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RESEARCH SUBMISSIONS

Risk of hypertension in erenumab-treated patients with migraine: Analyses of clinical trial and postmarketing data

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Abstract

Objective: To assess the risk of hypertension in patients with migraine who received erenumab in clinical trials and in the postmarketing setting.

Background: Erenumab is a monoclonal antibody for migraine prevention that targets the calcitonin gene-related peptide (CGRP) receptor. Hypertension is a theoretical risk for inhibitors of the CGRP pathway. Although no evidence of an association between erenumab treatment and hypertension was observed during the clinical development program, adverse events (AEs) of hypertension have been identified in the postmarketing setting.

Methods: Safety data from four phase 2 and phase 3 clinical trials were used to perform a pooled analysis of hypertension AEs in patients with migraine receiving erenumab. Postmarketing AEs of hypertension were identified from the Amgen Global Safety database from May 17, 2018, through January 31, 2020.

Results: In the pooled analysis of clinical trials, hypertension AEs (placebo, 9/1043 [0.9%]; erenumab 70 mg, 7/893 [0.8%]; erenumab 140 mg, 1/507 [0.2%]) and percentage of patients initiating medication to treat hypertension (12/1043 [1.2%], 7/893 [0.8%], 1/507 [0.2%], respectively) were similar across treatment groups. A total of 362 AEs of hypertension were identified from the postmarketing setting, 26.2% (95/362) of which were serious, >245,000 patient-years of exposure. The exposure-adjusted incidence of hypertension was 0.144 per 100 patient-years.

Conclusions: Clinical trials did not demonstrate an increased risk of hypertension with erenumab compared with placebo, and AE rates of hypertension reported with erenumab in the postmarketing setting were generally low. Additional data are needed to fully characterize the extent to which hypertension is a risk associated with erenumab.

Abbreviations: AEs, adverse events; BP, blood pressure; CGRP, calcitonin gene-related peptide; CI, confidence interval; DBTP, double-blind treatment phase; FDA, Food and Drug Administration; SAEs, serious adverse events.

In addition to Annual Headache Cooperative of the Pacific Winter Conference, selected data were also presented as encores at the American Academy of Neurology (AAN) and the 63rd Annual Scientific Meeting of the American Headache Society (AHS).

KEYWORDS
blood pressure, calcitonin gene-related peptide, drug safety, hypertension, individual case safety report, postmarketing surveillance

INTRODUCTION

Hypertension is a common condition characterized by higher-than-normal blood pressure (BP; systolic and diastolic BP ≥140/90 mm Hg) and is associated with increased risk of cardiovascular disease.[1] The estimated prevalence of hypertension in the United States between 2011 and 2014 was 46%, based on the American College of Cardiology/American Heart Association thresholds, and 32%, based on Joint National Committee thresholds, and prevalence increases with age.[2] At least two BP measurements obtained on at least two occasions should be used to confirm a diagnosis of hypertension.[2] Hypertension is more commonly reported in patients with migraine than in migraine-free individuals (33.1% vs. 27.5%, odds ratio 1.4, 95% confidence interval [CI] 1.3–1.6).[3] Because calcitonin gene-related peptide (CGRP) can mediate vasodilation, migraine therapies targeting the CGRP pathway could potentially have cardiovascular effects.[4]

Erenumab (in the United States, erenumab-aooe), an anti-CGRP receptor monoclonal antibody, was approved in the United States in May 2018 for the preventive treatment of migraine in adults.[5] Because of the theoretical risk of cardiovascular effects described above, a number of preclinical and clinical studies were performed to evaluate the cardiovascular safety profile of erenumab. Preclinical data demonstrated that supratherapeutic concentrations of erenumab affected neither the vascular tone of isolated human coronary arteries nor the vasoconstrictive effects of sumatriptan when applied in combination.[6] In telemeterized cynomolgus monkeys, no biologically significant changes in systolic, diastolic, or mean arterial pressures were observed with a single dose of erenumab at 225 mg/kg (yielding a systemic exposure 150 times higher than that in humans at the 140 mg dose level).[6]

