# Efficacy and safety of erenumab in participants with episodic migraine in whom 2-4 prior preventive treatments had failed

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RESEARCH ARTICLE

# Efficacy and Safety of Erenumab in Participants With Episodic Migraine in Whom 2–4 Prior Preventive Treatments Had Failed

## LIBERTY 3-Year Study

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## Abstract

### Background and Objectives

The LIBERTY study assessed the efficacy and safety of erenumab in participants with episodic migraine (EM) and 2–4 prior preventive treatment failures. The results have been presented after 3 years of erenumab exposure in its open-label extension phase (OLEP).

### Methods

Participants completing the 12-week double-blind treatment phase (DBTP) of the LIBERTY study could enter the OLEP and receive 140 mg of erenumab once monthly for 3 years. The main outcomes included the proportion of participants achieving ≥50% reduction in monthly migraine days (MMDs), the mean MMD change from baseline, and tolerability and safety.

### Results

Overall, 240/246 (97.6%) participants entered the OLEP and 168/240 (70.0%) completed the study (85/118 continuing erenumab [n = 1 lost during follow-up]; 83/122 switching from placebo [n = 2 lost during follow-up]). In the overall population, 79/151 participants (52.3%) with valid data points achieved ≥50% reduction in MMDs at week 168 (i.e., responders). In the continuous erenumab group, 35/117 participants (29.9%) were ≥50% responders at week 12 of the DBTP and 26/35 (74.3%) remained ≥50% responders in at least half of OLEP visits. Of the 82/117 participants (70.1%) not achieving responder status at week 12 in the continuous erenumab group, 17/82 (20.7%) converted to ≥50% responders in at least half of OLEP visits. Of 103/120 participants (85.8%) not achieving responder status at week 12 in the placebo-erenumab group, 42/103 (40.8%) converted to ≥50% responders in at least half of OLEP visits after switching to erenumab. Overall, the mean (SD) MMD change from baseline showed sustained improvement over 3 years (−4.4 [3.9] days at week 168). The most common treatment-emergent AEs (per 100 person-years) were nasopharyngitis (28.8), influenza (7.5), and back pain (5.8). Overall, 9.6% (3.9 per 100 person-years) and 6.7% (2.7 per 100 person-years) of participants reported events of treatment-emergent hypertension and constipation, respectively. The safety and tolerability profile remained consistent with earlier studies.

### Discussion

Erenumab (140 mg) showed sustained efficacy over 3 years in participants with EM and 2–4 prior preventive treatment failures. No new safety signals were observed.

### Trial Registration Information

ClinicalTrials.gov Identifier: NCT03096834.

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## Glossary

**AE** = adverse event; **AMSM** = acute migraine-specific medication; **BP** = blood pressure; **CGRP** = calcitonin gene–related peptide; **CM** = chronic migraine; **DBP** = diastolic BP; **DBTP** = double-blind treatment phase; **EA** = everyday activities; **EM** = episodic migraine; **FDA** = US Food and Drug Administration; **HIT-6** = Headache Impact Test–6; **LIBERTY** = A 12-week double-bLind, randomIzed, multicenter study comparing the efficacy and safety of once-monthly suBcutanEous 140 mg erenumab against placebo in adult episodic migRaine paTients who have failed 2–4 prophYlactic treatments; **MMD** = monthly migraine day; **MPFID** = Migraine Physical Function Impact Diary; **OLEP** = open-label extension phase; **PI** = Physical Impairment; **PTAP** = post-trial access phase; **QoL** = quality of life; **SBP** = systolic BP; **WPAI** = Work Productivity and Activity Impairment.

## Introduction

Erenumab (erenumab-aooe in the United States), a fully human immunoglobulin G2 monoclonal antibody, is a highly potent and selective antagonist of the canonical calcitonin gene–related peptide (CGRP) receptor.[1] Clinical trials have demonstrated the safety and superior efficacy of erenumab vs placebo in participants with episodic migraine (EM) and chronic migraine (CM).[2-6] In a head-to-head study, erenumab also demonstrated superior tolerability and significantly higher efficacy compared with standard-of-care therapy with topiramate.[7] During the 5-year open-label treatment period of a Phase 2 EM prevention study, participants receiving erenumab achieved sustained reductions in monthly migraine days (MMDs) and in use of acute migraine-specific medications (AMSMs), along with improvements in health-related quality of life (QoL).[8] Moreover, the safety profile was consistent with that observed during the double-blind treatment phase (DBTP), with no increase in adverse events (AEs) and no new safety signals over 5 years of exposure.[8] The safety and clinical benefit of erenumab continue to be observed in real-world studies.[9,10]

We previously demonstrated that 140 mg of erenumab was effective and generally well tolerated in individuals with difficult-to-treat EM (2–4 unsuccessful prior preventive therapies) in the 12-week DBTP of the Phase 3b LIBERTY study (NCT03096834).[11] Subsequent follow-up demonstrated that the efficacy and safety profile of erenumab was maintained throughout the first[12] and second[13] years of the open-label extension phase (OLEP). In this final report from the LIBERTY study, we present the detailed 3-year efficacy and safety data for the entire study population and a subset of participants who entered a 6-month post-trial access phase (PTAP).

We were particularly interested to see whether the response after erenumab or placebo treatment was persistent in participants who achieved ≥50% reduction in MMDs in the LIBERTY DBTP and whether the response improved in participants who did not achieve ≥50% response with placebo or erenumab in the DBTP after receiving erenumab in the OLEP. Considering a recent update to the erenumab US Prescribing Information to include the risk of hypertension,[14] based on retrospective analyses of postmarketing experience,[15] and a recent request by the US Food and Drug Administration (FDA) to change the safety label to indicate possible erenumab-induced constipation and hypertension,[16] we paid particular attention to events and signals related to hypertension and constipation.

These long-term data should help clinicians to make informed treatment decisions in partnership with participants for whom prior migraine preventive treatments were unsuccessful. Data were presented in abstract form at the 20th International Headache Congress (September 8–12, 2021, Dublin, Ireland).[17]

## Methods

### Study Design

LIBERTY was a 12-week, double-blind, placebo-controlled, randomized, multicenter, Phase 3b study in adults with EM in whom up to 4 prior migraine preventive treatments were unsuccessful. Eligible participants were randomized 1:1 to receive either monthly subcutaneous injections of erenumab (140 mg) or placebo. Participants completing the core 12-week DBTP could enter a 3-year OLEP.

