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DERP Surveillance: Calcitonin Gene-Related Peptide Inhibitors for Migraine and Cluster Headache

September 2021

Table of Contents

Objectives

This Drug Effectiveness Review Project (DERP) surveillance report previews the volume and nature of new research and relevant clinical information that has emerged since the most recent systematic review update on calcitonin gene-related peptide (CGRP) inhibitors for migraines (Table 1). The literature search for this report focuses on new randomized controlled trials (RCTs), as well as actions taken by the US Food and Drug Administration (FDA) since the most recent systematic review update, including approval of new drugs, formulations, or indications, and identification of serious harms. Comprehensive searches, quality assessment, and synthesis of evidence would follow only if DERP participants commission an updated review or another research product type for this topic. Comprehensive searches might identify additional eligible studies.

Topic History and Context

This report is the first surveillance document on the topic since the most recent systematic review update (April 2020). The search strategy for that review was through March 31, 2020.

Table 1. Topic History and Search Dates

Document Type	Date Presented	Search Dates
Systematic Review Update	April 2020	July 1, 2018 to March 31, 2020
Surveillance Report	September 2019	February 1, 2019 to August 1, 2019
Surveillance Report	March 2019	July 1, 2018 to February 1, 2019
Systematic Review	October 2018	Date of database inception to July 1, 2018

PICOS

Population

- Adults with episodic or chronic migraines with no previous treatment history, or adults who have not responded to other migraine therapies
- Adults with episodic or chronic cluster headaches with no previous treatment history, or adults who have not responded to other migraine therapies
- Adults with acute migraine headaches

Interventions

Table 2. List of Included CGRP Inhibitors

Generic Name	Brand Name	Indication	Date of FDA Approval
Eptinezumab	Vyepti	Preventive treatment of chronic and episodic migraine in adults	February 2020
Erenumab	Aimovig	Preventive treatment of chronic and episodic migraine in adults	May 2018
Fremanezumab	Ajovy	Preventive treatment of chronic and episodic migraine in adults	September 2018
Galcanezumab	Emgality	Preventive treatment of chronic and episodic migraine in adults	September 2018
		Treatment of episodic cluster headache	June 2019
Rimegepant	Nurtec ODT	Acute treatment of migraine with or without aura in adults	February 2020
		Preventive treatment of episodic migraine in adults	**May 2021**
Ubrogepant	Ubrelvy	Acute treatment of migraine with or without aura in adults	December 2019

Note. ***Bold*** *indicates a newly approved indication since the last research product.*
Abbreviations. CGRP: calcitonin gene-related peptide; FDA: US Food and Drug Administration; ODT: orally disintegrating tablet.

Comparators

- CGRP inhibitors compared to each other (head-to-head)
- Pharmacological agents aimed at treating or preventing migraines or cluster headaches (e.g., amitriptyline, ergotamine, onabotulinumtoxinA)
- Sham or placebo

Outcomes

- Migraine events (including frequency, intensity, and duration)
- Pain (including intensity, duration, and pain scale range)
- Other symptoms (e.g., nausea, vomiting, photophobia, phonophobia)
- Functional ability (including cognitive)
- Disability
- Quality of life (QoL)
- Other patient-reported outcomes (e.g., depression, anxiety, difficulties in interpersonal relationships)
- Employment-related outcomes (e.g., unemployment, work productivity loss, absenteeism)
- Use of rescue therapies
- Number of emergency department, number of primary care provider visits
- Tolerability
- Adverse events (AEs)
- Serious adverse events (SAEs)
- Discontinuations due to AEs

Study Designs

- RCTs

Key Questions

KQ1. What is the effectiveness of CGRP inhibitors for:
   a. Prevention of chronic migraine headache?
   b. Prevention of episodic migraine headache?
   c. Acute treatment of migraine headache?
   d. Prevention of cluster headache?