Clinical studies of erenumab designed to evaluate the theoretical risk of cardiovascular effects did not demonstrate evidence of an association between erenumab treatment and vascular events.[7] The effect of erenumab in combination with sumatriptan on resting BP was evaluated in a phase 1, randomized, parallel-group, double-blind, placebo-controlled trial performed in healthy participants.[8] No differences were observed in time-weighted averages of mean arterial pressure between intravenous erenumab plus sumatriptan versus sumatriptan plus placebo. Additionally, a post hoc analysis demonstrated that erenumab alone did not affect resting BP. The effect of erenumab on ambulatory BP was evaluated in a phase 1, randomized, double-blind, placebo-controlled, multiple ascending dose study of healthy participants and patients with migraine.[9] Ambulatory BP was evaluated by outpatient, 24-h, continuous BP monitoring 7 days after erenumab or placebo administration, and no statistically significant differences were observed in BP parameters in healthy participants between erenumab (21, 70, 140, or 280/210 mg subcutaneous) and placebo groups.[9] The mean and nocturnal systolic BP were significantly higher with erenumab 21 mg compared with placebo at day 36 (difference from placebo 6.65 and 7.47 mm Hg, respectively; $p < 0.05$ for both) in patients with migraine; however, these differences may have been an artifact because no statistical differences were observed at the higher dose levels (70, 140, or 280/210 mg) or at other time points.[9] A phase 2, randomized, double-blind, placebo-controlled treadmill study further evaluated the effect of erenumab on potential cardiovascular effects in patients with stable angina.[10] The change from baseline in total exercise time for the erenumab 140 mg intravenous group was noninferior to placebo after 12 weeks of treatment, and there was no difference in peak systolic or diastolic BP between erenumab and placebo groups during an exercise treadmill test. Changes from baseline in systolic and diastolic BP were similar for erenumab and placebo groups at all time points evaluated (4, 8, and 12 weeks), and all were <1.5 mm Hg in magnitude. In phase 2 and 3 placebo-controlled trials, subcutaneous injections of erenumab had no effect on BP or rate of hypertension adverse events (AEs), respectively.[11,12]

AEs of elevated BP or hypertension have been reported following the use of erenumab in the postmarketing setting, and an analysis of postmarketing reports of hypertension AEs following treatment with erenumab was recently published by Saely and colleagues from the US Food and Drug Administration (FDA).[13] In April 2020, the US Prescribing Information for erenumab was updated to include the risk of hypertension based on postmarketing experience.[5,13]

Given the findings described above, it is important to provide a comprehensive review of the risk of hypertension with erenumab. To provide a holistic assessment of the risk of hypertension among patients with migraine receiving erenumab, the present analysis provided a consolidated evaluation of both clinical trial data, by expanding on the work done by Kudrow et al.[7] (focused only on the 12-week, double-blind treatment phase [DBTP] of four published phase 2[12,14] and 3[11,15] studies) and data from the postmarketing setting.

METHODS

Hypertension AEs and BP data included in this analysis were collected from phase 2 and phase 3 clinical trials and postmarketing surveillance of erenumab; data from clinical trials and postmarketing surveillance were analyzed separately.

Clinical trial study design

Safety data from the 12-week, placebo-controlled DBTP of four phase 2 and 3 studies[11,12,14,15] were used to perform a pooled analysis of patients with migraine aged ≥18 to ≤60 or ≤65 years.[7] The clinical trials included in this pooled safety analysis are summarized in

Table 1. Patients with episodic migraine or chronic migraine received erenumab 70 or 140 mg or placebo once monthly throughout a 12- or 24-week DBTP. Of studies with a 24-week DBTP, only the first 12 weeks of the DBTP were included in the analysis. All studies were approved by independent ethics committees or institutional review boards, and patients provided informed consent.[11,12,14,15]

Data collection

Clinical trials

BP measurements for the pooled safety analysis were obtained from patients in the phase 2 and 3 clinical trials according to the time points in Table 1. BP data for each patient were based on the average of at least two measurements (separated by at least 5 min) and were obtained after the patient had been in a semirecumbent or supine position in a rested state for at least 5 min. The position used for BP measurement for each patient was consistent throughout the study.

Postmarketing surveillance

Postmarketing hypertension AE data were collected from spontaneous reports made to Amgen Global Safety from May 17, 2018 (date of erenumab approval in the United States), through January 31, 2020. Solicited reports of hypertension AE data were obtained from organized data collection systems, such as patient support programs. Reporting of AE data to the Amgen Global Safety database is voluntary for healthcare professionals, patients, and caregivers; nonetheless, Amgen widely promotes the program to ensure healthcare professionals, patients, and caregivers are aware of the process for reporting AEs.[16] Furthermore, all manufacturers are required to examine reports from the scientific literature and from marketing experience in other countries. That information is also added to the Amgen Global Safety database.[17]

Statistical analysis

All authors had access to study data. AEs of hypertension were identified in clinical trials using the standardized Medical Dictionary for Regulatory Activities (v20.0) query for hypertension (narrow and broad search terms).[7] Hypertension AEs were designated as serious based on regulatory criteria (Code of Federal Regulations, 21CFR314.80; resulted in death, were life-threatening, required hospitalization, resulted in disability, congenital anomaly, and/or were deemed medically significant).[18] Integrated analyses of pooled clinical trials were conducted over 12 weeks of double-blind treatment by treatment received; exposure-adjusted incidence rates were calculated for hypertension AEs by dividing the number of patients with at least one reported occurrence of the event by the sum of time at risk (patient-year) for reporting the event.[7] Time at risk is the time from the first dose of erenumab or placebo to the onset of the first event during the 12-week DBTP. If no event was reported, time at risk is up to the end of the DBTP or the last dose date + 84 days (for the 70 mg dose) or 112 days (for the 140 mg dose), whichever is earlier. Data were analyzed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Descriptive statistics were provided including mean and standard deviation for continuous variables and frequency and percentage for categorical variables.

