Effects of Erenumab on Non-pain Symptoms in Patients with Chronic Migraine

Stewart J Tepper,[1] Uwe Reuter,[2] Messoud Ashina,[3] Jan L Brandes,[4] Feng Zhang,[5] Nan Sun,[6] Xiangyi Meng,[6] Ahmad Abdrabboh,[6] Ronald Zielman,[7] Denise E Chou,[5] Paul Winner[8]

[1]Geisel School of Medicine at Dartmouth, Hanover, NH, CA, USA; [2]Dept Neurology, Charité Universitätsmedizin Berlin, Berlin, Germany; [3]Dept Neurology, Danish Headache Center, Rigshospitalet Glostrup, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark; [4]Nashville Neuroscience Group and Vanderbilt University Department of Neurology, Nashville, TN, USA; [5]Amgen Inc., Thousand Oaks, CA, USA; [6]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [7]Novartis Pharma AG, Basel, Switzerland; [8]Premiere Research Institute, Nova Southeastern University, West Palm Beach, FL, USA

One Sentence Summary: A post-hoc analysis of a Phase 2 pivotal chronic migraine (CM) trial suggests that erenumab therapy reduces the burden of some migraine-associated non-pain symptoms.

Background: Non-pain symptoms are frequently cited by patients as their most bothersome migraine- associated symptoms, and are often disabling. However, changes in non-pain migraine symptoms are inconsistently assessed in migraine prevention trials, resulting in a paucity of evidence to inform clinical practice. In a Phase 2 pivotal study of adults with CM (NCT02066415), erenumab treatment (both 70 mg and 140 mg) led to a greater reduction from baseline in mean monthly migraine days (MMDs) compared to placebo [-2.5 days, 95% CI (-3.5, -1.4), $p<0.001$]. The objective of this post-hoc analysis was to assess potential effects of erenumab (erenumab-aooe in the US) on migraine-associated non-pain symptoms.

Methods: Patient-reported non-pain symptoms included nausea, phonophobia, photophobia, and vomiting. Severity of non-pain symptoms was collected on days where patients reported a headache, and was assessed using a categorical scale (0, symptom-free; 1, mild; 2, moderate; 3, severe). Endpoints for this post-hoc analysis included change from baseline in number of non-pain symptom days, cumulative monthly symptom severity (the sum of patient-reported daily worst symptom score per monthly interval), and average monthly symptom severity. The ANCOVA model was applied to all analyses. Treatment effects at Week 12 were reported as differences [least-squares mean (95% confidence interval)] in changes from baseline relative to placebo; p values are nominal without

multiplicity adjustment. These analyses were conducted only on subjects with ≥1 day of a given symptom at baseline.

Results: Baseline characteristics, including MMDs, of subjects in the overall study (efficacy analysis set) were generally similar between treatment groups (Table 1). Treatment with erenumab led to reductions from baseline in the number of days with photophobia relative to placebo [70 mg: -1.55, 95% CI (-2.67, -0.43), p = 0.007; 140 mg: -1.84, 95% CI (-2.97, -0.72), p = 0.001]. Similarly, erenumab led to reductions from baseline in the number of days with phonophobia relative to placebo [70 mg: -1.51, 95% CI (-2.64, -0.37), p = 0.010; 140 mg: -1.30, 95% CI (-2.43, -0.17), p = 0.024)]. The change from baseline in days with nausea compared to placebo for erenumab 70 mg was -0.86 [95% CI (-1.76, 0.04), p = 0.062] and for 140 mg was -1.16 [95% CI (-2.07, -0.24), p = 0.013]. The change from baseline in days with vomiting compared to placebo for erenumab 70 mg was -0.72 [95% CI (-1.60, 0.17), p = 0.111] and for 140 mg was -0.12 [95% CI (-1.01, 0.78), p = 0.797]. Relative to placebo, erenumab treatment led to a reduction from baseline in cumulative monthly symptom severity of photophobia and phonophobia ($p < 0.05$). Change from baseline in average monthly non-pain symptom severity was largely similar between treatment groups.