KQ2. What is the frequency of AEs with CGRP inhibitors for the prevention and treatment of episodic and chronic migraine and cluster headache and for the acute treatment of migraine?

KQ3. Are there subgroups of people based on demographics (e.g., age, racial groups, gender), comorbidities (e.g., drug-disease interactions), or other medications for which CGRP inhibitors differ in effectiveness or harms?

KQ4. What are the characteristics of ongoing studies of CGRP inhibitors for the prevention and treatment of episodic and chronic migraine and cluster headache or the acute treatment of migraine?

Methods

Using the PICOS outlined above, Center for Evidence-based Policy (Center) researchers searched ClinicalTrials.gov, the ISRCTN registry, and the FDA website for eligible RCTs. Using relevant clinical trial numbers and other identifiers, we then searched Ovid MEDLINE ALL from April 1, 2020 to August 1, 2021. We used the Google search engine to identify studies published since the implementation of the search strategy in the updated systematic review (April 2020). We used limits for English language and human participants. We also searched the FDA website to identify newly approved drugs, formulations, indications, and new serious harms (e.g., boxed warnings) or warnings for included interventions. To identify new drugs, we used Google and searched CenterWatch (a privately owned database of clinical trials information), IPD Analytics, and the FDA website.

Findings

New Drugs or Formulations

No new drugs were identified since the updated systematic review was completed in April 2020. However, atogepant (AGN-246189), an oral agent being manufactured by AbbVie for the prevention of migraines, will likely be reviewed by the FDA for approval in the third quarter of 2021.[1]

New Indications

Rimegepant (Nurtec ODT [orally disintegrating tablet]) was approved for the treatment of acute migraines with or without aura in adults in February 2020.[2] On May 27, 2021, the FDA expanded the drug label to include prevention of episodic migraines.[2]

New Serious Harms or Warnings

No new serious harms or warnings were identified since the searches in the most recent updated systematic review.

Randomized Controlled Trials

We identified 9 new published RCTs during this surveillance period,[3-11] along with 1 published abstract on an RCT comparing erenumab and topiramate[12] (Table 3):

- 2 RCTs for eptinezumab on prevention of chronic migraines[7] and treatment of episodic migraines[11]
- 3 RCTs (1 abstract) for erenumab on the prevention of episodic migraines[8,10,12] and chronic migraines[8,12]
  - 1 head-to-head trial comparing erenumab and topiramate[12]
- 1 RCT for fremanezumab on the prevention of episodic and chronic migraines[5]
  - 3 other trials[13-15] reported results on ClinicalTrials.gov, but we could not identify a publication
- 3 RCTs for galcanezumab on the prevention of episodic migraine,[6,9] chronic migraine,[6] and chronic cluster headaches[4]
- 1 RCT for rimegepant on the prevention of episodic and chronic migraine[3]
  - 1 trial[16] reported results on ClinicalTrials.gov, but we could not identify a publication

We did not identify any new RCTs of ubrogepant for migraines published during this surveillance period.

Table 3. New Published RCTs of CGRP Inhibitors for Migraines

Author, Year Study Name Study Number	Population Sample Size	Intervention Comparator Follow-up	Primary Outcome(s)
Eptinezumab			
Lipton et al., 2021[7] PROMISE-2 NCT02974153	Adults (18 to 65) with a diagnosis of migraine at ≤ 50 years of age and currently experiencing chronic migraines N = 1,121	Eptinezumab (preventive) Placebo 12 weeks	• Change from baseline in mean monthly migraine days over weeks 1 to 12
Winner et al., 2021[11] RELIEF NCT04152083	Adults (18 to 75) with > 1 year history of migraine and episodic migraines 3 months prior to screening N = 480	Eptinezumab (treatment during a moderate to severe migraine attack) Placebo 24 hours	• Time to headache pain freedom • Time to absence of most bothersome symptom (nausea, photophobia, or phonophobia)