TABLE 1 Summary of pooled placebo-controlled trials that evaluated the effect of erenumab on hypertension adverse events and blood pressure[7]

Study identifier	Phase	Study population	Cardiovascular exclusion criteria	Time points for BP collection
NCT01952574[12,30]	2	Patients with episodic migraine	Poorly controlled hypertension (systolic BP ≥150 mm Hg and/or diastolic BP ≥90 mm Hg)	Every 2–4 weeks of 12-week DBTP; every 4 weeks through Week 64 of OLTP then every 12 weeks for Weeks 76–268
NCT02456740[11,31]	3	Patients with episodic migraine	None for BP	Every 4 weeks of 24-week DBTP and 28-week ATP
NCT02483585[15,32]	3	Patients with episodic migraine	None for BP	Every 4 weeks of 12-week DBTP and 28-week OLTP
NCT02066415[14,33]	2	Patients with chronic migraine	Poorly controlled hypertension in the judgement of the investigator *or* systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg	Every 2–4 weeks of 12-week DBTP; every 4 weeks during 13-month OLTP
All pooled studies[7]			Myocardial infarction, stroke, TIA, unstable angina, or coronary artery bypass surgery or other revascularization procedure within 12 months before screening	Safety follow-up visit

Abbreviations: ATP, active treatment phase; BP, blood pressure; DBTP, double-blind treatment phase; OLTP, open-label treatment phase; TIA, transient ischemic attack.

Postmarketing case reports (cases) from the Amgen Global Safety database suggestive of hypertension were identified using standardized Medical Dictionary for Regulatory Activities (v22.1) query for hypertension (using broad and narrow hypertension-related search terms); cases may not reflect unique individuals. All cases identified using this search strategy were included in the analysis, including reports that contained limited information and those that described an alternative etiology for the development of hypertension. Medical history, BP measurements, concomitant medications, and event outcome data were extracted from the reports as available. Hypertension AEs were designated as serious based on regulatory criteria. The estimation of patient exposure (>245,000 patient-years) in the postmarketing setting is based on the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guideline E2C (R2) on Periodic Benefit-Risk Evaluation Report.[19] In cases where information on individual patients was unknown, alternative measures (e.g., number of prescriptions and drug sales) were used to estimate exposure. Specifically, estimates of patient-years of exposures in the postmarketing setting were based on unit sales data (i.e., vials or syringes) and on observed drug utilization parameters. Worldwide unit sales were recorded monthly by country and converted to a monthly estimate of person-count (when feasible) or person-time using region- and product-specific utilization parameters and algorithms (see below). These parameters included the average dose per administration, average length of treatment, days between administrations, patient turnover rates, market penetration rates, and average revenue per patient. These drug utilization parameters can change over time to best represent the current patient and market experience. Product formulations included a 70 mg/ml, single-dose, prefilled autoinjector one-pack, two 70 mg/ml, single-dose, prefilled autoinjectors (140 mg/2 ml), a 70 mg/ml, single-dose, prefilled syringe one-pack, and 70 mg/ml, single-dose, prefilled syringes two-pack (140 mg/2 ml). For the algorithm used to estimate exposure, each one-pack and each two-pack represented one patient-month of exposure as patients consumed one 70 mg syringe per month or two 70 mg syringes per month. All packs from a particular time interval were added together and divided by 12 to obtain patient-years of exposure.

RESULTS

Clinical trials

Pooled hypertension analyses from phase 2 and 3 clinical studies

In the pooled clinical trials, patients with migraine received placebo ($N = 1043$), erenumab 70 mg ($N = 893$), or erenumab 140 mg ($N = 507$) during the placebo-controlled DBTP.[7] Baseline patient characteristics were similar across treatment groups and are presented in Table 2. The percentage of patients with a baseline history of hypertension ranged from 5.7% (51/893) to 8.9% (93/1043).[7] High BP at screening, defined as systolic BP >140 mm Hg or diastolic BP >90 mm Hg measured on ≥2 occasions, occurred in 6.5% (58/893) to 7.0% (73/1043) of patients.[7] The incidence of hypertension AEs (placebo, 9/1043 [0.9%]; erenumab 70 mg, 7/893 [0.8%]; erenumab 140 mg, 1/507 [0.2%]),[7] the exposure-adjusted incidence of hypertension AEs (3.6 [95% CI, 1.2, 5.9], 3.3 [95% CI, 0.8, 5.7], and 0.8 [95% CI, 0.0, 2.4] per 100 patient-years, respectively), and percentage of patients initiating medication to treat hypertension (12/1043 [1.2%], 7/893 [0.8%], 1/507 [0.2%], respectively) during the DBTP were similar across treatment groups (Table 3). There were no reports of serious hypertension AEs across the treatment groups.

