DBTP baseline in monthly migraine days (MMDs); change from baseline in MMD, Headache Impact Test (HIT-6) score, and Migraine Physical Function Impact Diary (MPFID) everyday activities (EA) and physical impairment (PI). Achievement of a ≥50% reduction in MMDs or 50% responder rate was defined as achievement of at least a 50% reduction in MMDs from individual baseline.[16]

Individual ≥50% response to erenumab therapy to week 112 of the OLEP is presented using heat maps, where fluctuations in individual ≥50% MMD reduction response are visualised over time. In each column, the response status of each participant is presented at each visit across the entire study until week 112. After reaching the initial ≥50% response threshold, a <40% response versus baseline was always considered non-responder. To accommodate for small fluctuations in response, an MMD reduction between 40% and 50% was acceptable and the participant was considered as a ≥50% responder for that visit if the response at the next visit was ≥50% once more. A participant with a <50% response at two consecutive visits was considered a non-responder for both periods. For instance, if a participant had a 55% reduction at week 12 and they were considered a responder; at week 16, if the MMD reduction compared with baseline had dropped to 44%, this participant would still be considered a responder for that period if the reduction had reverted to ≥50% by week 20. If, however, the participant had a <50% reduction (ie, a <50% reduction for two consecutive 4-week periods), they would be considered a non-responder over both periods.

Safety was evaluated by monitoring AEs, vital signs, changes in laboratory evaluations, and electrocardiograms.[16 17] The Medical Dictionary for Regulatory Activities V.22.1 (21)[21] was used to code treatment-emergent AEs (TEAEs).[16 17] AEs were graded according to severity based on the Common Terminology Criteria for Adverse Events system, V.4.03.[16 17 22]

Statistical analysis

Statistical analyses used in the OLEP have been presented previously for the 64 weeks data.[17] Participants receiving at least one dose of erenumab during the OLEP were included in the open-label analysis set. Descriptive statistics were used to summarise continuous endpoints by each treatment group at each visit and the number and percentage of participants were used for categorical endpoints.[17] Participants with missing MMD data were imputed as non-responders. Multiplicity adjustment was not performed in this study.[18]

AEs were evaluated as frequency and exposure-adjusted participant incidence rates.[16 17]

RESULTS

Demographic and disease characteristics

Of the 246 participants randomised to receive erenumab (n=121) or placebo (n=125), 240 (97.6%) completed the 12-week DBTP of the LIBERTY study and were enrolled in the OLEP. In each arm, three participants discontinued and did not enter the OLEP (figure 1).[16] In total, 118 participants continued on erenumab, and 122 switched from placebo to erenumab. Of these, 181/240 (75.4%) reached 112 weeks of the OLEP.

Overall, 59/240 (24.6%) participants discontinued the OLEP at the time of the planned interim analysis at week 112: 27/118 (22.9%) participants from the erenumab group and 32/122 (26.2%) previously on placebo. Of the 59 participants who discontinued the OLEP, the main reasons for discontinuation were lack of efficacy in 26/59 (44.0%), participant's decision in 22/59 (37.0%), AEs in 7/59 (12.0%), new therapy for study indication (migraine OR migraine prophylaxis) in 2/59 (3.4%), and pregnancy and physician decision in 1/59 (1.7%) each. Of these participants, 36/59 (61.0%) entered the 12-week safety follow-up, of which 34/36 (94.0%) completed follow-up. The reasons for the two discontinuations at this stage were new therapy for study indication (migraine OR migraine prophylaxis) and participant decision (figure 1).

Baseline demographic and disease characteristics were well-balanced across both treatment groups (those continuing

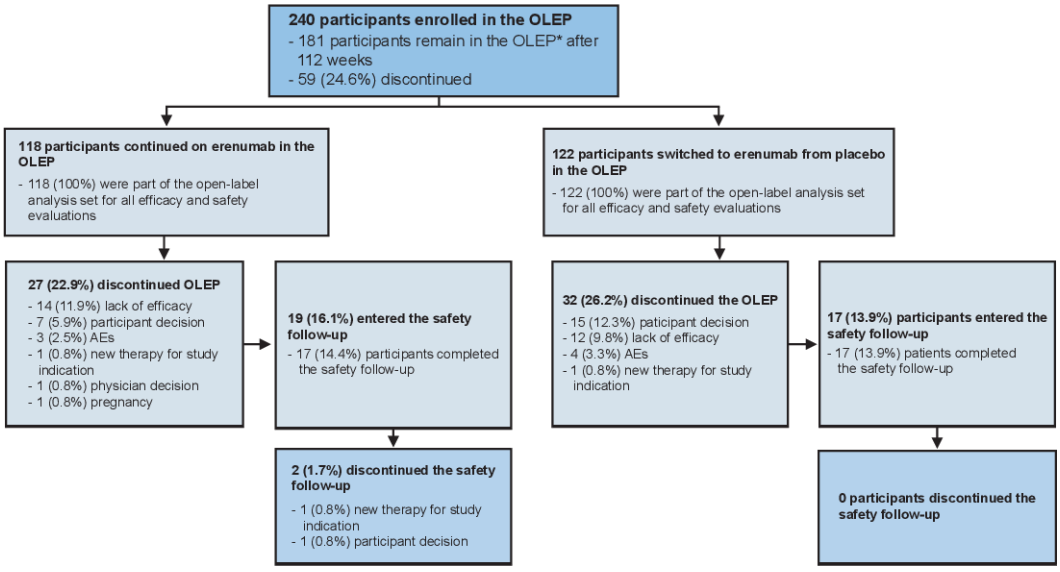


Figure 1 Participant disposition during the liberty study OLEP. *Participants continuing in the 3-year OLEP of the liberty study. This is a new figure and approved by all authors. The authors confirm that this figure was not used previously in any other publication. AE, adverse event; OLEP, open-label extension phase.