Author, Year Study Name Study Number	Population Sample Size	Intervention Comparator Follow-up	Primary Outcome(s)
Erenumab			
Reuter et al., 2021[12] (*abstract*) HER-MES NCT03828539	Adults in Germany with episodic migraines N = 777	Erenumab (70 mg or 140 mg; preventive) Oral topiramate (highest tolerated dose: 50 to 100 mg/day) 24 weeks	• Proportion of patients who discontinued study medication due to an AE during the double-blind phase
Takeshima, et al., 2021[8] NCT03812224	Adults (20 to 65) in Japan with ≥ 1 year history of migraine prior to screening with episodic or chronic migraines N = 261	Erenumab (70 mg; preventive) Placebo 24 weeks	• Change from baseline in mean monthly migraine days over 6 months
Wang et al., 2021[10] EMPOwER NCT03333109	Adults (18 to 65) with a diagnosis of migraine and experiencing episodic migraines N = 900	Erenumab (70 mg or 140 mg; preventive) Placebo 3 months	• Change from baseline in monthly migraine days at Month 3
Fremanezumab			
Goadsby et al., 2020[5] HALO NCT02638103	Adults (18 to 70) in Japan with ≥ 1 year history of migraine prior to screening with episodic or chronic migraines N = 1,890	Fremanezumab (monthly and quarterly; preventive) Placebo 12 months	• Proportion of patients who experienced an AE
Galcanezumab			
Dodick et al., 2020[4] NCT02438826	Adults (18 to 65) with a history of chronic cluster headache, without a remission period, or with remissions lasting < 1 month, for ≥ 1 year N = 237	Galcanezumab (300 mg; preventive) Placebo 52 weeks	• Mean change from baseline in weekly attack frequency
Kuruppu et al., 2021[6] CONQUER NCT03559257	Adults (18 to 75) with episodic or chronic migraines who did not benefit from commonly prescribed preventive treatments N = 462	Galcanezumab (120 mg; 240 mg loading dose; preventive) Placebo 3 months	• Mean change from baseline in the number of monthly migraine headache days at 3 months

Author, Year Study Name Study Number	Population Sample Size	Intervention Comparator Follow-up	Primary Outcome(s)
Tatsuoka et al., 2021[9] NCT02959177	Adults (18 to 65) in Japan with ≥ 1 year history of migraine prior to screening with episodic migraines N = 459	Galcanezumab (120 mg or 240 mg; preventive) Placebo 6 months	• Monthly migraine headache days for 1 to 6 months
Rimegepant			
Croop et al., 2021[3] NCT03732638	Adults (≥ 18) with ≥ 1 year history of migraine prior to screening with episodic or chronic migraines N = 747	Rimegepant (75 mg; preventive) Placebo 12 weeks	• Change from baseline in mean number of migraine days per month at 12 weeks

Abbreviations. AE: adverse event; CGRP: calcitonin gene-related peptide; NCT: national clinical trial; RCT: randomized controlled trial.

Ongoing Studies

Overall, we identified 19 ongoing studies that would be eligible for this topic, if published:

- 4 RCTs of eptinezumab
  - Sample sizes range: 182 to 892
  - Estimated completion dates: July 2021 to February 2023
- 4 RCTs of erenumab
  - Sample sizes range: 29 to 621
  - Estimated completion dates: July 2021 to December 2022
- 6 RCTs of fremanezumab
  - Sample sizes range: 50 to 571
  - Actual or estimated completion dates: November 2019 to December 2023
- 2 RCTs of galcanezumab
  - Sample sizes: 300 and 486
  - Estimated completion dates: July 2021 to February 2023
- 2 RCTs of rimegepant
  - Sample sizes: 1,485 and 1,800
  - Actual and estimated completion dates: January 2018 (abstracts published April 2021[17,18]) and March 2022
- 1 RCT of ubrogepant
  - Sample size: 600
  - Estimated completion dates: March 2022

The scope of this report focuses only on adults with migraines, which is consistent with FDA-approved indications for CGRP inhibitors. However, we also identified 2 ongoing studies in children and adolescents: 1 on rimegepant (acute treatment of migraine)[19] and 1 on eptinezumab

(chronic migraine).[20] These studies of children and adolescents may be important in the future if the FDA expands approved indications for CGRP inhibitors.