Postmarketing surveillance

Events related to hypertension from the Amgen Global Safety Database

A total of 362 hypertension AEs in 355 cases were reported in the postmarketing setting during the specified time frame (a total of >245,000 patient-years of exposure). The exposure-adjusted incidence rate was 0.144 per 100 patient-years, meaning that hypertension AEs were reported for 1.4 (approximately 2) patients out of every 1000 patients treated annually. The majority of patients

TABLE 2 Baseline characteristics of patients in the phase 2 and 3 pooled safety analysis[7]

Baseline characteristic	Placebo ($N = 1043$)	Erenumab 70 mg ($N = 893$)	Erenumab 140 mg ($N = 507$)
Age, years, mean (SD)	41.8 ± 11.1	41.7 ± 11.2	41.3 ± 11.2
Female, *n* (%)	869 (83.3)	755 (84.5)	431 (85.0)
White, *n* (%)	934 (89.5)	813 (91.0)	475 (93.7)
Body mass index, kg/m^2, mean (SD)	26.8 (5.8)	26.9 (5.8)	26.7 (6.0)
History of vascular disorders, *n* (%)	77 (7.4)	59 (6.6)	50 (9.9)
Vascular risk factors			
History of diabetes mellitus, *n* (%)	21 (2.0)	17 (1.9)	6 (1.2)
History of hypertension, *n* (%)	93 (8.9)	51 (5.7)	34 (6.7)
High blood pressure at screening,[a] *n* (%)	73 (7.0)	58 (6.5)	34 (6.7)

Abbreviations: BP, blood pressure; SD, standard deviation.

[a]Defined as systolic BP >140 mm Hg or diastolic BP >90 mm Hg measured on ≥2 occasions.

TABLE 3 Pooled analysis of hypertension AEs and antihypertensive medication use during the 12-week DBTP

	Placebo (*N* = 1043)	Erenumab 70 mg (*N* = 893)	Erenumab 140 mg (*N* = 507)
Incidence of hypertension AEs, *n* (%)[7]	9 (0.9)	7 (0.8)	1 (0.2)
Serious hypertension AEs, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Exposure-adjusted incidence rates of hypertension, per 100 patient-years	3.6	3.3	0.8
Patients without antihypertensive medication at baseline, *n*	972	859	485
Patients initiating antihypertensive medication[a] during 12-week DBTP, *n* (%)[b]	12 (1.2)	7 (0.8)	1 (0.2)

Note: *N* = number of patients in the analysis set.

Abbreviations: AEs, adverse events; DBTP, double-blind treatment phase.

[a]Antihypertensive medications with a reported indication of hypertension.

[b]Percentage calculated based on number of patients without antihypertensive medication at baseline.

were female (73.5%), and median age (range) was 53 (24–87) years (Table 4). Of the hypertension AEs, 26.2% (95/362) were determined to be serious, and 73.8% (267/362) were determined to be nonserious. There was an approximately equal distribution of solicited events (47.0%; 170/362) and spontaneous reports (53.0%; 192/362), and almost half of the events were medically confirmed by a healthcare provider (46.1%; 167/362). A total of 66.0% (239/362) of hypertension AEs were from the United States, and 34.0% (123/362) were from outside the United States. Of hypertension AEs from outside the United States, 45.5% (56/123) were from Canada, the majority of which were solicited.

TABLE 4 Postmarketing surveillance of patient demographics in cases of hypertension

	N = 355 cases
Sex, *n* (%)	
Female	261 (73.5)
Male	45 (12.7)
Unknown	49 (13.8)
Age,[a] years	
Mean	53.1
Median (range)	53 (24–87)
Age group,[a] years, *n* (%)	
24–30	12 (4.8)
31–40	25 (9.9)
41–50	58 (23.0)
51–60	80 (31.7)
61–70	55 (21.8)
71–80	17 (6.7)
81–87	5 (2.0)

[a]Based on data available for 252 cases.

Event characteristics were evaluated for reports of verbatim preferred terms (hypertension, hypertensive, or preeclampsia/eclampsia [i.e., hypertension during pregnancy]; *n* = 44 events) versus nonverbatim preferred terms describing a change or increase in BP only (e.g., BP abnormal, BP increased; *n* = 318 events) (Table 5). Events were based on one reported instance of BP elevation in 61.4% (27/44) of verbatim events and 95.9% (305/318) of nonverbatim events.