erenumab and those initiating erenumab in the OLEP) as reported previously.[16–18]

A temporary technical issue in July 2018 resulted in the loss of electronic diary data for the efficacy endpoints for a subset of participants at week 60/week 64 of the OLEP; ~25% of participants had missing data for the week 64 visit for efficacy endpoints based on daily electronic diary and week 60 for HIT-6. Subsequently, a lower number of data points were reported for these visits. There was no impact on the collection of safety data.[17]

Efficacy

Monthly migraine days

The proportion of participants achieving a ≥50% reduction from baseline in MMD were 46.7% (64/137) at Week 64% and 57.2% (99/173) at week 112 (figure 2A). The proportion of patients achieving a ≥75% reduction from baseline in MMD were 23.4% (32/137) at week 64% and 30.6% (53/173) at week 112 (figure 2B); the proportion of patients achieving a 100% reduction from baseline in MMD were 12.4% (17/137) at week 64% and 16.2% (28/173) at week 112 (figure 2C).

Individual participant responses to erenumab therapy from weeks 0 to 112 are presented in the heat maps (figure 3).

Among the 35/118 (29.7%) participants from the active arm who had a ≥50% response at week 12, 24/35 (68.6%) maintained their responder status at more than half of the visits during the 2 years of OLEP and 15/35 (42.9%) at ≥80% of the visits (online supplemental table 1). Among the 17/121 (13.9%) participants from the placebo arm who had a ≥50% response at Week 12, and who then switched from placebo to erenumab, 12/17 (70.6%) remained as ≥50% responders at at-least half the visits during the 2 years of OLEP and in 7/17 (41.2%) at ≥80% of the visits.

In the active arm, of the ≥75% responders at week 12, 7/13 remained ≥75% responders in at-least half of the visits and 4/13 were ≥75% responders at ≥80% of the visits. Of the 100% responders at week 12, 4/6 remained ≥100% responders in at least half of the visits and 1/6 were ≥100% responders at ≥80% of the visits.

In the placebo arm, of the ≥75% responders at Week 12, 1/5 converted to ≥75% responder in at least half of the visits and 1/5 converted to ≥75% responders in at least 80% of visits.

Of the non-responders from the active arm at week 12, 16/82 (19.5%) converted to ≥50% responders in at least half of the visits and 6/82 (7.3%) converted to ≥50% responder in at-least 80% of visits.

Of 103 non-responders from the placebo arm at Week 12, 44 (42.7%) converted to ≥50% responders in at least half of the visits and 18 (17.5%) converted to ≥50% responder in at least 80% of the visits (online supplemental table 1).

The overall population reported a mean reduction in MMDs from baseline in the OLEP as −2.0 days (N=237) at weeks 13–16, −3.6 days (N=137) at weeks 61–64, and −4.2 days (N=173) at the weeks 109–112 assessment (figure 4). The mean (SD) change from baseline in MMD at week 112 for the continuous erenumab group was −3.9 (5.5) days (N=88) and for those who switched from placebo to erenumab in the OLEP was −4.6 (4.6) days (N=85).

Functional outcomes

The mean (SD) change in HIT-6 score at week 108 was −9.5 (8.7) for the overall population (N=181), −8.5 (8.0) for the continuous erenumab group (N=91) and −10.4 (9.3) for those who switched to erenumab in the OLEP (N=90) (table 1).

The mean (SD) change in MPFID-PI scores at weeks 109–112 was −4.5 (10.3) for the overall population (N=174), −4.1 (9.1) for the continuous erenumab group (N=88) and −5.0 (11.4) for those who switched to erenumab in the OLEP (N=86). The mean (SD) change in MPFID-EA scores at weeks 109–112 was −5.4 (10.3) for the overall population (N=174),−4.9 (9.7) for the continuous erenumab group (N=88), and −6.0 (10.9) for those who switched to erenumab in the OLEP (N=86) (table 1).

Safety

A total of 70 (59.3%) participants in the erenumab arm and 68 (55.7%) in the placebo arm experienced at least one TEAE during the DBTP. The corresponding exposure-adjusted patient