Table 4. Ongoing Studies of CGRP Inhibitors for Migraine Headache

Trial Number Trial Name Phase	Treatment Groups Trial Design	Enrollment (N) Treatment Duration	Study Completion Date	Primary Outcome(s)
Eptinezumab				
NCT04418765[21] A Study to Evaluate the Efficacy and Safety of Eptinezumab for the Prevention of Migraine in Patients That Are Not Helped by Previous Preventive Treatments (DELIVER) Phase 3	100 mg or 300 mg, placebo Blinded	N = 892 (actual) 24 weeks	July 2021 (estimated)	Change from baseline in the number of monthly migraine days at 12 weeks
NCT04772742[22] Eptinezumab in Adults With Migraine and Medication Overuse Headache (Sunlight) Phase 3	100 mg, placebo Blinded	N = 182 (estimated) 12 weeks	April 2022 (estimated)	Change from baseline in the number of monthly migraine days at 12 weeks
NCT04688775[23] Eptinezumab in Participants With Episodic Cluster Headache (ALLEVIATE) Phase 3	Dose 1, placebo Blinded	N = 304 (estimated) 4 weeks	January 2023 (estimated)	Change from baseline in number of weekly attacks, averaged over weeks 1 to 2
NCT04921384[24] Eptinezumab as Preventive Treatment of Migraine in Adults With Migraine (Sunrise) Phase 3	100 mg or 300 mg, placebo Blinded	N = 513 (estimated) 12 weeks	February 2023 (estimated)	Change from baseline in the number of monthly migraine days at 12 weeks
Erenumab				
NCT03912337[25] Effect of Erenumab-aooe on Disability and Work Productivity in Employed Subjects With Episodic Migraine Phase 4	Dose 1, placebo Blinded	N = 29 (actual) 6 months	July 2021 (estimated)	Sum of monthly changes from baseline in modified Migraine Disability Assessment at 6 months
NCT03867201[26] Study of Efficacy and Safety of Erenumab in Adult	Dose 1, placebo Blinded	N = 559 (actual) 12 weeks	August 2021 (estimated)	Change from baseline in monthly migraine days during the last 4 weeks of the 12-

Trial Number Trial Name Phase	Treatment Groups Trial Design	Enrollment (N) Treatment Duration	Study Completion Date	Primary Outcome(s)
Chronic Migraine Patients (DRAGON) Phase 3				week treatment period
NCT03927144[27] Study of Sustained Benefit of Erenumab in Adult Episodic Migraine Patients Phase 4	Dose 1, 2, oral prophylactic Open-label	N = 621 (actual) 12 months	October 2021 (estimated)	Proportion of subjects who complete initially assigned treatment and achieve at least 50% reduction from baseline in monthly migraine days at 12 months
NCT04970355[28] Efficacy of Erenumab in Chronic Cluster Headache (CHERUB01) Phase 2	280 mg loading dose and 140 mg at week 4, placebo Blinded	N = 118 (estimated) 10 weeks	December 2022	Change in weekly cluster headache attack frequency from baseline over the last 2 weeks of the trial
Fremanezumab				
NCT03303092[29] Efficacy and Safety of Subcutaneous Administration of TEV-48125 for the Preventive Treatment of Episodic Migraine Phase 2 and 3	225 mg, 675 mg, placebo Blinded	N = 453 (actual) 12 weeks	November 2019 (actual)	Change in mean monthly migraine days from baseline to 12 weeks
NCT03303079[30] Efficacy and Safety of Subcutaneous Administration of TEV-48125 for the Preventive Treatment of Chronic Migraine Phase 2 and 3	225 mg, 675 mg, placebo Blinded	N = 571 (actual) 12 weeks	November 2019 (actual)	Change in mean monthly headache days of at least moderate severity from baseline to 12 weeks
NCT03303105[31] Long-term Safety and Tolerability of Subcutaneous Administration of TEV-48125 for the Preventive Treatment of Migraine Phase 3	225 mg, 675 mg, placebo Blinded	N = 50 (actual) 18 months	June 2020 (actual)	Percentage of participants with adverse events at 562 days