BP data were available for 47 of 94 serious cases (Figure 1). In 21 of these cases, BP was reported to have reached American Heart Association criteria for hypertensive crisis (systolic BP >180 mm Hg and/or diastolic BP >120 mm Hg) based on available highest systolic or diastolic BP level measured by patients or healthcare professionals.

Reports of hypertension AEs were evaluated for potential risk factors (Table 6). Previously documented diagnosed hypertension was identified as a risk factor in 33.7% (32/95) of hypertension-related serious AEs (SAEs) and 11.2% (30/267) of nonserious hypertension AEs. Other potential risk factors were unknown for approximately half of the events.

For nonserious hypertension AEs, acute elevation of BP associated with migraine pain was identified in 29.2% (78/267) of events. The time to onset of hypertension was ≤1 day in 12.0% (32/267) of events; time to onset was not documented for most hypertension AEs (71.9% [192/267]). Most hypertension AEs were based on a single reported instance of elevated/high BP (94.4% [252/267]) and did not include details of any treatment for the event (92.1% [246/267]).

For SAEs, acute elevation of BP associated with migraine pain was identified in 4.2% (4/95) of events. Time to onset of hypertension was not documented for approximately half of SAEs (51.6% [49/95]); of those documented, the time to onset was ≤1 day in 23.9% (11/46) of events (Table 6). Similar to nonserious AEs, most SAEs were based on a single reported instance of BP elevation (84.2% [80/95]) and did not include details of any treatment for the event (78.9% [75/95]). When the intervention required at the time of the report was known, 37.9% (36/95) of patients discontinued treatment for SAEs; the intervention required was unknown in 45.2% [43/95] of SAEs. Antihypertensive medication was initiated for 10.5% (10/95) of SAEs. Four patients with SAEs with no documented preexisting history of hypertension reported reoccurrence of increased BP following rechallenge after the second and/or third dose of erenumab; the outcome of all four events was discontinuation of erenumab. For all hypertension AEs, when the outcome of hypertension at the time of reporting was assessed, the proportion of events with outcome reported as recovered/resolved was similar for patients who discontinued erenumab treatment (23.1%) and for those who remained on erenumab and did not change the treatment (21.9%).

TABLE 5 Postmarketing hypertension event counts based on reported terms

	Containing verbatim terms hypertension, hypertensive, or preeclampsia/eclampsia (44 events), *n* (%)	Describing change or increase in blood pressure only (318 events), *n* (%)
Number of SAEs	17 (38.6)	78 (24.5)
Medically confirmed (initial or follow-up from HCP)	38 (80.9)	129 (40.6)
With medical history of hypertension	9 (20.5)	53 (16.7)
Without medical history of hypertension, but with other risk factors for hypertension	9 (20.5)	85 (26.7)
Number of cases with only one reported instance of BP elevation	27 (61.4)	305 (95.9)
Started antihypertension medication(s)	6 (13.6)	20 (6.3)
Restarted or changed dose of previous antihypertension medication(s)	4 (9.1)	11 (3.4)

Abbreviations: BP, blood pressure; HCP, heathcare provider; SAE, serious adverse event.