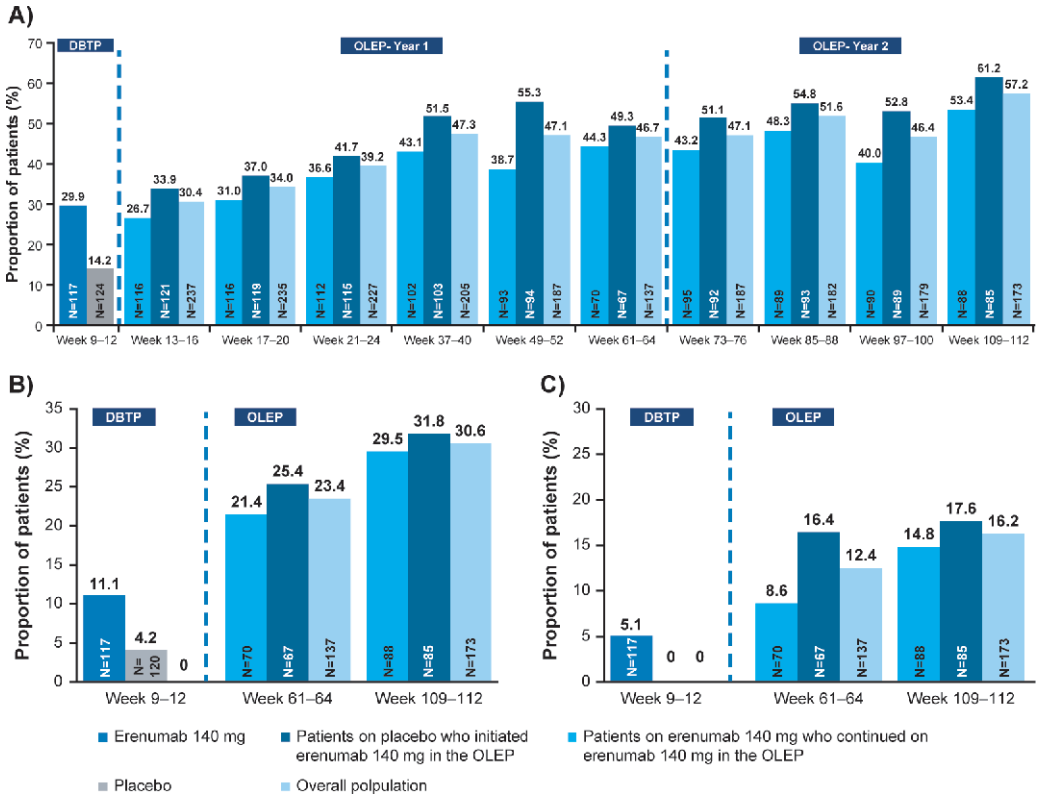


Figure 2 Responder rates over 112 weeks: (A) ≥50%, (B) ≥75% and (C) 100% reduction in MMDs. A total of six participants (three in each arm) discontinued the DBTP and did not enter the OLEP. Data in the graph are provided for a time point only if a participant had a valid baseline diary and a diary at the respective time point. This is a new figure and approved by all authors. The authors confirm that this figure was not used previously in any other publication. DBTP, double-blind treatment phase; MMD, monthly migraine day; N, total number of participants in treatment arm with response variable defined; OLEP, open-label extension phase.

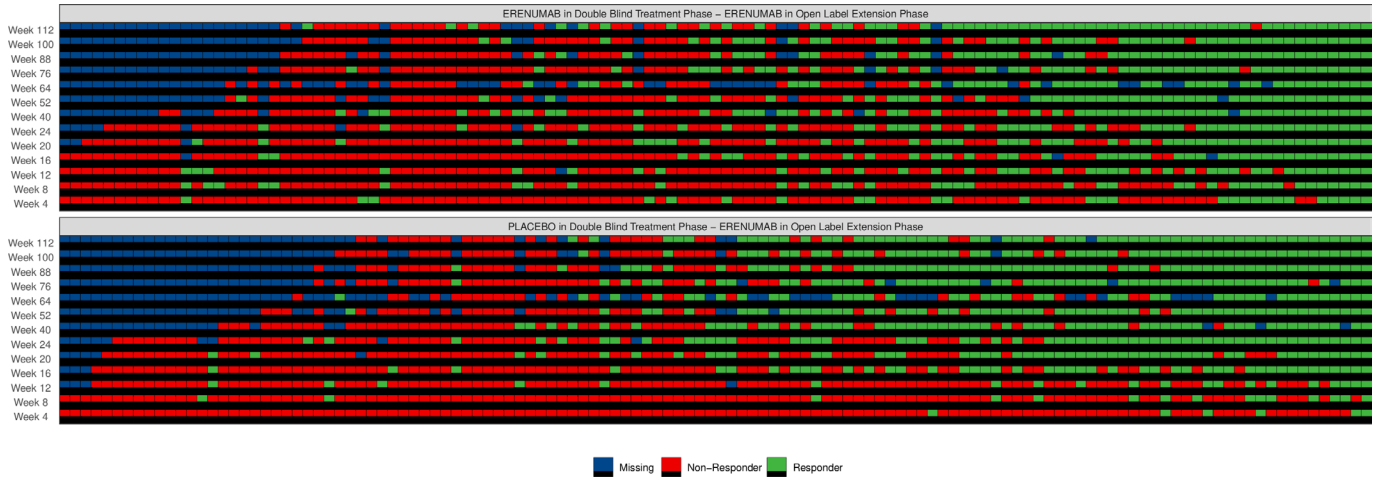
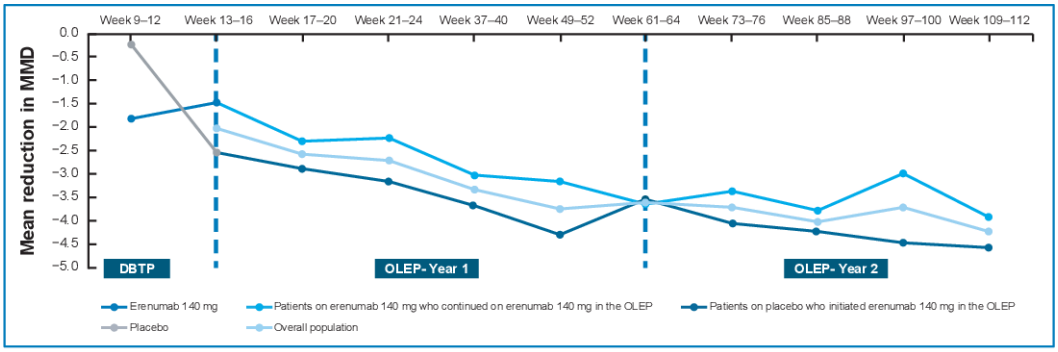