Trial Number Trial Name Phase	Treatment Groups Trial Design	Enrollment (N) Treatment Duration	Study Completion Date	Primary Outcome(s)
NCT04041284[32] A Study to Evaluate the Efficacy and Safety of Fremanezumab for Preventive Treatment of Migraine in Patients With Major Depressive Disorder Phase 4	225 mg, placebo Blinded	N = 340 (estimated) 12 weeks	May 2022 (estimated)	Mean change in monthly average number of migraine days at 12 weeks
NCT04458857[33] A Study to Test if Fremanezumab is Effective in Preventing Episodic Migraine in Patients 6 to 17 Years of Age Phase 3	Dose A or B, placebo Blinded	N = 288 (estimated) 3 months	December 2022 (estimated)	Change in monthly average number of migraines from baseline to 3 months
NCT04464707[34] A Study to Test if Fremanezumab is Effective in Preventing Chronic Migraine in Patients 6 to 17 Years of Age Phase 3	Dose A or B, placebo Blinded	N = 418 (estimated) 3 months	December 2023 (estimated)	Change in monthly average number of migraines from baseline to 3 months
Galcanezumab				
NCT03963232[35] A Study of Galcanezumab (LY2951742) in Participants With Episodic Migraine Phase 3	Dose 1, placebo Blinded	N = 486 (estimated) 3 months	July 2021 (estimated)	Mean change from baseline in the number of monthly migraine headache days at 3 months
NCT04616326[36] A Study of Galcanezumab (LY2951742) in Participants 12 to 17 Years of Age With Chronic Migraine (REBUILD-2) Phase 3	Dose 1, placebo Blinded	N = 300 (estimated) 3 months	February 2023 (estimated)	Change from baseline in the number of monthly migraine headache days at 3 months
Rimegepant				
NCT03235479[37] Safety and Efficacy Study in Adult Subjects With Acute Migraines Phase 3	75 mg, placebo Blinded	N = 1,485 (actual) 2 hours	January 2018 (actual) Abstracts published April 2021[17,18]	Number of participants reporting no pain at 2 hours postdose; number of participants reporting the absence of their most bothersome

Trial Number Trial Name Phase	Treatment Groups Trial Design	Enrollment (N) Treatment Duration	Study Completion Date	Primary Outcome(s)
				symptom at 2 hours postdose
NCT04574362[38] Safety and Efficacy Trial of BHV3000 (Rimegepant) 75 mg for the Acute Treatment of Migraine Phase 3	75 mg, placebo Blinded	N = 1,800 (estimated) 24 hours	March 2022 (estimated)	Pain freedom and freedom from most bothersome symptom at 2 hours postdose
Ubrogepant				
NCT04492020[39] Study to Evaluate Oral Ubrogepant in the Acute Treatment of Migraine During the Prodrome in Adult Participants (PRODROME) Phase 3	100 mg (treatment sequences A and B), placebo Blinded	N = 600 (estimated) 48 hours	March 2022 (estimated)	Percentage of participants reporting absence of headache of moderate/severe intensity within 24 hours postdose

Abbreviation. CGRP: calcitonin gene-related peptide.