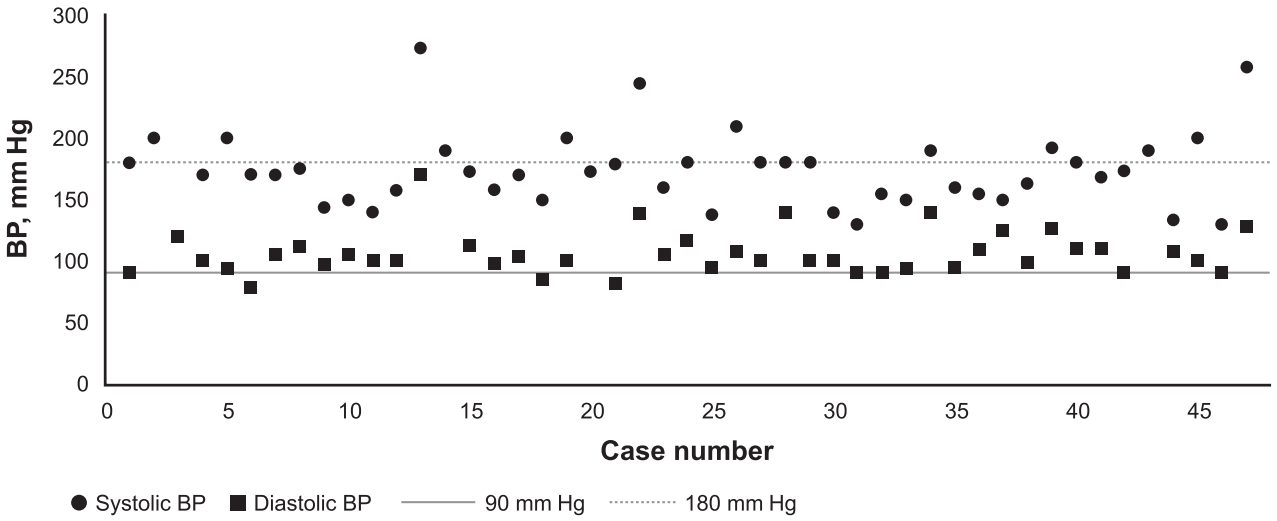

FIGURE 1 BP measurements reported for serious cases of hypertension following erenumab during postmarketing surveillance. BP values were available for 47/94 serious cases. BP, blood pressure; DBP, diastolic BP; SBP, systolic BP

DISCUSSION

Using BP measurement methods that were designed to reduce variability and inaccuracy (e.g., serial measurements and consistent body position), results from pooled safety analyses of phase 2 and 3 clinical trials demonstrated that erenumab had no effect on BP or incidence of hypertension AEs compared with placebo.[7] Furthermore, there was no difference in the proportion of patients initiating antihypertensive medication while on placebo or erenumab 70 or 140 mg during the 12-week DBTP. Rates of hypertension AEs were low during the 12-week DBTP for placebo, erenumab 70 mg, and erenumab 140 mg treatment groups, as well as during open-label erenumab treatment. Additionally, mean changes in systolic and diastolic BP across study visits were small, similar between erenumab and placebo groups, and showed no evidence of dose response.[7]

In a long-term, open-label study of patients with episodic migraine, no meaningful changes in BP (i.e., increase of >2–3 mm Hg) were observed with up to 5 years of treatment with erenumab.[20] Exposure-adjusted rates of hypertension with erenumab 70 and 140 mg during open-label treatment were low compared with pooled rates observed in patients who received placebo during double-blind treatment (1.9 vs. 3.8 per 100 patient-years, respectively), a finding similar to that observed in the current analysis (placebo, 3.6 per 100 patient-years; erenumab 70 mg, 3.3 per 100 patient-years; erenumab 140 mg, 0.8 per 100 patient-years). Similar to erenumab, safety analyses from clinical trials of other anti-CGRP monoclonal antibody migraine-preventive therapies did not reveal an increase in BP, an increase in the proportion of patients with categorical increases in BP, or an increased risk of hypertension compared with placebo.[21–24] Additionally, gepants, which are small-molecule CGRP receptor antagonists, have not shown an association with hypertension or increased BP.[25–27]

In the postmarketing setting, using the Amgen Global Safety Database, hypertension AEs following the use of erenumab were identified, some of which occurred in patients who had preexisting hypertension (11.2%, AEs; 33.7%, SAEs) or risk factors for hypertension including diabetes and cardiovascular disease. More than half of the postmarketing hypertension AEs (71.9%, AEs; 51.6%, SAEs)

TABLE 6 Characteristics of hypertension AEs from postmarketing reports

Event characteristics	Hypertension SAEs (95 events), *n* (%)	Hypertension non-SAEs (267 events), *n* (%)
Risk factors[a]		
Previous documented hypertension	32 (33.7)	30 (11.2)
Diabetes	5 (5.3)	8 (3.0)
Cardiovascular disease	4 (4.2)	3 (1.1)
Obstructive sleep apnea	2 (2.1)	1 (0.04)
Obesity	5 (5.3)	5 (1.9)
Thyroid disease	7 (7.4)	6 (2.3)
Triptan or ergot alkaloid use for acute migraine exacerbation	8 (8.4)	10 (3.7)
Acute elevation of BP associated with migraine pain	4 (4.2)	78 (29.2)
Prior history of preeclampsia in earlier pregnancy[b]	1 (1.1)	0 (0)
Documented smoker	1 (1.1)	6 (2.3)
Unknown	51 (53.7)	153 (57.3)
Time to onset		
≤1 day	11 (11.6)	32 (12.0)
>1 day to ≤1 week	9 (9.5)	4 (1.5)
>1 week to ≤2 weeks	5 (5.3)	9 (3.4)
>2 weeks to ≤1 month	6 (6.3)	8 (3.0)
>1 month to ≤2 months	4 (4.2)	7 (2.6)
>2 months to ≤3 months	6 (6.3)	2 (0.7)
>3 months	5 (5.3)	13 (4.9)
Unknown	49 (51.6)	192 (71.9)
Intervention required with erenumab at the time of report		
Discontinued	36 (37.9)	70 (26.2)
No change	13 (13.7)	51 (19.1)
Temporarily withheld	1 (1.1)	4 (1.5)
Dose decreased	0 (0)	3 (1.1)
Dose increased	2 (2.1)	5 (1.9)
Unknown	43 (45.2)	134 (50.2)
Number of elevated BP measures documented		
1	80 (84.2)	252 (94.4)
2	12 (12.6)	9 (3.4)
3	2 (2.1)	1 (0.4)
4	1 (1.1)	5 (1.9)
Treatment for the hypertension event		
No treatment documented	75 (78.9)	246 (92.1)
Restarted or changed previously discontinued antihypertension medication	10 (10.6)	5 (1.9)
Started new antihypertension medication	10 (10.5)	16 (6.0)

Abbreviations: AEs, adverse events; BP, blood pressure; SAEs, serious adverse events.