Figure 3 Heat maps presenting individual participant response to erenumab therapy until week 112 of the OLEP. Each vertical column denotes the responder status (≥50% reduction in MMDs) of an individual participant through their journey in the trial at each time point. The visit names are provided along the y-axis. in each participant-column, the colour of the cell denotes Responder status (green=responder, red=non-responder, blue=missing). Columns are sorted according to Responder status with those on the right side of the plot with a higher number of visits as responders and those on the left side with fewer visits than non-responders. After reaching the initial ≥50% response threshold, a <40% response vs baseline was always considered a non-responder status (red). An MMD reduction of between 40% and 50% was acceptable and considered a ≥50% Responder (green) for that visit if the response at the next visit was ≥50% once more. A <50% response at two consecutive visits was considered non-responder over both periods. Week 12 presents the DBTP wherein participants received subcutaneous injections of either placebo or erenumab. On completion of the DBTP, participants receiving placebo had a choice to continue erenumab for 3 years of the OLEP. This is a new figure and approved by all authors. The authors confirm that this figure was not used previously in any other publication. DBTP, double-blind treatment phase; MMD, monthly migraine day; OLEP, open-label extension phase.



Change in MMD from DBTP baseline of the Overall population (N) by visit	*Week 9-12	Week 13-16	Week 17-20	Week 21-24	Week 37-40	Week 49-52	Week 61-64	Week 73-76	Week 85-88	Week 97-100	Week 109-112
	−1.0, N=237	−2.0, N=237	−2.6, N=235	−2.7, N=227	−3.3, N=205	−3.7, N=187	−3.6, N=137	−3.7, N=187	−4.0, N=182	−3.7, N=179	−4.2, N=173

Figure 4 Change in MMD until week 112 of the OLEP. *At each time point, mean values for a week are determined for a 3-week time period. This is a new figure and approved by all authors. The authors confirm that this figure was not used previously in any other publication. DBTP, double-blind treatment phase; MMD, monthly migraine day; OLEP, open-label extension phase.

incidence rates were 402.6/100 patient-years for erenumab and 377.9/100 patient-years for placebo (table 2).

During the first year, 194 (80.8%) participants experienced TEAEs; over the 2-year OLEP, 207 (86.3%) participants experienced TEAEs. The exposure-adjusted patient incidence rates were 242.9/100 patient-years in the first year and 198.0/100 patient-years over the 2-year study duration.

During the 2-year duration, the exposure-adjusted incidence rates were 157.6/100 patients-years in the continuous erenumab group, and 255.7/100 patients-years in those who switched to

Table 1 Functional outcome measures over 112 weeks of the LIBERTY study (open-label analysis set)

Outcomes	Time point (weeks)	Participants continuing on erenumab 140 mg, N=118	Participants switching from placebo to erenumab 140 mg, N=122	Overall population entering OLEP, N=240
Change from baseline in HIT-6*	12	−5.2 (6.6), n=116	−2.3 (5.9), n=122	−3.7 (6.4), n=238
	16	−5.9 (6.6), n=114	−6.9 (7.6), n=120	−6.4 (7.2), n=234
	36	−7.9 (8.2), n=103	−8.6 (9.0), n=105	−8.3 (8.6), n=208
	48	−7.9 (7.6), n=97	−10.6 (9.2), n=99	−9.2 (8.6), n=196
	60	−8.5 (7.4), n=88	−9.7 (10.0), n=82	−9.0 (8.7), n=170
	72	−8.2 (7.7), n=94	−9.3 (9.3), n=97	−8.7 (8.5), n=191
	84	−8.8 (8.0), n=91	−8.9 (8.5), n=97	−8.8 (8.2), n=188
	96	−9.2 (8.0), n=88	−10.4 (9.6), n=89	−9.8 (8.8), n=177
	108	−8.5 (8.0), n=91	−10.4 (9.3), n=90	−9.5 (8.7), n=181
Change from baseline in MPFID-PI†	9–12	−2.0 (8.8), n=117	1.3 (8.9), n=120	−0.3 (9.0), n=237
	13–16	−1.3 (8.5), n=116	−2.4 (8.7), n=121	−1.9 (8.6), n=237
	37–40	−3.2 (8.7), n=102	−4.7 (8.6), n=103	−3.9 (8.7), n=205
	49–52	−4.6 (7.8), n=93	−5.5 (8.7), n=94	−5.1 (8.2), n=187
	61–64	−5.2 (6.9), n=70	−4.5 (8.4), n=67	−4.9 (7.6), n=137
	73–76	−3.2 (8.3), n=95	−4.8 (9.7), n=92	−4.0 (9.0), n=187
	85–88	−3.8 (8.1), n=89	−4.5 (9.4), n=93	−4.1 (8.8), n=182
	97–100	−2.2 (10.5), n=90	−4.3 (10.3), n=89	−3.2 (10.4), n=179
	109–112	−4.1 (9.1), n=88	−5.0 (11.4), n=86	−4.5 (10.3), n=174
Change from baseline in MPFID-EA†	9–12	−3.3 (8.8), n=117	0.4 (8.9), n=120	−1.4 (9.0), n=237
	13–16	−2.6 (9.1), n=116	−3.7 (8.5), n=121	−3.2 (8.8), n=237
	37–40	−4.6 (8.8), n=102	−5.5 (8.8), n=103	−5.0 (8.8), n=205
	49–52	−5.7 (7.6), n=93	−6.7 (8.5), n=94	−6.2 (8.1), n=187
	61–64	−6.6 (7.7), n=70	−5.1 (9.3), n=67	−5.9 (8.5), n=137
	73–76	−4.4 (9.1), n=95	−5.6 (9.8), n=92	−5.0 (9.5), n=187
	85–88	−4.9 (8.2), n=89	−5.4 (9.4), n=93	−5.2 (8.8), n=182
	97–100	−3.4 (11.1), n=90	−5.4 (10.5), n=89	−4.4 (10.8), n=179
	109–112	−4.9 (9.7), n=88	−6.0 (10.9), n=86	−5.4 (10.3), n=174