To maximize the opportunity of treatment continuity post OLEP in countries where erenumab was not yet available, and where possible, participants who remained in the OLEP and who demonstrated clinical benefit from erenumab per investigator opinion (e.g., using criteria of benefit through Clinical Global Impression-Severity) were invited to participate in a 6-month open-label PTAP. These participants could receive erenumab until it became available through country-level launch and subsequent reimbursement decision or until December 2020, whichever came first (eFigure 1). The detailed study design has been previously reported (also see eAppendix 1).[11-13,18]

### Study Participants

#### Eligibility and Exclusion Criteria

Detailed participant eligibility and exclusion criteria have been previously reported[11-13,18] and are provided in eAppendix 2. In brief, the key inclusion criteria were male and female participants aged 18–65 years with a documented history of EM (4–14

baseline MMD and <15 monthly headache days), for whom 2–4 previous migraine preventive treatments failed due to lack of efficacy or tolerability. Prior preventive treatment failure comprised (1) unsuccessful treatment with 2–4 of the following medications: propranolol or metoprolol, topiramate, flunarizine, valproate or divalproex, amitriptyline, venlafaxine, lisinopril, candesartan, or other locally approved preventive agents; (2) unsuccessful treatment with one and deemed unsuitable for a second preventive treatment with the following medications: propranolol or metoprolol, topiramate, or flunarizine; and (3) unsuccessful treatment with or deemed unsuitable for valproate or divalproex.[12,13] Participants were deemed unsuitable for specific preventive medications by physicians for medical reasons, including contraindications or precautions included in local labels, national guidelines, or other locally binding documents, or for other medically relevant reasons.[12]

### Outcome Measures

All endpoints in the OLEP were exploratory to monitor the efficacy and safety of erenumab in an open-label setting. Safety assessments included monitoring for hypertension (the corresponding mean of 3 readings of blood pressure [BP] during each scheduled visit of each participant was considered as the observation for that visit. Hypertension was defined as BP measurements exceeding systolic BP (SBP) ≥ 140 mm Hg and diastolic BP (DBP) ≥ 90 mm Hg. The incidence of hypertension was based on Standardized MedDRA Query search for hypertension, including AE-preferred terms of hypertension, labile hypertension, systolic hypertension, and BP increased) and incidence of constipation. In this article, *baseline* refers to the DBTP baseline. The endpoints reported are proportion of participants with ≥30%, ≥50%, ≥75%, and 100% reduction from baseline in MMDs, determined at each 4-week diary collection time point throughout the OLEP; change in MMD from baseline; change from baseline in AMSM; change in Headache Impact Test (HIT)–6 total score, Migraine Physical Function Impact Diary (MPFID) Everyday Activities (EA) and Physical Impairment (PI), and Work Productivity and Activity Impairment (WPAI); and safety and tolerability. Further details on these patient-reported outcomes are provided in eAppendix 3.

### Statistical Analysis

The statistical analyses used in the OLEP for 64-week and 112-week data were previously published.[12,13] Efficacy data collected during the OLEP were summarized using the open-label analysis set, defined as participants who received ≥1 dose of erenumab in the OLEP. This set was used to summarize the efficacy and safety data during the OLEP.[12,13,18]

Efficacy parameters for continuous endpoints were analyzed using descriptive statistics for each treatment group and for all participants. For continuous endpoints, descriptive statistics included the number of participants, mean, and SD. For categorical endpoints, frequency and percentage were used. No formal testing was performed, and descriptive summaries were computed based on available data. There was no imputation for any efficacy endpoint.

AEs were evaluated as frequency-adjusted and exposure-adjusted participant incidence rates. There was no imputation for missing data points for safety analyses. Follow-up time–adjusted participant incidence rate of treatment-emergent AEs was tabulated overall and by randomized treatment group.[12,13]

### Standard Protocol Approvals, Registrations, and Participant Consents

LIBERTY was conducted as per the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use E6 Guidelines for Good Clinical Practice that have their origin in the Declaration of Helsinki. The study was approved by an Independent Ethics Committee or Institutional Review Board at each study site (details are available in eAppendix 4). All centers complied with local regulations. Written informed consent was obtained from all participants before screening and before any study-specific procedure was performed.

### Data Availability

The study data for the analyses described in this report may be made available on request by the author investigators or Novartis Pharma AG, the sponsor of this clinical research.

## Results

### Demographics and Disease Characteristics

Baseline demographic characteristics were collected at the start of the DBTP and were generally well balanced between treatment groups. Most participants were female (>80%) and Caucasian (>90%), with a median age of 46 years. Baseline disease characteristics were also well balanced between the erenumab and placebo groups, with mean (SD) MMDS of 9.2 (2.6) and 9.3 (2.7), monthly headache days of 10.1 (2.8) and 10.1 (2.7), and monthly AMSM days of 4.8 (2.9) and 4.4 (2.8), respectively.[11-13]

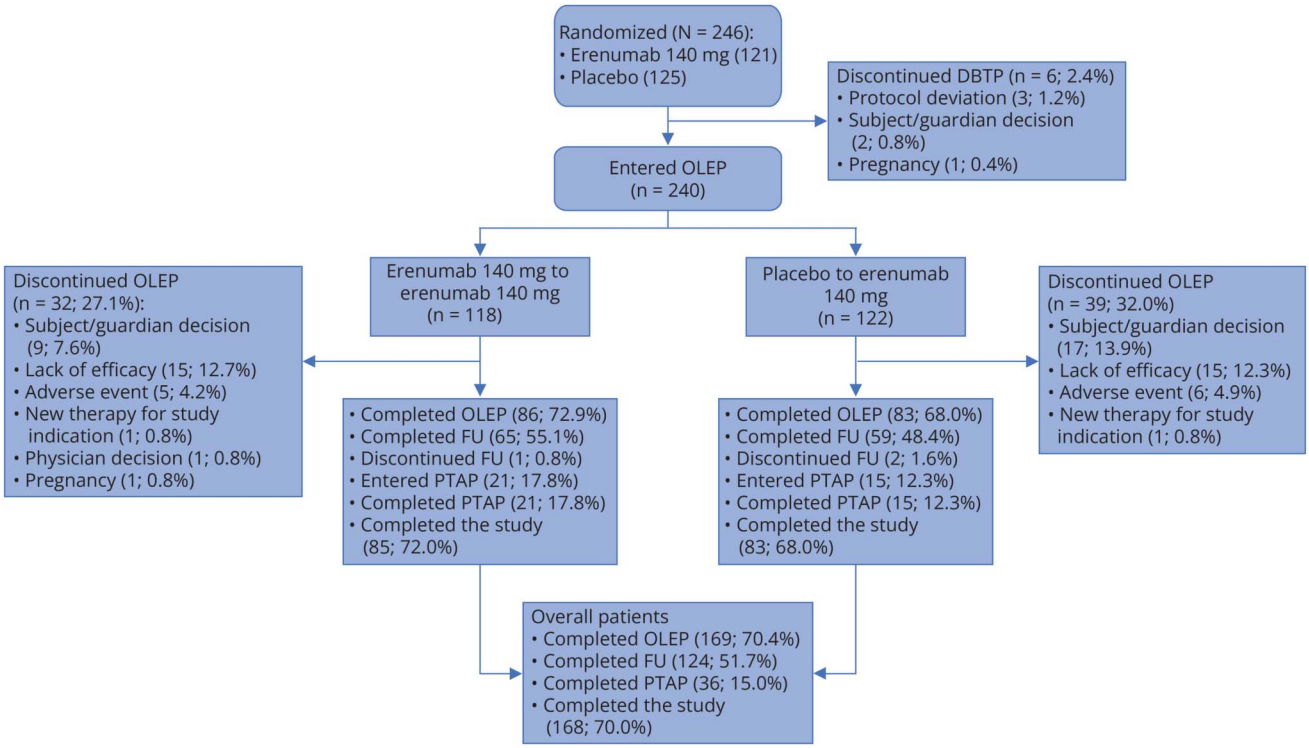
### Participant Disposition: OLEP

Of 246 participants randomized to receive 140 mg of erenumab (n = 121) or placebo (n = 125) in the DBTP, 240 (97.6%) entered the 3-year OLEP (Figure 1). In the OLEP, 118/240 participants continued erenumab (140 mg) (continuous erenumab group) and 122/240 participants switched from placebo to erenumab (140 mg) (placebo-erenumab group). Overall, 169/240 (70.4%) participants completed the entire 3-year OLEP, and 168 (70%) were classified as having completed the study (see Study Completers section below). Discontinuations (71/240 [29.6%]) were due to lack of efficacy (12.5%, n = 30), subject/guardian decision (10.8%, n = 26), AEs (4.6%; n = 11, single case per AE), new therapy choice for migraine or migraine prophylaxis (0.8%, n = 2), and physician decision and pregnancy (0.4%, n = 1 each).