[a]Some hypertension AEs were associated with >1 risk factor.

[b]One event of preeclampsia in a 37-year-old female who had similar issues in a previous pregnancy (before erenumab).

did not describe the time to hypertension onset; of the AEs with this information available, approximately half occurred within 1 week of the first administration of erenumab. Where data were available, a causal attribution to erenumab was unclear because of medical history of hypertension, preexisting risk factors of hypertension, and improbable time to pharmacologic onset (within 1 h to 1 day). Given that the peak serum concentration of erenumab is reached in approximately 6 days, the time to onset of <1 day would appear unlikely to be related to erenumab.[5] Furthermore, results from a recent analysis of the Marketscan Early View Claims Database showed that unadjusted rates of hypertension among new users of erenumab, fremanezumab, and galcanezumab, from May 17, 2018, through January 31, 2020, were similar regardless of the presence of hypertension at baseline or severity of the hypertension outcome.[28]

Saely et al. from the US FDA Center for Drug Evaluation and Research recently published an analysis of postmarketing reports of hypertension AEs following treatment with erenumab.[13] Postmarketing data were obtained from the FDA Adverse Event Reporting System database or published reports. Unlike our analysis, which included all postmarketing reports regardless of the extent of information available, the FDA analysis excluded reports that contained limited information, and causality was considered probable only if event time to onset was ≤4 weeks and potential confounding factors were absent. Between May 17, 2018, and April 30, 2020, 61 cases of elevated BP were identified. Similar to our findings, elevated BP was most frequently observed within 1 week of erenumab (≤7 days, 46% [28/61]; 8 to ≤14 days, 6.6% [4/61]; 15 to ≤21 days, 3.3% [2/61]; 22 to ≤28, 16.4% [10/61]; unspecified, 27.9% [17/61]). Additionally, most cases reported a single, elevated BP measurement, and baseline BP measurements were available for 49% of cases.[13] BP measurements may vary with acute use of caffeine or nicotine, bladder distension, device-related inaccuracy, and body position; overestimation of BP can have important clinical implications, thus highlighting the need to obtain multiple measurements before making treatment decisions or assigning a diagnosis of hypertension.[2,29] It is interesting to note that in our analysis of postmarketing reports, hypertension events resolved regardless of whether patients discontinued (23.1%) or continued (21.9%) erenumab treatment.

Our analyses have several limitations. Although hypertension was generally not an exclusion criterion for the clinical trials

included in this analysis, the proportion of patients with a history of hypertension or high BP at screening was low. As such, the patients included in this clinical trial analysis may not fully reflect the patient population receiving erenumab in real-world clinical practice. Limitations of the postmarketing cases include incomplete information, lack of a control arm, and the possibility of duplicate reports. Additionally, the definition of hypertension used (i.e., elevated BP vs. hypertension, often based on a single BP measurement) and the method of BP measurement are unknown from postmarketing reports. Finally, outcomes from postmarketing surveillance cannot easily be compared with those from clinical trials, owing to differences in underlying population groups, differences in data collected, and larger variances in the size of the populations under investigation. However, these are common limitations of postmarketing reports, and postmarketing reports do provide vital information for monitoring patient safety.

CONCLUSIONS

Clinical trials did not demonstrate an increased risk of hypertension in patients with migraine treated with erenumab compared with placebo. In the postmarketing setting, hypertension AEs have been reported following the use of erenumab, many of which occurred in patients who had preexisting hypertension or risk factors for hypertension. Additional data are needed to fully characterize those at risk, as well as the nature, timing, and extent to which hypertension is a risk associated with erenumab and other CGRP-pathway antagonists.

