Changes in blood pressure category with erenumab: a pooled analysis of phase 2 and phase 3 clinical trials

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INTRODUCTION

- The efficacy of the fully human monoclonal antibody erenumab (erenumab-aooe in the United States [US]) is well-established, with significant reductions in migraine frequency and improved quality of life observed in patients with chronic and episodic migraine.[1-5]
- Based on postmarketing case reports submitted to the FDA Adverse Event Reporting System, the US prescribing information for erenumab contains a warning and precaution regarding new-onset or worsening of pre-existing hypertension (HTN).[1,6]
- The objective of this pooled analysis was to determine if erenumab treatment in phase 2 and 3 clinical trials was associated with a worsening of blood pressure (BP) category compared with placebo in patients with normal BP, elevated BP, or HTN at baseline.

METHODS

- Data were pooled from two phase 2 and two phase 3 clinical trials that evaluated erenumab versus placebo for migraine prevention[2-5] (**Table 1**).
- Patients were grouped into American College of Cardiology/American Heart Association (ACC/AHA) categories of BP in adults[7] (**Figure 1**).
- The ACC/AHA guideline recommends to use an average of ≥ 2 readings obtained on ≥ 2 occasions to assign patients to a BP category.[7]
- Thus, patients were categorized based on mean systolic BP (SBP) and mean diastolic BP (DBP) measured over the initial screening period and pre-first dose on Day 1 ('baseline'), and during months 1–3 of the double-blind treatment phase (DBTP) ('post-baseline').
- The primary outcome was the proportion of patients with a worsening of BP category over months 1–3 of the DBTP relative to baseline.
- The secondary outcome was the proportion of patients with a worsening of BP category over months 4–6 of the DBTP relative to baseline in Study NCT02456740.

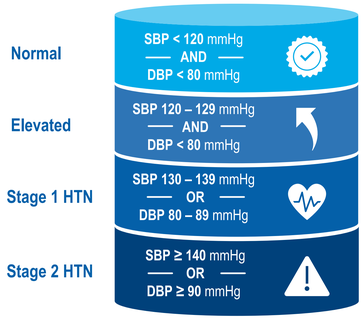
Table 1. Details of pooled erenumab studies

Study	Phase	Patients	Treatment	Frequency of BP Collection
NCT01952574	2	N = 483 episodic migraine	• 12-week DBTP – Placebo – Erenumab 7 mg – Erenumab 21 mg – Erenumab 70 mg	• Initial screening • Baseline phase (Week -4 and Day 1) • Weeks 2, 4, 8, and 12 of the DBTP
NCT02066415	2	N = 667 chronic migraine	• 12-week DBTP – Placebo – Erenumab 70 mg – Erenumab 140 mg	• Initial screening • Baseline phase (Week -4 and Day 1) • Weeks 2, 4, 8, and 12 of the DBTP
NCT02456740	3	N = 955 episodic migraine	• 24-week DBTP – Placebo – Erenumab 70 mg – Erenumab 140 mg	• Initial screening • Baseline phase (Week -4 and Day 1) • Every 4 weeks during the 24-week DBTP
NCT02483585	3	N = 577 episodic migraine	• 12-week DBTP – Placebo – Erenumab 70 mg	• Initial screening • Baseline phase (Week -4 and Day 1) • Every 4 weeks during the 12-week DBTP

BP, blood pressure; DBTP, double-blind treatment phase.

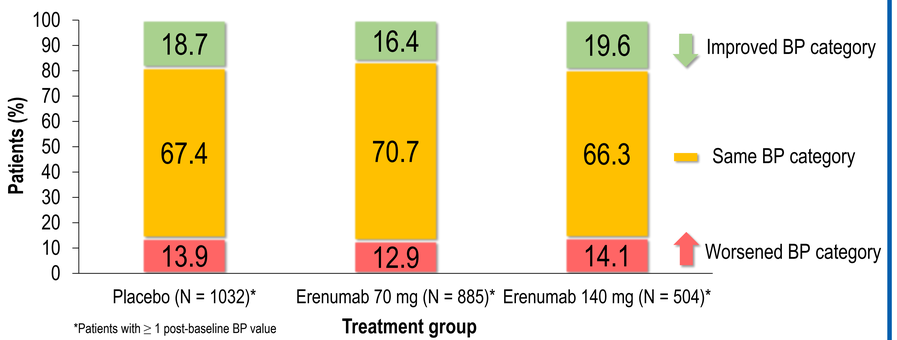
In clinical trials, **worsening of ACC/AHA BP category was similar between erenumab and placebo** in patients with normal BP, elevated BP, or HTN at baseline