Data are presented as mean (SD). Change from baseline=postbaseline−baseline. The baseline period is defined as the period between week −4 visit and the day prior to first dose. The baseline value is the prorated number to 28-day equivalents during baseline period.
*HIT-6 total score was assessed by visit.
†At each time point, mean (SD) values for week are determined for a daily collection during the respective 4-week periods.
EA, everyday activities; HIT-6, Headache Impact Test; MPFID, Migraine Physical Function Impact Diary; N, number of participants included in the analysis set; n, number of participants who responded; OLEP, open-label extension phase; ; PI, physical impairment.

Table 2 Summary of treatment-emergent AEs in the DBTP and OLEP (open-label analysis set)

	DBTP		OLEP	
			1 year	1-year+2 years
Event	Erenumab 140 mg N=118, n (%)/e(r)	Placebo N=122, n (%)/e(r)	Overall population N=240, n (%)/e(r)	Overall population N=240, n (%)/e(r)
Any AE	70 (59.3)/17.4(402.6)	68 (55.7)/18.0(377.9)	194 (80.8)/79.9(242.9)	207 (86.3)/104.6(198.0)
Any SAE	2 (1.7)/27.9(7.2)	1 (0.8)/29.1(3.4)	16 (6.7)/222.7(7.2)	25 (10.4)/398.4(6.3)
Any AE leading to discontinuation of treatment	1 (0.8)/27.9(3.6)	0 (0)/29.3(0)	4 (1.7)/229.3(1.7)	9 (3.8)/422.9(2.1)
Any treatment-related AE	21 (17.8)/24.2(86.7)	24 (19.7)/25.2(95.1)	57 (23.8)/189.3(30.1)	66 (27.5)/334.2(19.8)
Most frequently reported treatment-emergent AEs (per 100 patient-years) during the DBTP and OLEP, by preferred term				
Nasopharyngitis	6 (5.1)/26.9(22.3)	12 (9.8)/27.7(43.3)	74 (30.8)/178.6(41.4)	99 (41.3)/291.6(33.9)
Influenza	–	–	31 (12.9)/212.6(14.6)	39 (16.3)/379.6(10.3)
Back pain	5 (4.2)/27.2(18.4)	2 (1.6)/28.9(6.9)	18 (7.5)/219.5(8.2)	26 (10.8)/393.6(6.6)
Sinusitis	1 (0.8)/27.9(3.6)	1 (0.8)/29.1(3.4)	10 (4.2)/224.0(4.5)	20 (8.3)/405.6(4.9)
Migraine	1 (0.8)/27.9(3.6)	2 (1.6)/28.9(6.9)	10 (4.2)/224.8(4.4)	19 (7.9)/405.1(4.7)
Urinary tract infection	0 (0)/28.1(0)	1 (0.8)/29.1(3.4)	10 (4.2)/225.9(4.4)	18 (7.5)/405.9(4.4)
Gastroenteritis	1 (0.8)/27.9(3.6)	0 (0)/29.3(0)	11 (4.6)/222.9(4.9)	16 (6.7)/408.3(3.9)
Oropharyngeal pain	1 (0.8)/27.8(3.6)	0 (0)/29.3(0)	6 (2.5)/227.4(2.6)	16 (6.7)/410.9(3.9)
Arthralgia	1 (0.8)/28.0(3.6)	4 (3.3)/28.6(14.0)	8 (3.3)/225.5(3.5)	15 (6.3)/411.0(3.7)
Bronchitis	2 (1.7)/27.8(7.2)	1 (0.8)/29.1(3.4)	11 (4.6)/223.7(4.9)	15 (6.3)/406.4(3.7)
Injection site pain	7 (5.9)/27.0(26.0)	7 (5.7)/28.1(24.9)	13 (5.4)/221.5(5.9)	14 (5.8)/403.7(3.5)
Fatigue	3 (2.5)/27.4(10.9)	2 (1.6)/28.8(6.9)	12 (5.0)/223.0(5.4)	14 (5.8)/406.4(3.4)
Hypertension	1 (0.8)/28.0(3.6)	1 (0.8)/29.3(3.4)	7 (2.9)/225.3(3.1)	14 (5.8)/410.6(3.4)
Constipation	1 (0.8)/27.9(3.6)	2 (1.6)/29.0(6.9)	6 (2.5)/226.4(2.7)	13 (5.4)/415.0(3.1)
Nausea	3 (2.5)/27.6(10.9)	2 (1.6)/29.0(6.9)	7 (2.9)/226.5(3.1)	13 (5.4)/414.1(3.1)
Dizziness	3 (2.5)/27.7(10.8)	2 (1.6)/28.9(6.9)	12 (5.0)/222.0(5.4)	12 (5.0)/404.7(3.0)
Cystitis	1 (0.8)/27.9(3.6)	2 (1.6)/28.9(6.9)	11 (4.6)/224.6(4.9)	12 (5.0)/410.0(2.9)
Upper respiratory tract infection	4 (3.4)/27.6(14.5)	0 (0)/29.3(0)	9 (3.8)/224.2(4.0)	12 (5.0)/408.5(2.9)