### Participant Disposition: PTAP

All 36 participants who entered the PTAP completed this study period.

**Figure 1** Participant Disposition




A participant is defined as an OLEP completer if the participant status is ticked as n*completed* at the end of the OLEP. A participant is defined as an FU completer if the participant status is ticked as *completed* at the end of the FU. A participant is defined as a study completer if (1) the participant completed the OLEP and the safety follow-up visit, if not continuing on commercial erenumab, or (2) completed the OLEP and continuing on commercial erenumab, or (3) completed the PTAP erenumab. Of the 26 participants who discontinued due to participant/guardian decision, 5 discontinued due to commercially available erenumab during the OLEP. A total of 3 participants discontinued the safety follow-up. Two of these 3 participants had entered the safety follow-up after discontinuing the OLEP; the other 1 participant completed the OLEP before discontinuing the follow-up. DBTP = double-blind treatment phase; FU = follow-up; OLEP = open-label extension phase; PTAP = posttrial access phase.

## Study Completers

In total, 168 participants (70.0%) completed the study. A participant was defined as a study completer if their status at the end of OLEP was ticked as *completed*. For this to be ticked, any one of the following criterion had to be fulfilled: (1) participant completed OLEP and the safety follow-up (if not continuing on commercial erenumab); (2) participant completed OLEP and continued on commercial erenumab; (3) participant completed both OLEP + PTAP (for the subset of participants who entered PTAP).

## Efficacy

The denominators mentioned below represent the number of participants in each analysis with data available (i.e., had that response variable defined at the respective time point).

### Monthly Migraine Days

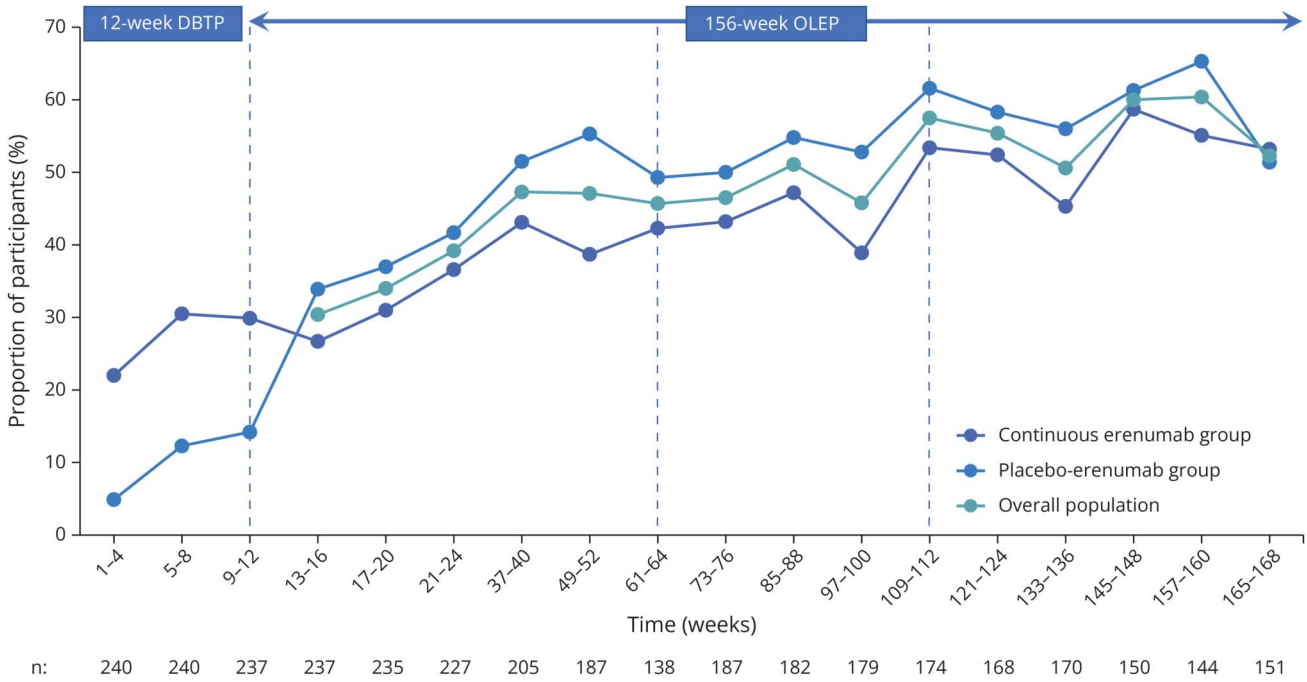
In the overall population, the proportion of participants achieving ≥50% reduction from baseline in MMDs (≥50% responders) was 45.7% (63/138) at week 64, 57.5% (100/174) at week 112, and 52.3% (79/151) at week 168 (Figure 2). No clinically meaningful difference was noted in the proportion of ≥50% responders between the 2 treatment groups from week 16 onward. Of note, in the placebo-erenumab group, the proportion of ≥50% responders was higher at week 16 (33.9%) vs week 12 (14.2%), the earliest time point when efficacy was assessed after entry into the OLEP.

The proportion of ≥30% responders was 66.7% (92/138) at week 64, 69.5% (121/174) at week 112, and 72.8% (110/151) at week 168 (eFigure 2). For ≥75% responders, the proportion was 22.5% (31/138) at week 64, 29.9% (52/174) at week 112, and 33.1% (50/151) at week 168. The proportion of ≥30% and ≥75% responders increased from baseline through week 168, showing sustained improvement during the 3-year OLEP. At weeks 64, 112, and 168, the proportion of 100% responders was 12.3% (17/138), 16.1% (28/174), and 13.2% (20/151), respectively.

### Change From Baseline in MMDs

The mean (SD) change from baseline in MMDs was −3.5 (4.2) days at week 64, −4.3 (4.7) days at week 112, and −4.4 (3.9) days at week 168 in the overall population (eFigure 3). The change in MMD from baseline was similar for the 2 treatment groups from week 16 onward. In the placebo-

**Figure 2** Proportion of Participants With ≥50% Reduction in MMDs From Baseline (Open-Label Analysis Set)




The number of participants with valid data points at a given week were considered for the responder calculation. DBTP = double-blind treatment phase; MMD = monthly migraine day; n = the total number of participants in the treatment group with response variable defined in the respective visit; OLEP = open-label extension phase.

erenumab group, the mean change from baseline was much greater at week 16 (−2.5 [4.3] days) vs the last assessment preswitch (week 12, −0.2 [4.4] days).