Summary

Since the completion of the DERP systematic review update in April 2020, we identified:

- 9 new published RCTs and 1 published abstract
  - 9 placebo-controlled trials
  - 1 abstract of erenumab versus topiramate
- 19 ongoing studies
  - 1 head-to-head RCT of erenumab versus an oral prophylactic
  - 18 placebo-controlled trials
- 1 new indication
  - Rimegepant for the prevention of episodic migraines
- No new drugs, formulations, warning, or serious harms

Using the *Is There a There There Scale* (ITS) (Table 5), we rated this topic as *yes* (see Appendix B for ratings and definitions).

Table 5. Summary and ITS Rating

Clinical Evidence	Yes How many?	No
New Comparative Trial	☑ 1 (erenumab vs. topiramate)	
New Placebo-Controlled Trial	☑ 9	
New Meaningful[a] Study	☑ 4	
Ongoing Study Likely to be Published in the Next Year	☑ 7	
FDA Actions	**Yes Description**	**No**
New Drug or Formulation		☒
New Indication	☑ 1 (rimegepant for the prevention of episodic migraines)	
New Serious Harm or Warning		☒
ITS Rating: *Yes*		

Note. [a] *Large studies (≥ 600 participants), studies that have long-term follow-up (≥ 12 months for prevention and 24 hours for acute treatment), studies that compare one drug with another that is considered the standard of care or has not been reported and is clinically important, and studies that include an intervention or outcome not previously reported in the literature or is clinically important (e.g., mortality) and adds to the body of literature. Abbreviation. ITS: Is There a There There Scale.*

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Appendix A. Abstracts of New Eligible Studies

Croop R, Lipton RB, Kudrow D, et al. Oral rimegepant for preventive treatment of migraine: a phase 2/3, randomised, double-blind, placebo-controlled trial. *Lancet*. 2021;397(10268):51-60. doi: 10.1016/S0140-6736(20)32544-7.

Background: Rimegepant is a calcitonin gene-related peptide receptor antagonist that has shown efficacy and safety in the acute treatment of migraine. We aimed to compare the efficacy of rimegepant with placebo for preventive treatment of migraine.

Methods: We did a multicentre, phase 2/3, randomised, double-blind, placebo-controlled trial at 92 sites in the USA. Adults with at least a 1-year history of migraine were recruited. After a 4-week observation period, eligible participants were randomised using an interactive web response system to oral rimegepant 75 mg or matching placebo every other day for 12 weeks (double-blind treatment phase). The primary efficacy endpoint was change from the 4-week observation period in the mean number of migraine days per month in the last 4 weeks of the double-blind treatment phase (weeks 9–12). Participants who received at least one dose of their assigned study medication and who had 14 days or more of data in the observation period and 14 days or more of data for at least one 4-week interval during the double-blind treatment phase were analysed for efficacy. Those who received at least one dose of study medication were analysed for safety. This study is registered with ClinicalTrials.gov, NCT03732638.

Findings: Between Nov 14, 2018, and Aug 30, 2019, 1591 participants were recruited and assessed for eligibility, of whom 747 were randomly allocated either rimegepant (n=373) or placebo (n=374). 695 participants were included in the analysis for efficacy, of whom 348 were assigned rimegepant and 347 were allocated placebo. Rimegepant was superior to placebo on the primary endpoint of change in the mean number of migraine days per month during weeks 9–12. The change from the observation period in mean number of migraine days per month during weeks 9–12 was −4·3 days (95% CI −4·8 to −3·9) with rimegepant and −3·5 days (−4·0 to −3·0) with placebo (least squares mean difference −0·8 days, 95% CI −1·46 to −0·20; p=0·0099). 741 participants received study medication and were included in the safety analysis. 133 (36%) of 370 patients who received rimegepant reported an adverse event, compared with 133 (36%) of 371 who received placebo. Seven (2%) participants who received rimegepant and four (1%) who received placebo discontinued the study due to an adverse event; no patients died.

Interpretation: Taken every other day, rimegepant was effective for preventive treatment of migraine. Tolerability was similar to that of placebo, and no unexpected or serious safety issues were noted.