Time at risk during the OLEP is the time from the start of OLEP to onset of the first event in the OLEP or the minimum (end of study date, data cut-off date, last investigational product dose+112). Data cut-off date: Week 116 or if participant discontinued prior Week 116 then minimum (end of study date, last patient last week 116) - Double-blind treatment (either erenumab 140 mg or placebo) was given at day 1, week 4 and week 8 visit then open label erenumab 140 mg was given during OLEP starting from week 12 visit. MedDRA V.22.1 was used for the reporting of AEs. The 1-year+2-year overall population data are cumulative of the data from DBTP, first and second year of OLEP. In the 'overall population' column, preferred terms are sorted by AE frequency in decreasing order.

e, sum across all participants, the total time at risk in the OLEP in years r, exposure-adjusted patient rate per 100 patient-years (n/e × 100).

AE, adverse event; DBTP, double-blind treatment phase; n, number of participants reporting at least one occurrence of an AE in that class; N, number of participants in the analysis set; OLEP, open-label extension phase; SAE, serious AE.

erenumab in the OLEP. The most frequently reported TEAEs (exposure-adjusted patient rate of ≥10%) were nasopharyngitis, influenza and back pain. Hypersensitivity was reported in one participant continuing erenumab in the OLEP. Constipation was reported in eight participants continuing erenumab in the OLEP and in five participants that switched to erenumab. The exposure-adjusted incidence rate of constipation was 3.1/100 patient-years in the overall population; 3.9/100 patient-years for those continuing erenumab and 2.4/100 patient-years for those who switched to erenumab.

The rate of serious AEs remained stable over the 2 years. The exposure-adjusted incidence of serious AEs in the erenumab arm during DBTP was 7.2/100 patient-years. The exposure-adjusted incidence of serious AEs in the overall population was 7.2/100 patient-years during the first year and 6.3/100 patient-years during the overall OLEP. In the second year of OLEP, the most commonly reported serious AEs were migraine (3/240 participants) and depression (2/240 participants).

Rates of treatment discontinuation due to AEs were low. The exposure-adjusted incidence rate of discontinuation of treatment due to AEs in the erenumab arm during the DBTP was 3.6/100 patient-years. The exposure-adjusted incidence rate of discontinuation of treatment due to AEs in the overall population was 1.7/100 patient-years in the first year and 2.1/100 patient-years in second year. In the second year of OLEP, 4 (3.4%) participants in the continuous erenumab group and 5 (4.1%) participants who switched to erenumab in OLEP discontinued the study treatment due to AEs.

The proportion of treatment-related AEs in the erenumab arm was comparable with that of placebo during the DBTP. Exposure-adjusted incidence rate of any treatment-related AEs during the DBTP in the erenumab arm was 86.7/100 patient-years and 95.1/100 patient-years in the placebo arm. The exposure-adjusted incidence rates of any treatment-related AE in the overall population was 30.1/100 patient-years in the first year and 19.8/100 patient-years in the second year of OLEP.

There were no clinically meaningful differences between treatment arms during the OLEP for laboratory parameters, vital signs or ECG parameters. No deaths were reported, and no new safety findings were reported in participants during the 2-year OLEP.

DISCUSSION

In this 2-year open-label follow-up study on the long-term effects of monthly erenumab 140 mg in individuals with EM in whom 2–4 migraine preventives had failed, ~70% of ≥50% responders in the erenumab treatment arm at the onset of the extension study maintained a good response in half of the visits and 42% in ≥80% of the visits in the 2-year OLEP. A sustained ≥75%

response of this difficult-to-treat population was observed in over half of ≥75% responders at the onset of the extension study, in at least half of the visits and in nearly one third in ≥80% of the visits in the 2-year OLEP. Sustained 100% response was seen in two thirds of the 100% responders at the onset of the extension study, in at least half of the visits and in nearly one fifth in ≥80% of the visits in the 2-year OLEP.

Erenumab was safe and well tolerated over the 2-year follow-up period, in line with the safety profile observed in other long-term studies with erenumab[6–11] and other CGRP inhibitors[23 24] in migraine populations that were not specifically selected for prior failure to migraine preventives.

The number of participants achieving a≥50% reduction in MMDs at year 2 in this population with difficult-to-treat EM (57.2%) was slightly lower than those seen in EM with <2 previous treatment failures: 71.0% at Year 5 of the 5-year OLEP study,[12] 64.9% at week 52 of the STRIVE study,[7] and 59.0% at week 52 of the OLEP in participants with CM,[11] but remained clinically relevant.