Conclusion: This post-hoc analysis suggests that preventive treatment with erenumab in CM may reduce days with migraine-associated non-pain symptoms, highlighting the potential benefit of erenumab therapy in improving disease burden beyond migraine headache frequency.

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Table: Baseline patient characteristics and outcomes at Week 12 by treatment group.

Variables	PlaceboN = 281	Erenumab 70 mg N = 188	Erenumab 140 mg N = 187
Mean Age – years (SD)	42.07 (11.41)	41.16 (11.29)	43.07 (11.05)
Female Gender – n (%)	224 (79.7)	165 (87.8)	159 (85.0)
Monthly Migraine Days Baseline Mean (SD) Week 12 Mean (SD) Change from Baseline, days (SE) Placebo-adjusted difference*, days 95% CI; *p*-value	 18.24 (4.72) 14.05 (7.11) -4.20 (0.39) - -	 17.94 (4.36) 11.17 (7.50) -6.85 (5.89) -2.64 -3.84, -1.45; $p < 0.001$	 17.78 (4.68) 11.26 (7.46) -6.70 (0.47) -2.49 -3.68, -1.30; $p < 0.001$

Days with Photophobia Baseline Mean (n, SD) Week 12 Mean (n, SD) Change from Baseline, days (SE) Placebo-adjusted difference, days 95% CI; *p*-value	13.9 (264, 7.29) 8.4 (256, 7.24) -5.40 (0.36) - -	13.8 (176, 6.76) 7.0 (162, 7.29) -6.95 (0.45) -1.55 -2.67, -0.43; $p = 0.007$	13.5 (169, 7.14) 6.5 (160, 6.77) -7.25 (0.45) -1.84 -2.97, -0.72; $p = 0.001$
Days with Phonophobia Baseline Mean (n, SD) Week 12 Mean (n, SD) Change from Baseline, days (SE) Placebo-adjusted difference, days 95% CI; *p*-value	12.4 (246, 7.04) 7.3 (237, 7.16) -5.13 (0.37) - -	12.3 (167, 7.21) 5.8 (153, 6.94) -6.64 (0.45) -1.51 -2.64, -0.37; $p = 0.010$	12.5 (166, 7.41) 6.1 (158, 6.89) -6.43 (0.45) -1.30 -2.43, -0.17; $p = 0.024$

N=number of patients in the efficacy analysis set; n=number of patients analyzed

*Adjusted least squares mean treatment difference vs placebo. Pairwise comparisons were made between eacherenumab treatment group vs placebo with nominal p-value without multiplicity adjustment.

CI, confidence interval; SD, standard deviation; SE, standard error

Days with Nausea			
Baseline Mean (n, SD)	9.5 (256, 6.31)	9.1 (169, 5.95)	10.2 (156, 6.93)
Week 12 Mean (n, SD)	5.4 (246, 5.87)	4.3 (157, 5.03)	4.7 (149, 5.87)
Change from Baseline, days (SE)	-4.19 (0.29)	-5.05 (0.36)	-5.35 (0.37)
Placebo-adjusted difference, days	-	-0.86	-1.16
95% CI; *p*-value	-	-1.76, 0.04; $p = 0.062$	-2.07, -0.24; $p = 0.013$
Days with Vomiting			
Baseline Mean (n, SD)	3.1 (86, 2.60)	3.3 (53, 2.57)	3.4 (54, 4.16)
Week 12 Mean (n, SD)	1.3 (85, 2.90)	0.7 (48, 1.07)	1.3 (49, 3.91)
Change from Baseline, days (SE)	-1.81 (0.28)	-2.53 (0.36)	-1.93 (0.36)
Placebo-adjusted difference, days	-	-0.72	-0.12
95% CI; *p*-value	-	-1.60, 0.17; $p = 0.111$	-1.01, 0.78; $p = 0.797$

N=number of patients in the efficacy analysis set; n=number of patients analyzed

*Adjusted least squares mean treatment difference vs placebo. Pairwise comparisons were made between each erenumab treatment group vs placebo with nominal p-value without multiplicity adjustment.

CI, confidence interval; SD, standard deviation; SE, standard error