### Individual Participant Response

The heat maps in Figure 3 show the individual participant responses (≥50% reduction in MMD) to erenumab therapy from week 0 through week 168. At week 12, more participants treated with erenumab than placebo were responders. Following the switch in the OLEP, a clear improvement in the placebo-erenumab group was observed, with even more nonresponders converting to responders, vs continuous erenumab. This is further supported by the responder status data presented below and in the shift table (eTable 1).

### Treatment Group Responder Status Throughout the OLEP

Of the 118 participants originally randomized to erenumab who entered the OLEP, 117 had valid MMD values at week 12. Similarly, of the 122 participants originally randomized to placebo who entered OLEP, 120 had valid MMD values at week 12.

### Maintenance of ≥50% MMD Response

In participants of the continuous erenumab group who entered the OLEP, 35/117 (29.9%) were ≥50% responders at week 12. Of them, 26/35 (74.3%) maintained their ≥50% responder status in at least half of OLEP visits and 16/35 (45.7%) in at least 80% of OLEP visits (eTable 1). In the placebo-erenumab group, 17/120 (14.2%) participants were ≥50% responders at week 12. Following the switch to erenumab in OLEP, 12/17 participants (70.6%) maintained their ≥50% responder status in at least half of OLEP visits and 8/17 (47.1%) in at least 80% of OLEP visits.

### Maintenance of ≥75% and 100% Response

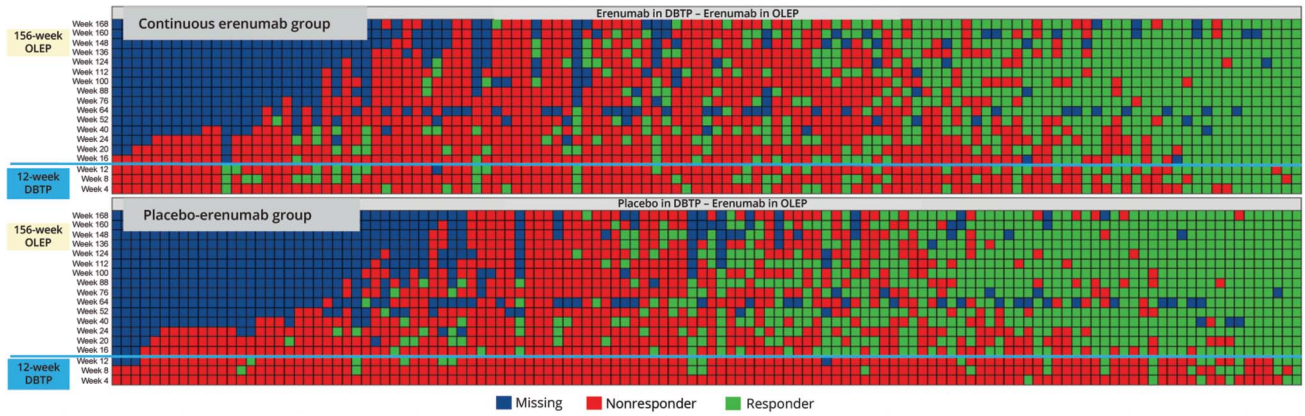
In the continuous erenumab group, 13/117 participants (11.1%) had ≥75% response at week 12. Of these 13 participants, 7 (53.8%) remained ≥75% responders in at least half of OLEP visits and 4 (30.8%) in ≥80% of OLEP visits. A 100% reduction from baseline was observed in 6/117 (5.1%) participants in the continuous erenumab group at week 12; 5/6 (83.3%) remained 100% responders at ≥50% of OLEP visits and 2/6 (33.3%) at ≥80% of OLEP visits.

In the placebo-erenumab group, 5/120 participants (4.2%) were ≥75% responders at week 12; 1/5 (20.0%) remained ≥75% responders in at least half of OLEP visits, with none remaining ≥75% responders in at least 80% of OLEP visits. No 100% responders were observed at week 12.

### ≥50% Responder Rates During the OLEP in Nonresponders at Week 12

Of the 117 participants in the continuous erenumab group, 82 (70.1%) were classified as nonresponders (<50% reduction from baseline in MMD) at week 12. Of them, 17/82 (20.7%) converted to ≥50% responders in at least half of OLEP visits and 6/82 (7.3%) converted to ≥50% responders in at least 80% of OLEP visits. Of the 103/120 (85.8%) participants

**Figure 3** Heat Maps: Participant Responder Status Throughout the Study




Each vertical column denotes the responder status (≥50% reduction in MMD) of an individual participant through their journey in the trial at each time point. The visit names are provided along the y-axis. The individual responses of participants treated with erenumab and those treated with placebo up to week 12 of the DBTP is presented below the horizontal blue line. In each participant-column, the color of the cell denotes responder status (green = responder, red = nonresponder, and 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 as nonresponders. After reaching the initial ≥50% response threshold, a <40% response vs baseline was always considered a nonresponder status (red). An MMD reduction of between 40% and 50% was acceptable and considered ≥50% responder (green) for that visit if the response at the next visit was ≥50% once more. A <50% response at 2 consecutive visits was considered a nonresponder over both periods. Up to week 12 represents 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. DBTP = double-blind treatment phase; MMD = monthly migraine day; OLEP = open-label extension phase.

originally randomized to placebo and classified as nonresponders at week 12, 42/103 (40.8%) converted to ≥50% responders in at least half of OLEP visits and 17/103 (16.5%) converted to ≥50% responders in at least 80% of OLEP visits after switching to erenumab (eTable 1).

### AMSM Treatment Days

The mean (SD) monthly AMSM treatment days decreased from baseline (4.62 [2.9] days) throughout the first year of treatment in the OLEP and were maintained throughout the 3 years. The mean (SD) change from baseline values in monthly AMSM treatment days were −1.8 (3.2) days at week 64, −2.3 (3.1) days at week 112, and −2.3 (3.0) days at week 168 (eTable 2).

### Patient-Reported Functional Outcomes

#### *Headache Impact Test-6*

At baseline, the mean (SD) HIT-6 total score for the overall population (N = 240) was 62.4 (4.6), which decreased to 52.6 (8.5) at the end of the OLEP. The scores decreased from baseline through year 1, and the reduction was maintained throughout the 3-year OLEP. Mean (SD) changes in HIT-6 scores from baseline were −9.0 (8.7) at week 60, −9.3 (8.6) at week 120, and −9.7 (8.9) at week 164 (Figure 4A).

#### *Migraine Physical Function Impact Diary*

Similar to the HIT-6 scores, there was a noticeable reduction in the MPFID-PI and MPFID-EA scores from baseline in the first year of treatment in the OLEP, which was maintained throughout the 3-year OLEP. The mean (SD) change from baseline for PI was −4.8 (7.6) at week 64, −4.5 (10.3) at week 112, and −5.1 (7.6) at week 168. The mean (SD) change from baseline for EA was −5.9 (8.5) at week 64, −5.4 (10.3) at week 112, and −6.1 (8.2) at week 168 (eTable 2).