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CONFLICT OF INTEREST

David W. Dodick reports the following conflicts within the past 12 months: Consulting: AEON, Amgen, Clexio, Cerecin, Cooltech, Ctrl M, Allergan, Alder, Biohaven, GSK, Linpharma, Lundbeck, Promius, Eli Lilly, eNeura, Novartis, Impel, Satsuma, Theranica, WL Gore, Nocira, XoC,Zosano,Upjohn(DivisionofPfizer),Pieris,Praxis,Revance,Equinox. Honoraria: Clinical Care Solutions, CME Outfitters, Curry Rockefeller Group, DeepBench, Global Access Meetings, KLJ Associates, Academy for Continued Healthcare Learning, Majallin LLC, Medlogix Communications, MJH Lifesciences, Miller Medical Communications, Southern Headache Society (MAHEC), WebMD Health/Medscape, Wolters Kluwer, Oxford University Press, Cambridge University Press. Research Support: Department of Defense, National Institutes of Health, Henry Jackson Foundation, Sperling Foundation, American Migraine Foundation, Patient Centered Outcomes Research Institute (PCORI). Stock Options/Shareholder/Patents/Board of Directors: Ctrl M (options), Aural analytics (Options), ExSano (Options), Palion (Options), Healint (Options), Theranica (Options), Second Opinion/Mobile Health (Options), Epien (Options/Board), Nocira (Options), Matterhorn (Shares/Board), Ontologics (Shares/Board), King-Devick Technologies (Options/Board), Precon Health (Options/Board). Patent 17189376.1–1466:vTitle: Botulinum Toxin Dosage Regimen for Chronic Migraine Prophylaxis. Stewart Tepper reports consulting for Aeon, Alexsa, Allergan/Abbvie, Alphasights, Amgen, Aperture Venture Partners, Aralez Pharmaceuticals Canada, Axsome Therapeutics, Becker Pharmaceutical Consulting, BioDelivery Sciences International, Biohaven, ClearView Healthcare Partners, CoolTech, CRG, Currax, Decision Resources, DeepBench, DRG, Eli Lilly and Company, Equinox, ExpertConnect, GLG, Guidepoint Global, Impel, InteractiveForums, M3 Global Research, Magellan Rx Management, Medicxi, Navigant Consulting, Neurolief, Nordic BioTech, Novartis, Palion Medical, Pulmatrix, Reckner Healthcare, Relevale, Satsuma, Slingshot Insights, Spherix Global Insights, Teva, Theranica, Thought Leader Select, Trinity Partners, Unity HA, XOC, and Zosano; speaking and CME teaching for American Academy of Neurology, American Headache Society, Catamount Medical Education, Cleveland Clinic Foundation, Diamond Headache Clinic, Elsevier, Forefront Collaborative, Hamilton General Hospital (Ontario, Canada), Headache Cooperative of New England, Henry Ford Hospital (Detroit), Inova, Medical Learning Institute Peerview, Medical Education Speakers Network, Miller Medical Communications, North American Center for CME, Physicians' Education Resource, PlatformQ Education, Rockpointe, ScientaCME, and WebMD/Medscape; employment with American Headache Society, Thomas Jefferson University, and Dartmouth-Hitchcock Medical Center; and other activities with Headache, Headache Currents, and Wiley Blackwell. He has received research grants exclusively paid to Dartmouth-Hitchcock Medical Center without personal compensation from Allergan, Amgen, ElectroCore, Eli Lilly, Lundbeck, Neurolief, Novartis, Satsuma, and Zosano. Jessica Ailani has received consulting fees from Allergan/Abbvie, Axsome, Amgen, Aeon, Biohaven, Lundbeck, GlaxoSmithKline, Eli Lilly, Impel, Satsuma, Theranica, Nesos, Teva, Medscape, and NeurologyLive; stock options from CtrlM, honoraria for participation on speakers bureau from Allergan/Abbvie, Amgen, Lundbeck, Eli Lilly, and Teva; her institution has received grant support for clinical trials from Allergan/Abbvie, American Migraine Foundation, Eli Lilly, Satsuma, and Zosano, and she serves as section editor for Current Pain and Headache Reports, medical editor for SELF, and an editor for NeurologyLive. Nicola Pannacciulli, Marco Navetta, Brett Loop, Feng Zhang, and Ani C. Khodavirdi are employees and own stock in Amgen. Allison Mann, Ahmad Abdrabboh, and Jawed Kalim are employees of Novartis.

AUTHOR CONTRIBUTIONS

Study concept and design: Nicola Pannacciulli, Marco S. Navetta, Brett Loop, Ani C. Khodavirdi. *Acquisition of data*: Brett Loop, Feng Zhang. *Analysis and interpretation of data*: David W. Dodick, Stewart J. Tepper, Jessica Ailani, Nicola Pannacciulli, Marco S. Navetta, Brett Loop, Feng Zhang, Ani C. Khodavirdi, Allison Mann, Ahmad Abdrabboh, Jawed Kalim. *Drafting of the manuscript*: David W. Dodick, Stewart J. Tepper, Jessica Ailani, Nicola Pannacciulli, Marco S. Navetta, Brett Loop, Feng Zhang, Ani C. Khodavirdi, Allison Mann, Ahmad

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DATA AVAILABILITY STATEMENT

Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: http://www.amgen.com/datasharing.

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