The heat map presents the monthly (4 weeks) response status of individual participant responses to erenumab/placebo therapy from weeks 0 to 12 and erenumab therapy to the end for this 2-year analysis period (week 112). The heat map provides an overall visualisation of the fluctuation between responder and non-responder status of each participant providing a participant monthly journey of treatment benefits. Some participants had treatment benefit at each monthly time point while others had a consistent treatment effect with some months with lower response and still others had very few, if any, months with a treatment response. The heat map illustrates the nature of the disease, with some months being better than others, and indicates that participant response is variable even with continued treatment. The heat map also visually shows a clear switch to responders for participants treated with placebo during the first 12 weeks who switched to erenumab. A greater response was observed in participants that switched from placebo to erenumab where more non-responders converted to responder status on switching.

The group responder rate demonstrates that of the ≥50% responders at week 12, 69.2% remained responder on ≥50% and 42.3% on >80% of the visits and this can be visualised on the heat map. Of non-responders at week 12, 32.4% converted to ≥50% responder in at-least half the visits and 13.0% in at-least 80% of the visits. The heat maps and group responder rates validate the sustained response of erenumab over time on an individual as well as at a group level.

The mean reduction in MMDs of 4.2 days from a baseline of 9.2 days at 112 weeks is comparable to mean reductions of (1) 5.3 days from a baseline of 8.7 days in the phase 2 study[12]; (2) 3.1 days from 8.7 days in the subgroup analysis of the STRIVE (Study to Evaluate the Efficacy and Safety of Erenumab in Migraine Prevention) study in participants who had previously failed >2 migraine preventives[14] and (3) 8.8 days from 18.1 days in the 52-week OLEP in participants with CM.[11]

Other functional parameters, as measured by HIT-6 and MPFID scores, also showed a similar improvement from weeks 12 to 112. A higher and consistent improvement was observed in the change from baseline in MMDs and functional outcomes (HIT-6 and MPFID scores) in participants who switched to erenumab at week 12 compared with those who continued erenumab.

No new safety signals were observed throughout the 2 years OLEP. The safety profile of erenumab in the OLEP was consistent with that seen in the DBTP[16] and across the year 1 of the OLEP.[17] The most frequently reported TEAEs in the 2-year OLEP were nasopharyngitis, influenza, and back pain, similar to those reported in the DBTP and the first year of the OLEP.[16 17]

The safety profile of erenumab in the 5-year OLEP of a blinded phase 2 study was consistent with that observed in the DBTP, with no increase in AEs over 5 years of exposure.[12] The long-term safety of erenumab in participants with CM from the 52-week OLEP with a 12-week DBTP was consistent with the known safety profile of erenumab, with comparable AEs in both arms in the DBTP.[11]

Recent trials also demonstrated the efficacy and safety of two other CGRP inhibitors, galcanezumab[25] and fremanezumab,[26] in participants with 2–4 prior preventive treatment failures, extending the findings from LIBERTY.[16] Long-term follow-up data of galcanezumab and fremanezumab are, however, not yet available. Altogether, these findings show that CGRP inhibitors are a novel, safe and effective treatment option for difficult-to-treat migraine.

Overall, results from the 2-year OLEP demonstrated that erenumab 140 mg exhibited sustained efficacy, and was well-tolerated; these results coupled with a low dropout rate, are clinically meaningful outcomes in participants in whom 2–4 prior preventive treatment had failed with a high unmet need.

Limitations

Open-label trials are generally associated with a responder bias, with participants not responding to treatment dropping out, and those that do respond remaining in the trial thus inflating the overall treatment effect observed. This is an inherent limitation of these types of studies. The individual heat maps have been provided to show the treatment effect for each individual participant so a visual comparison could be made. The low drop-out rate and high retention rates (nearly 75% over 2 years) are reassuring and indicate that erenumab was safe and well tolerated, but do not address the potential efficacy bias. The potential efficacy bias could be influenced by fluctuations in participant numbers and individual effects with 36 (15.0%) participants discontinuing within the first year of the OLEP (19 (7.9%) discontinuing due to lack of efficacy) and an additional 23 (9.6%) participants discontinuing during the second year (7 (2.0%) discontinuing due to lack of efficacy). The numerical rise in individual responder rates may be due to missing values among non-responders that prematurely discontinued the study. Additionally, the sample size in this study was smaller compared with other studies conducted in similar populations,[14 25 26] and only participants with EM were included, whereas a mix of participants with EM and CM would be observed in clinical practice. This study had a limited scope for evaluation of the efficacy and safety of erenumab 140 mg in participants with EM when compared with real-life clinical practice due to inclusion of participants aged 65 years or younger that were predominantly Caucasians females. However, since its launch in May 2018, erenumab has been used by thousands of patients from different ethnicities and age groups, including older than 65 years and its risk-benefit assessment continues to be positive.

CONCLUSIONS

Monthly erenumab 140 mg was effective, safe and well tolerated in the preventive treatment of EM in individuals in whom up to four prior preventive medications had failed. The efficacy of erenumab was well sustained over a 2-year follow-up; the safety profile was in-line with that of previous reports. Erenumab is

a novel, effective and safe preventive treatment option for difficult-to-treat migraine.