#### *Work Productivity and Activity Impairment*

The degree of patient-reported work impairment was collected during the DBTP and OLEP (week 168), as measured by the 4 subscales of WPAI scores. The scores showed an improvement at week 168, the mean improvement (SD) for percent impairment while working was 17.8 (27.7); that for percent overall, work impairment was 16.5 (27.9); that for percent average activity impairment due to problem was 16.3 (29.2), and that for lost productivity score was 16.5 (27.9) in overall population (N = 240; Figure 4B). No apparent change was observed in percent of average work time missed due to illness.

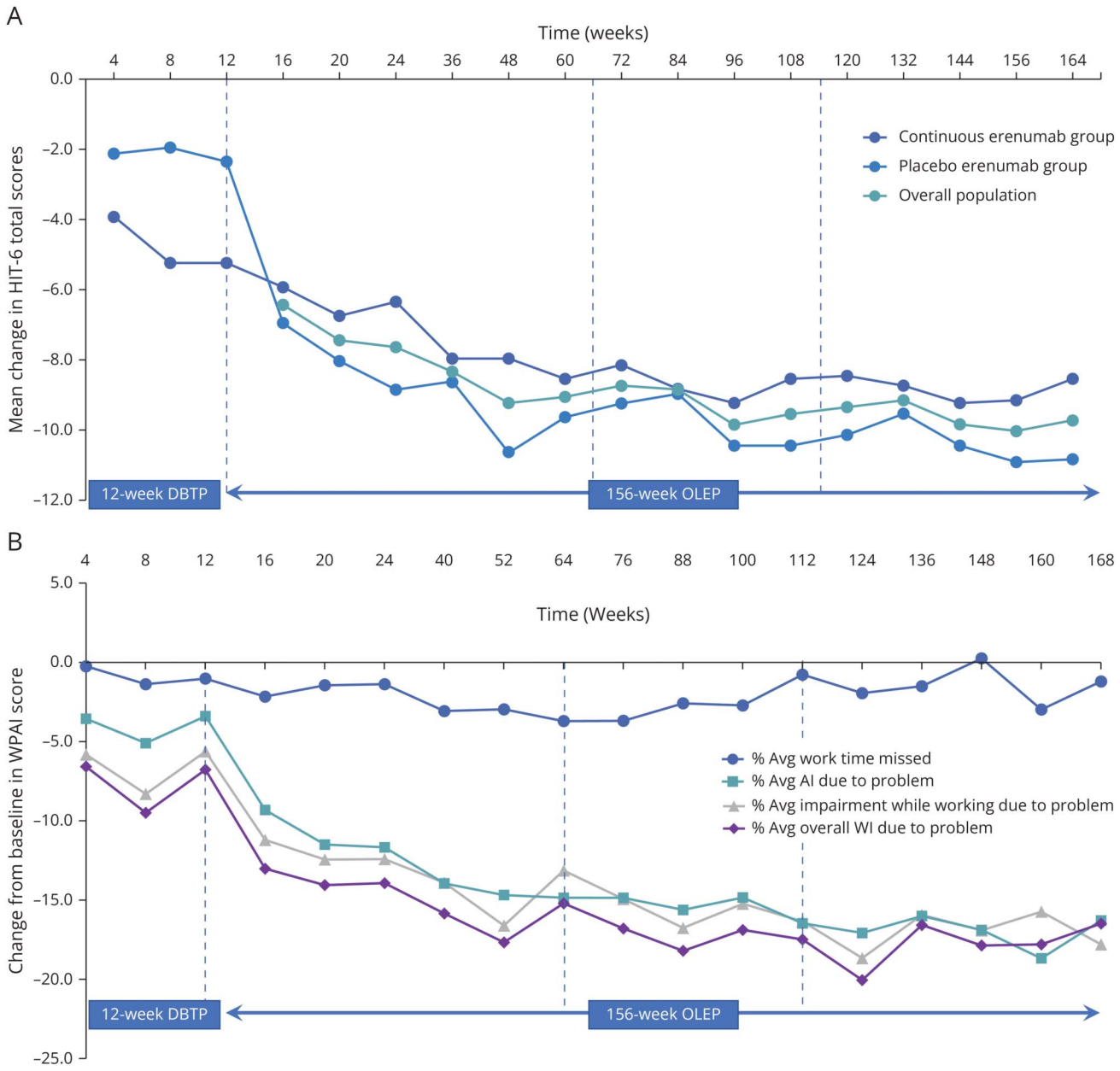
## Tolerability and Safety

The mean duration of exposure to erenumab was 129.1 weeks, with a total exposure of 593.9 person-years. Figure 5 shows the incidence of AEs of special interest, hypertension, and constipation throughout the OLEP + PTAP (156 weeks plus up to 26 additional weeks).

The incidence of treatment-emergent AEs of hypertension was 9.6% (23/240 participants [3.9/100 person-years]). All hypertension AEs were grade 1 (n = 17, 7.1%) or grade 2 (n = 6, 2.5%). Five (2.1%) of the grade 1 events of hypertension were reported as related to study treatment. In addition, 1 participant showing increased BP was also included under hypertension Standardized MedDRA Queries.

Table 1 summarizes how the incidence of elevated BP (>140 mm Hg SBP and >90 mm Hg DBP) varied over the