Figure 1. ACC/AHA categories of BP in adults



Similar proportions of patients in placebo and erenumab groups improved, worsened, or remained in the same ACC/AHA BP category

Figure 2. Changes in ACC/AHA BP category from baseline to mean over months 1 – 3 of the DBTP



*Patients with ≥ 1 post-baseline BP value

Table 2. Shifts in BP category from baseline to months 1.3 of the DBTP (NCT01952574, NCT02066415, NCT02456740 and NCT02483585)

Baseline BP category	BP Category Based on Mean SBP/DBP Over Months 1–3			
	Normal	Elevated	Stage 1 HTN	Stage 2 HTN
Placebo (Total N1 = 1032)				
Normal (N1 = 466)	392 (84.1)	38 (8.2)	35 (7.5)	1 (0.2)
Elevated (N1 = 129)	50 (38.8)	51 (39.5)	28 (21.7)	0 (0.0)
Stage 1 HTN (N1 = 354)	54 (15.3)	46 (13.0)	213 (60.2)	41 (11.6)
Stage 2 HTN (N1 = 83)	0 (0.0)	3 (3.6)	40 (48.2)	40 (48.2)
Erenumab 70 mg (Total N1 = 885)				
Normal (N1 = 423)	365 (86.3)	27 (6.4)	31 (7.3)	0 (0.0)
Elevated (N1 = 108)	34 (31.5)	41 (38.0)	32 (29.6)	1 (0.9)
Stage 1 HTN (N1 = 281)	44 (15.7)	36 (12.8)	178 (63.3)	23 (8.2)
Stage 2 HTN (N1 = 73)	0 (0.0)	1 (1.4)	30 (41.1)	42 (57.5)
Erenumab 140 mg (Total N1 = 504)				
Normal (N1 = 236)	194 (82.2)	24 (10.2)	18 (7.6)	0 (0.0)
Elevated (N1 = 68)	18 (26.5)	30 (44.1)	19 (27.9)	1 (1.5)
Stage 1 HTN (N1 = 160)	31 (19.4)	29 (18.1)	91 (56.9)	9 (5.6)
Stage 2 HTN (N1 = 40)	0 (0.0)	1 (2.5)	20 (50.0)	19 (47.5)

Table 3. Shifts in BP category from baseline to months 4–6 of the DBTP (NCT02456740 only)

Baseline BP category	BP Category Based on Mean SBP/DBP Over Months 4–6			
	Normal	Elevated	Stage 1 HTN	Stage 2 HTN
Placebo (Total N1 = 292)				
Normal (N1 = 121)	104 (86.0)	4 (3.3)	13 (10.7)	0 (0.0)
Elevated (N1 = 32)	15 (46.9)	9 (28.1)	8 (25.0)	0 (0.0)
Stage 1 HTN (N1 = 104)	26 (25.0)	14 (13.5)	50 (48.1)	14 (13.5)
Stage 2 HTN (N1 = 35)	2 (5.7)	1 (2.9)	18 (51.4)	14 (40.0)
Erenumab 70 mg (Total N1 = 298)				
Normal (N1 = 132)	114 (86.4)	6 (4.5)	12 (9.1)	0 (0.0)
Elevated (N1 = 37)	13 (35.1)	10 (27.0)	12 (32.4)	2 (5.4)
Stage 1 HTN (N1 = 98)	22 (22.4)	18 (18.4)	48 (49.0)	10 (10.2)
Stage 2 HTN (N1= 31)	0 (0.0)	2 (6.5)	11 (35.5)	18 (58.1)
Erenumab 140 mg (Total N1 = 299)				
Normal (N1 = 142)	123 (86.6)	9 (6.3)	10 (7.0)	0 (0.0)
Elevated (N1 = 34)	11 (32.4)	13 (38.2)	10 (29.4)	0 (0.0)
Stage 1 HTN (N1 = 96)	25 (26.0)	18 (18.8)	46 (47.9)	7 (7.3)
Stage 2 HTN (N1 = 27)	1 (3.7)	1 (3.7)	9 (33.3)	16 (59.3)

Data reported for patients with ≥ 1 post-baseline BP value. Data are n (%); % = n / N1 x 100. Red, orange and green colors denote worsening, no change, and improvement in BP category, respectively. BP, blood pressure; DBP, diastolic blood pressure; DBTP, double-blind treatment phase; HTN, hypertension; N1, total number of patients with observed values in BP categories; SBP, systolic blood pressure.