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REFERENCES

1 Dodick DW, Loder EW, Manack Adams A, *et al*. Assessing barriers to chronic migraine consultation, diagnosis, and treatment: results from the chronic migraine epidemiology and outcomes (CaMEO) study. *Headache* 2016;56:821–34.
2 Katsarava Z, Mania M, Lampl C, *et al*. Poor medical care for people with migraine in Europe - evidence from the Eurolight study. *J Headache Pain* 2018;19:10.
3 Lipton RB, Hutchinson S, Ailani J, *et al*. Discontinuation of acute prescription medication for migraine: results from the chronic migraine epidemiology and outcomes (CaMEO) study. *Headache* 2019;59:1762–72.
4 Hepp Z, Bloudek LM, Varon SF. Systematic review of migraine prophylaxis adherence and persistence. *J Manag Care Pharm* 2014;20:22–33.
5 Shi L, Lehto SG, Zhu DXD, *et al*. Pharmacologic characterization of AMG 334, a potent and selective human monoclonal antibody against the calcitonin gene-related peptide receptor. *J Pharmacol Exp Ther* 2016;356:223–31.
6 Goadsby PJ, Reuter U, Hallström Y, *et al*. A controlled trial of Erenumab for episodic migraine. *N Engl J Med* 2017;377:2123–32.
7 Goadsby PJ, Reuter U, Hallström Y, *et al*. One-Year sustained efficacy of erenumab in episodic migraine: results of the strive study. *Neurology* 2020;95:e469–79.
8 Dodick DW, Ashina M, Brandes JL, *et al*. Arise: a phase 3 randomized trial of erenumab for episodic migraine. *Cephalalgia* 2018;38:1026–37.
9 Tepper S, Ashina M, Reuter U, *et al*. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Neurol* 2017;16:425–34.
10 Brandes JL, Diener H-C, Dolezil D, *et al*. The spectrum of response to erenumab in patients with chronic migraine and subgroup analysis of patients achieving ≥50%, ≥75%, and 100% response. *Cephalalgia* 2020;40:28–38.
11 Tepper SJ, Ashina M, Reuter U, *et al*. Long-Term safety and efficacy of erenumab in patients with chronic migraine: results from a 52-week, open-label extension study. *Cephalalgia* 2020;40:543–53.
12 Ashina M, Goadsby PJ, Reuter U, *et al*. Long-Term efficacy and safety of erenumab in migraine prevention: results from a 5-year, open-label treatment phase of a randomized clinical trial. *Eur J Neurol* 2021;28:1716–25.
13 Ashina M, Tepper S, Brandes JL, *et al*. Efficacy and safety of erenumab (AMG334) in chronic migraine patients with prior preventive treatment failure: a subgroup analysis of a randomized, double-blind, placebo-controlled study. *Cephalalgia* 2018;38:1611–21.
14 Goadsby PJ, Paemeleire K, Broessner G, *et al*. Efficacy and safety of erenumab (AMG334) in episodic migraine patients with prior preventive treatment failure: a subgroup analysis of a randomized, double-blind, placebo-controlled study. *Cephalalgia* 2019;39:817–26.

15 Raffaelli B, Kalantzis R, Mecklenburg J, *et al*. Erenumab in chronic migraine patients who previously failed five first-line oral prophylactics and OnabotulinumtoxinA: a Dual-Center retrospective observational study. *Front Neurol* 2020;11:417.
16 Reuter U, Goadsby PJ, Lanteri-Minet M, *et al*. Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3B study. *Lancet* 2018;392:2280–7.
17 Goadsby PJ, Reuter U, Lanteri-Minet M, *et al*. Long-Term efficacy and safety of Erenumab: results from 64 weeks of the liberty study. *Neurology* 2021;96:e2724–35.
18 Lanteri-Minet M, Goadsby PJ, Reuter U, *et al*. Effect of erenumab on functional outcomes in patients with episodic migraine in whom 2-4 preventives were not useful: results from the liberty study. *J Neurol Neurosurg Psychiatry* 2021;92:466–72.
19 Reuter U, Goadsby PJ, Lanteri-Minet M. Sustained efficacy and safety of erenumab in patients with episodic migraine who failed 2-4 prior preventive treatments: 2-year interim results of the liberty open-label extension study. 62nd annual scientific meeting American headache Society®. *Headache: The Journal of Head and Face Pain* 2020;60:1–156.
20 Headache classification Committee of the International headache Society (IHS) the International classification of headache disorders, 3rd edition. *Cephalalgia* 2018;38:1–211.
21 Medical Dictionary for Regulatory Activities (MedDRA®). *Introductory Guide MedDRA Version 22.1. A registered trademark of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA). [Internet]*, 2019.
22 Common Terminology Criteria for Adverse Events (CTCAE). *Version 4.03 ed [Internet]*. United States Department of Health and Human Services, 2010.
23 Camporeale A, Kudrow D, Sides R, *et al*. A phase 3, long-term, open-label safety study of Galcanezumab in patients with migraine. *BMC Neurol* 2018;18:188.
24 Detke HC, Goadsby PJ, Wang S, *et al*. Galcanezumab in chronic migraine: the randomized, double-blind, placebo-controlled regain study. *Neurology* 2018;91:e2211–21.
25 Mulleners WM, Kim B-K, Láinez MJA, *et al*. Safety and efficacy of galcanezumab in patients for whom previous migraine preventive medication from two to four categories had failed (conquer): a multicentre, randomised, double-blind, placebo-controlled, phase 3B trial. *Lancet Neurol* 2020;19:814–25.
26 Ferrari MD, Diener HC, Ning X, *et al*. Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (focus): a randomised, double-blind, placebo-controlled, phase 3B trial. *Lancet* 2019;394:1030–40.