**Figure 4** Patient-Reported Functional Outcomes

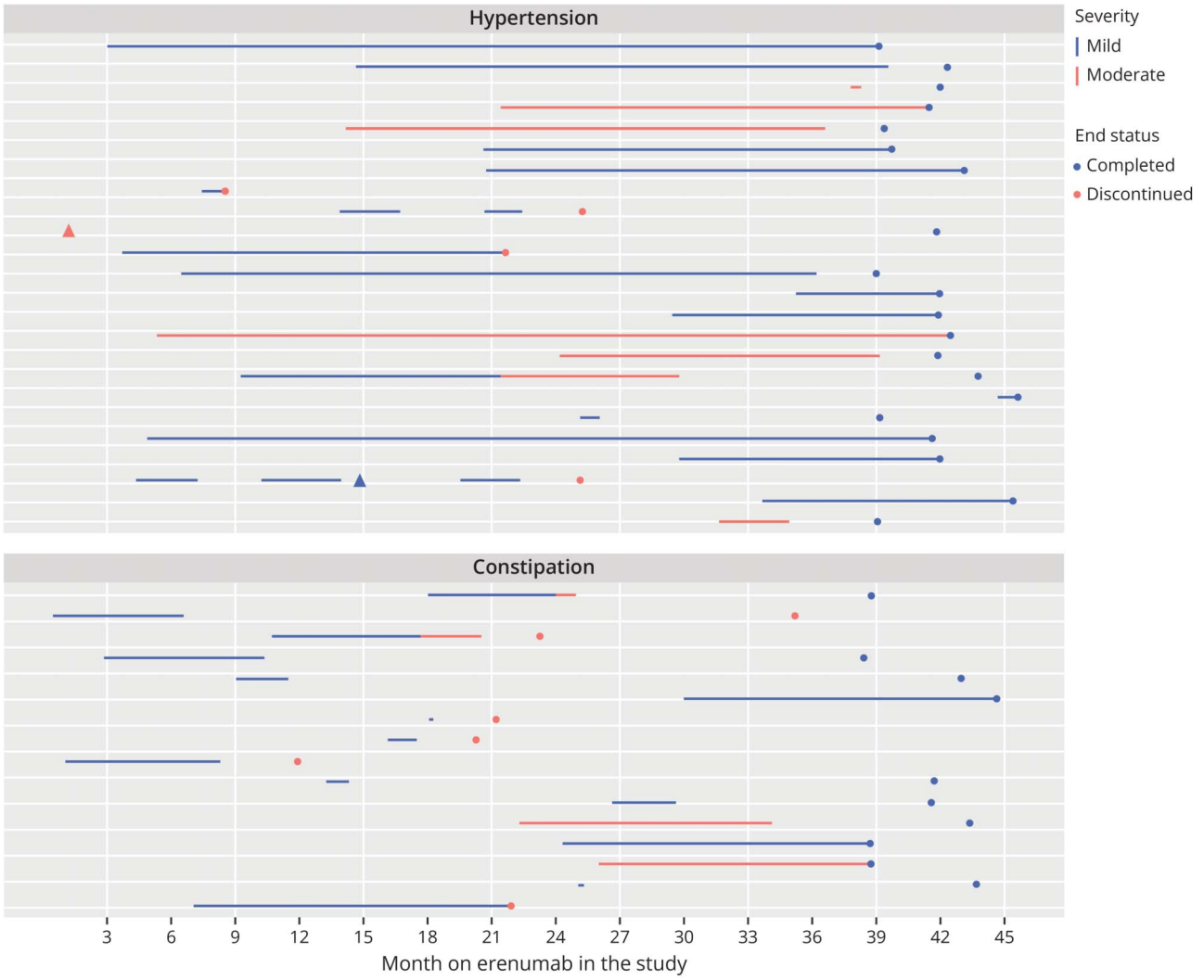



(A) Change in HIT-6 total score from baseline until week 164 of the OLEP (open-label analysis set). (B) Change from baseline of WPAI scores and subscores* during DBTP and OLEP (open-label analysis set). AI = activity impairment; Avg = average; DBTP = double-blind treatment phase; HIT-6 = Headache Impact Test; OLEP = open-label extension phase; WI = work impairment; WPAI = Work Productivity and Activity Impairment questionnaire. Data are mean (SD) of participants with nonmissing values at week 168. Change from baseline = postbaseline − baseline. The baseline period is defined as the period between the week 4 visit and the day before the first dose. The baseline value is the prorated number to 28-day equivalents during the baseline period. At each time point, only participants with a value at both baseline and that time point are included. *WPAI is a measure of level of impairment. The greater the negative scores in WPAI assessment, the higher is the improvement.

3-year OLEP. Of note, no participant with a normal BP measurement at both screening and baseline had elevated BP on 3 consecutive postbaseline assessments. Furthermore, only 1 participant showed elevated BP measurements at >50% of assessments over the 3-year OLEP. This 1 participant had an assessment of elevated BP at baseline but not at screening (Table 1). Twenty-four participants, including 2 with a medical history of hypertension, had hypertension events during the OLEP, with 8 cases of moderate severity and the rest of mild severity. Overall, 19 (7.9%) participants, previously naïve to antihypertensives before initiating erenumab in both groups, were treated for treatment-emergent hypertension (eTable 3). No participant discontinued the study due to hypertension.

Overall, 16/240 participants (6.7%, 2.7/100 person-years) had constipation events reported during the trial, and all were grade 1 (12 participants, 5.0%) or grade 2 (4 participants,

**Figure 5** Summary of AEs of Special Interest: Hypertension (SMQ) and Constipation (CMQ) in OLEP + PTAP (Safety Analysis Set)




Each line of data represents an individual participant. The bars represent the duration of each single event with start date and end date. Please note that events with duration <3 days are marked as triangles with the color of the corresponding AE severity category. AE = adverse event; CMQ = customized MedDRA query; OLEP = open-label extension phase; PT = preferred term; PTAP = posttrial access phase; SMQ = standardized MedDRA query. SMQ hypertension includes AE PT hypertension, labile hypertension, systolic hypertension, and blood pressure increased.

1.7%). Four (1.7%) of the grade 1 and 2 (0.8%) of the grade 2 events of constipation were reported as related to study treatment. No clear pattern of when constipation started could be observed, and no participant discontinued study treatment due to constipation.

The exposure-adjusted incidence of AEs for the overall population decreased in subsequent years (242.9/100 person-years after year 1, 198.0/100 person-years after year 2, and 176.2/100 person-years after year 3 + PTAP) (Table 2). Overall, the proportion of participants with treatment-emergent AEs was comparable between the continuous erenumab group (103 [87.3%]) and placebo-erenumab group in the OLEP (112 [91.8%]). The incidence rate of treatment-emergent AEs was higher for the placebo-erenumab group than that for the continuous erenumab group in the OLEP + PTAP treatment period, with an exposure-adjusted incidence rate of 142.8/100 person-years for the continuous group and 224.4/100 person-years for the switch group during the OLEP (data not shown). Overall, the most frequently reported exposure-adjusted AEs (≥5/100 person-years) were nasopharyngitis (28.8/100 person-years), influenza (7.5/100 person-years), and back pain (5.8/100 person-years). Most AEs were moderate (52.1%) or mild (25.4%) in severity, and only 12.1% of AEs were severe in nature.

Overall, 73/240 participants (30.4%) had ≥1 AE that was suspected to be related to the study treatment by the investigator. All AEs were of grade 1 or grade 2 severity (Common Terminology Criteria for Adverse Events) except for an event of grade 3 pneumonia reported in 1 participant.

**Table 1** BP: Change From Baseline Across the 3-Years OLEP (Safety Analysis Set)

| Postbaseline assessment criteria; n (%) | Screening and baseline (normal BP) (N = 211) | Screening (>140 mm Hg SBP and >90 mm Hg DBP) (N = 6) | Baseline (>140 mm Hg SBP and >90 mm Hg DBP) (N = 7) | Screening and baseline (>140 mm Hg SBP and >90 mm Hg DBP) (N = 3) |
|---|---|---|---|---|
| **Last 2 vital signs assessments** | 0 | 0 | 1 (14.3) | 0 |
| **2 or more postbaseline values elevated** | 14 (6.6) | 5 (83.3) | 7 (100.0) | 3 (100.0) |
| **3 or more postbaseline values elevated** | 7 (3.3) | 5 (83.3) | 7 (100.0) | 3 (100.0) |
| **5 or more postbaseline values elevated** | 3 (1.4) | 4 (66.7) | 4 (57.1) | 2 (66.7) |
| **2 consecutive postbaseline values elevated** | 8 (3.8) | 5 (83.3) | 5 (71.4) | 3 (100.0) |
| **3 consecutive postbaseline values elevated** | 0 | 3 (50.0) | 4 (57.1) | 2 (66.7) |
| **At least 50% postbaseline values elevated** | 0 | 0 | 1 (14.3) | 0 |
| **At least 75% postbaseline values elevated** | 0 | 0 | 1 (14.3) | 0 |

Abbreviations: BP = blood pressure; DBP = diastolic BP; OLEP = open-label extension phase; SBP = systolic BP.
N represents the total number in each group meeting the value. Data are presented as n (%).