Additional **postmarketing data generation is warranted** to further understand the risk of worsening BP in patients with migraine and pre-existing HTN treated with erenumab

RESULTS

- Overall, 1032, 885, and 504 patients received placebo, erenumab 70 mg, and erenumab 140 mg, respectively, and had ≥ 1 post-baseline BP value.
- At baseline, the mean age of the patients was 43 years and 80% were female. Approximately 40% of patients had ≥ 2 cardiovascular risk factors (e.g. diabetes mellitus, history of hypertension, high BP at screening, cigarette use, family history of coronary heart disease, history of dyslipidemia, high cholesterol level, high lipid level, BMI > 30 kg/m^2).
- In patients with available post-baseline BP data, worsening of BP category from baseline to Months 1–3 of the DBTP occurred in 12.9% and 14.1% of patients treated with erenumab 70 mg and 140 mg, respectively, compared with 13.9% of patients who received placebo (**Table 2; Figure 2**).
- In study NCT02456740, worsening of BP category from baseline to Months 4–6 of the DBTP occurred in 14.1% and 12.0% of patients treated with erenumab 70 mg and 140 mg, respectively, compared with 13.4% of patients who received placebo (**Table 3**).

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CONFLICTS OF INTERESTS

David W. Dodick: AbbVie (Consulting); AEON (Consulting); Alder (Consulting); American Migraine Foundation (Other Activities); Amgen (Consulting); Aural Analytics (Stock); Biohaven (Consulting); Cambridge University Press (Other Activities); Cerecin (Consulting); Clexio (Consulting); CME Outfitters (Other Activities); Ctrl M (Stock); Ctrl M (Consulting); Curry Rockefeller Group (Other Activities); DeepBench (Other Activities); Department of Defense (Other Activities); Eli Lilly (Consulting); eNeura (Consulting); Epien (Stock); Equinox (Consulting); ExSano (Stock); Global Access Meetings (Other Activities); Healint (Stock); Henry Jackson Foundation (Other Activities); Impel (Consulting); King-Devick Technologies (Stock); KLJ Associates (Other Activities); Linpharma (Consulting); Lundbeck (Consulting); Majallin LLC (Other Activities); Matterhorn (Stock); Medlogix (Other Activities); Miller Medical Communications (Other Activities); National Institutes of Health (Other Activities); Nocira (Stock); Nocira (Consulting); Novartis (Consulting); Ontologics (Stock); Oxford University Press (Other Activities); Palion (Stock); Patent 17189376.1-1466:vTitle: Botulinum Toxin Dosage Regimen for Chronic Migraine Prophylaxis (Other Activities) (Patent); Patient Centered Outcomes Research Institute (PCORI) (Other Activities); Pieris (Consulting); Precon Health (Stock); Promius (Consulting); Revance (Consulting); Second Opinion/Mobile Health (Stock); Southern Headache Society (MAHEC) (Other Activities); Sperling Foundation (Other Activities); Theranica (Stock); Theranica (Consulting); Upjohn (Division of Pfizer) (Consulting); WebMD Health/Medscape (Other Activities); WL Gore (Consulting); Wolters Kluwer (Other Activities); XoC (Consulting); Zosano (Consulting). Kavita Kalidas: AbbieVie (Consulting); Amgen (Consulting); Eli Lilly (Consulting); Lundbeck (Consulting); Novartis (Consulting). Carrie Dougherty: Abvie/Allergan (Consulting); Allergan (Consulting); Amgen (Other Activities) (research); Amgen (Speaking and Teaching); Biohaven (Consulting); Biohaven (Speaking and Teaching); Clearview Health Partners (Consulting); electroCore (Other Activities) (research); eletrocore (Consulting); Eli Lilly (Speaking and Teaching); Eli Lilly and Co (Consulting); Guidepoint Consulting (Consulting); Impel (Consulting); Lundbeck (Consulting); Lundbeck (Speaking and Teaching); Magellan Rx Management (Consulting); Novartis (Speaking and Teaching); Novartis (Consulting); Supernus (Consulting); TEVA (Consulting); Teva Pharmaceuticals (Speaking and Teaching); Theranica (Consulting). Rob Nelson, Nico Pannacciulli, Feng Zhang, Jose Flores-Arredondo, Jessica Choudhry: Amgen (employment). Fei Xue: Amgen (employment) at the time of the study.

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