No deaths were reported during the study. Overall, 34/240 participants (14.2%) reported an SAE during the OLEP/PTAP. Most SAEs were grade 2 or grade 3. Only 1 event of grade 3 severity (pneumonia) was suspected to be related to the study drug. The only grade 4 SAEs were allergy to arthropod sting, pulmonary embolism, and cerebral hemorrhage, reported in 1 participant each. Overall, the incidence of SAEs was low (6.0/100 person-years) in the OLEP/PTAP (Table 2). All SAEs were individual events occurring in single participants (incidence of 0.2/100 person-years), except for migraine (4 participants, 0.6/100 person-years) and biliary colic and depression (2 participants, 0.3/100 person-years for each SAE).

In the overall population, the exposure-adjusted incidence rate of discontinuation of treatment due to AEs was 1.9/100 person-years. No specific condition or type of event led to discontinuation, and all AE discontinuations were single events in individual participants. Of the AEs that led to discontinuation of study treatment, the medication overuse headache (grade 2), cervix carcinoma stage 0 (grade 3), and status migrainosus (grade 2) events were reported as SAEs. No trends were observed in the change from baseline values of hematologic or clinical chemistry parameters.

## Discussion

This final LIBERTY report details the >3 years' follow-up results of the efficacy, safety, and tolerability of 140 mg of erenumab in participants with EM in whom 2 to 4 prior migraine preventive treatments were unsuccessful or contraindicated. The high retention rate (70.4%) over a period of 3+ years confirms and extends the proven sustained efficacy and good tolerability of erenumab from earlier studies[2-6,8] to include a difficult-to-treat population.[11-13] This accords with previous findings from a 5-year long-term open-label extension study showing consistent efficacy and safety of erenumab over time in participants with EM.[8]

During the OLEP, the efficacy of erenumab improved in the first year and was maintained until the end of the 3 years. The proportion of participants who achieved ≥50% reduction in MMD from baseline increased in both the continuous erenumab and placebo-erenumab groups. A similar trend in improvement was observed in the proportion of participants who achieved ≥30%, ≥75%, and 100% reductions in MMDs.

In this 3-year OLEP, long-term erenumab treatment significantly improved patient-reported functional outcomes assessing the effect of migraine on everyday activities (MPFID-EA), physical impairment (MPFID-PI), work productivity (WPAI), and functional impairment (HIT-6 scores). This improvement in functional outcomes correlated with an improved QoL.

The positive long-term results in this difficult-to-treat population are in accordance with those obtained in populations with lower degrees of disease severity,[3,4,8] although the values for efficacy outcomes were slightly lower, likely reflecting the higher disability status. No new safety and tolerability signals were observed with long-term erenumab treatment compared with previous short-term and long-term studies.[2-6,17,18] The decrease in exposure-adjusted person incidence of AEs in the subsequent years confirmed the safety profile for long-term erenumab treatment. The most frequent AEs were nasopharyngitis, influenza, and back pain. These were in line with the AEs reported in earlier clinical trials for erenumab.[2-6,8,11] Most AEs were moderate or mild in severity, and the incidence of AEs leading to discontinuation was low.

The incidence of AEs leading to discontinuation of study treatment was low, and the range of AEs leading to

**Table 2** Summary of Treatment-Emergent AEs in the OLEP + PTAP (Safety Analysis Set)

| | DBTP | | OLEP | | |
|---|---|---|---|---|---|
| | | | Year 1 | Year 1 + 2 | Year 1 + 2 + 3 + PTAP |
| Event | Erenumab 140 mg (n = 118), m (%)/r | Placebo (n = 122), m (%)/r | Overall population (N = 240), m (%)/r | Overall population (N = 240), m (%)/r | Overall population (N = 240), m (%)/r |
| **Any AE** | 70 (59.3)/402.6 | 68 (55.7)/377.9 | 194 (80.8)/242.9 | 207 (86.3)/198.0 | 215 (89.6)/176.2 |
| **Any SAE** | 2 (1.7)/7.2 | 1 (0.8)/3.4 | 16 (6.7)/7.2 | 25 (10.4)/6.3 | 34 (14.2)/6.0 |
| **Any AE leading to discontinuation of treatment** | 1 (0.8)/3.6 | 0 (0)/0 | 4 (1.7)/1.7 | 9 (3.8)/2.1 | 12 (5.0)/1.9 |
| **Any treatment-related AE** | 21 (17.8)/86.7 | 24 (19.7)/95.1 | 57 (23.8)/30.1 | 66 (27.5)/19.8 | 73 (30.4)/15.4 |
| **Most frequently reported treatment-emergent AEs (per 100 person-years) during DBTP and OLEP and PTAP, by preferred term** | | | | | |
| **Nasopharyngitis** | 6 (5.1)/22.3 | 12 (9.8)/43.3 | 74 (30.8)/41.4 | 99 (41.3)/33.9 | 113 (47.1)/28.8 |
| **Influenza** | — | — | 31 (12.9)/14.6 | 39 (16.3)/10.3 | 41 (17.1)/7.5 |
| **Back pain** | 5 (4.2)/18.4 | 2 (1.6)/6.9 | 18 (7.5)/8.2 | 26 (10.8)/6.6 | 33 (13.8)/5.8 |
| **Urinary tract infection** | 0 (0)/0 | 1 (0.8)/3.4 | 10 (4.2)/4.4 | 18 (7.5)/4.4 | 24 (10.0)/4.1 |
| **Gastroenteritis** | 1 (0.8)/3.6 | 0 (0)/0 | 11 (4.6)/4.9 | 16 (6.7)/3.9 | 23 (9.6)/3.9 |
| **Hypertension** | 1 (0.8)/3.6 | 1 (0.8)/3.4 | 7 (2.9)/3.1 | 14 (5.8)/3.4 | 23 (9.6)/3.9 |
| **Migraine** | 1 (0.8)/3.6 | 2 (1.6)/6.9 | 10 (4.2)/4.4 | 19 (7.9)/4.7 | 23 (9.6)/3.9 |
| **Sinusitis** | 1 (0.8)/3.6 | 1 (0.8)/3.4 | 10 (4.2)/4.5 | 20 (8.3)/4.9 | 23 (9.6)/3.9 |
| **Arthralgia** | 1 (0.8)/3.6 | 4 (3.3)/14.0 | 8 (3.3)/3.5 | 15 (6.3)/3.7 | 21 (8.8)/3.6 |
| **Oropharyngeal pain** | 1 (0.8)/3.6 | 0 (0)/0 | 6 (2.5)/2.6 | 16 (6.7)/3.9 | 19 (7.9)/3.2 |
| **Bronchitis** | 2 (1.7)/7.2 | 1 (0.8)/3.4 | 11 (4.6)/4.9 | 15 (6.3)/3.7 | 17 (7.1)/2.9 |
| **Fatigue** | 3 (2.5)/10.9 | 2 (1.6)/6.9 | 12 (5.0)/5.4 | 14 (5.8)/3.4 | 17 (7.1)/2.9 |
| **Constipation** | 1 (0.8)/3.6 | 2 (1.6)/6.9 | 6 (2.5)/2.7 | 13 (5.4)/3.1 | 16 (6.7)/2.7 |
| **Injection site pain** | 7 (5.9)/26.0 | 7 (5.7)/24.9 | 13 (5.4)/5.9 | 14 (5.8)/3.5 | 16 (6.7)/2.7 |
| **Upper respiratory tract infection** | 4 (3.4)/14.5 | 0 (0)/0 | 9 (3.8)/4.0 | 12 (5.0)/2.9 | 16 (6.7)/2.7 |
| **Nausea** | 3 (2.5)/10.9 | 2 (1.6)/6.9 | 7 (2.9)/3.1 | 13 (5.4)/3.1 | 15 (6.3)/2.5 |
| **Cystitis** | 1 (0.8)/3.6 | 2 (1.6)/6.9 | 11 (4.6)/4.9 | 12 (5.0)/2.9 | 15 (6.3)/2.5 |
| **Dizziness** | 3 (2.5)/10.8 | 2 (1.6)/6.9 | 12 (5.0)/5.4 | 12 (5.0)/3.0 | 12 (5.0)/2.0 |

Abbreviations: AE = adverse event; DBTP = double-blind treatment phase; N = number of participants in analysis set; OLEP = open-label extension phase; PTAP = posttrial access phase; SAE = serious adverse event.
Preferred terms are sorted in descending frequency of AEs in all the participants of year 1 + 2 + 3 + PTAP column. N = number of participants in the analysis set. m = number of participants reporting at least 1 occurrence of an AE in that class. e = sum across all participants, the total time at risk in OLEP in years. Time at risk during OLEP is the time from start of OLEP to onset of the first event in OLEP or the minimum (end of study date, last investigational product dose date + 112 days). r = exposure-adjusted person rate per 100 person-years (n/e × 100). MedDRA version 23.1 was used for the reporting of AEs. Year 1 + 2 + 3 + PTAP overall population are cumulative of data from all 3 years of OLEP and PTAP.

discontinuation was diverse (the AE was different for each of the 12 participants who discontinued study treatment). Three AEs leading to discontinuation of study treatment were reported as SAEs (medication overuse headache, cervix carcinoma, and status migrainosus); none were deemed related to study medication.

As CGRP is a vasodilator, we paid attention to the potential cardiovascular effects of CGRP inhibitors.[19,20] Development of new-onset hypertension and worsening of preexisting hypertension has been reported following the use of erenumab in a postmarketing setting.[21] Sixty-one cases of elevated BP associated with erenumab were identified from the FDA

Adverse Event Reporting System between May 17, 2018, and April 30, 2020.[15] Per the FDA's public dashboard, almost one-third (19/61, 31.1%) of participants had preexisting hypertension and 46 (75.4%) had cardiovascular disease risk factors. The onset or worsening of hypertension was reported after the first dose in 28/61 participants (45.9%), and although the event could occur at any time during treatment, it was most frequently reported within 7 days of dose administration. Erenumab was discontinued in 24/61 of the reported cases (39.3%).[15] In the Phase 3b CONQUER study reporting the efficacy and safety of galcanezumab in participants with multiple prior migraine preventive treatment failures over a 12-week DBTP, followed by a 12-week OLEP, 4/29 participants (14%) aged 65–75 years experienced treatment-emergent high DBP; however, these elevations were transient, and all 4 participants had a preexisting history of hypertension or experienced previous elevations before starting galcanezumab.[22] A prospective 12-month follow-up study of participants with migraine treated with CGRP receptor antagonists in a real-world setting assessed safety regarding BP at 3-month intervals. The mean SBP (maximum, 5.2 mm Hg) and DBP (maximum, 3.5 mm Hg) increased following CGRP mAb initiation. In the erenumab group, both SBP and DBP were significantly increased at all time points vs baseline.[23] Most of the participants remained within the normal BP limits, but ∼4% of participants (4/109) with normal baseline BP required antihypertensives after erenumab initiation.[23] In view of the postmarketing hypertension reports, the US Prescribing Information for erenumab was revised to add hypertension as a warning and an adverse drug reaction. However, the administration of erenumab in studies in male participants with stable angina and coronary artery disease undergoing an exercise treadmill test, in combination with sumatriptan vs sumatriptan alone, or in studies assessing 24-hour ambulatory BP showed no evidence of elevated BP.[24-26] In an integrated analysis across erenumab placebo-controlled trials, hypertension AEs were reported in 0.9% (placebo), 0.8% (erenumab 70 mg), and 0.2% (erenumab 140 mg) of participants.[26] Erenumab treatment for 12 weeks had no relevant effect on BP compared with placebo for resting measurements at monthly study visits in participants with EM or CM.[26] In this LIBERTY follow-up study, the incidence of treatment-emergent AEs of hypertension was <10%; all events were grade 1 or 2, with 5 of the grade 1 events reported as related to treatment. No apparent pattern was observed for time to onset of hypertension, and evident variability was present in BP across the duration of the OLEP. Indeed, even among the few participants who had an assessment of elevated BP at either baseline and/or screening, only 1 showed elevated BP (>140 mm Hg SBP and >90 mm Hg DBP) on >50% of postbaseline assessments. Of importance, no participant discontinued the study due to hypertension.

Constipation is another AE frequently reported in the postmarketing setting with the use of erenumab. In a retrospective cohort analysis using the MarketScan Research databases with 584,475 patients with migraine, it was reported that incidence rates for any constipation was 3.41/100 person-years and 0.63/100 person-years for serious constipation.[27] Incidence rates of constipation were higher with the use of acute or preventive migraine treatments.[27] Reported risk factors of constipation in participants with migraine include age and number of prior preventive treatments used. In a general population-based study (N = 645), the incidence of constipation increased with increasing age and was higher in female participants (18.3%) than in male participants (9.2%), younger than 50 years.[28] The incidence of treatment-emergent AEs of constipation over the OLEP + PTAP of the LIBERTY study was low, and all were grade 1 or 2. No discontinuations were due to constipation.

An inherent limitation of the study is that the OLEP is an open-label design, and such trials are generally associated with a responder bias (participants not responding to treatment drop out and those who do respond remain in the trial, thus inflating the overall treatment effect observed). The OLEP design may introduce bias through unblinding and dose switching at different time points. Despite this limitation, the data do show a clear trend for improvement followed by a stable maintenance of treatment effect across all efficacy parameters.

In conclusion, this follow-up with 3+ years of study data suggests long-term positive clinical effects of erenumab, which will help physicians in making an informed treatment decisions for participants with migraine. The exposure-adjusted rate of overall and most frequently reported AEs remained low, and the incidence of hypertension and constipation were ∼10% (∼4/100 person-years) and ∼7% (∼3/100 person-years), respectively. Erenumab was well tolerated, with no new safety signals reported after long-term exposure and sustained prevention of migraine attacks over at least a 3-year period in participants with difficult-to-treat EM in whom up to 4 prior migraine preventive treatments were unsuccessful or contraindicated.

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## Disclosure

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## Appendix *(continued)*

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