Dodick DW, Goadsby PJ, Lucas C, et al. Phase 3 randomized, placebo-controlled study of galcanezumab in patients with chronic cluster headache: Results from 3-month double-blind treatment. *Cephalalgia*. 2020;40(9):935-948. doi: 10.1177/0333102420905321.

OBJECTIVE: To report efficacy and safety of galcanezumab in adults with chronic cluster headache. BACKGROUND: Galcanezumab is a humanized monoclonal antibody that binds to calcitonin gene-related peptide and inhibits its biological activity.

METHODS: This study comprised a prospective baseline period, a 12-week double-blind, placebo-controlled treatment period, and a 52-week open-label period. Up to six protocol-specified concomitant preventive medications were allowed if patients were on a stable dose for 2 months prior to the prospective baseline period. Patients were randomized 1:1 to monthly subcutaneous galcanezumab (300 mg) or placebo. The primary endpoint was overall mean change from baseline in weekly attack frequency with galcanezumab compared to placebo. Key secondary endpoints were ≥50% response rate and percentage of patients meeting sustained response. Results from the double-blind treatment period are reported.

RESULTS: A total of 237 patients were randomized and treated (120 placebo; 117 galcanezumab). At baseline, the mean age was 45 years and 63% were using ≥1 preventive drug. The primary endpoint was not met; mean change in weekly attack frequency was -4.6 placebo versus -5.4 galcanezumab (p = 0.334). Key secondary endpoints also were not met. Injection site-related treatment-emergent adverse events were more common in the galcanezumab than the placebo group, with significantly more injection site erythema.

CONCLUSION: Treatment with galcanezumab 300 mg did not achieve its primary and key secondary endpoints. This study underscores the potential distinct biology of cCH as well as the significant unmet need for safe, effective, and well-tolerated preventive treatment. The safety profile of galcanezumab in cCH is consistent with that observed in trials of episodic CH and migraine.

TRIAL REGISTRATION: NCT02438826; https://www.clinicaltrials.gov/ct2/show/NCT02438826.

Goadsby PJ, Silberstein SD, Yeung PP, et al. Long-term safety, tolerability, and efficacy of fremanezumab in migraine. *Neurology*. 2020;95(18):e2487. doi: 10.1212/WNL.0000000000010600.

Objective: To assess the long-term safety, tolerability, and efficacy of fremanezumab, a fully humanized monoclonal antibody approved for the preventive treatment of migraine.

Methods: A 52-week, multicenter, randomized, double-blind, parallel-group study evaluated fremanezumab monthly or quarterly in adults with chronic migraine (CM) or episodic migraine (EM). Safety and tolerability were assessed by adverse event (AE) monitoring (performed by the investigators), systematic local injection-site assessments (immediately and 1 hour after injection), laboratory/vitals assessments, and immunogenicity testing. Prespecified exploratory evaluations included change from baseline in the monthly number of migraine days, headache days of at least moderate severity, and days with any acute headache medication use. Change from baseline in headache-related disability (6-item Headache Impact Test scores) was also measured.

Results: Of 1,890 patients enrolled, 551 and 559 patients with CM received quarterly and monthly dosing; 394 and 386 patients with EM received quarterly or monthly, respectively. The most commonly reported AEs were injection-site reactions (induration 33%, pain 31%, and erythema 26%). Fremanezumab reduced monthly migraine days (CM quarterly −7.2 days, CM monthly −8.0 days, EM quarterly −5.2 days, EM monthly −5.1 days) and headache days of at least moderate severity (CM quarterly −6.4 days, CM monthly −6.8 days, EM quarterly

−4.4, EM monthly −4.2 days) from baseline to 12 months. Reductions in any acute headache medication use and headache-related disability were also maintained over 12 months.

Conclusions Fremanezumab quarterly and fremanezumab monthly were well tolerated and demonstrated sustained improvements in monthly migraine days, headache days, and headache-related disability for up to 12 months in patients with migraine.ClinicalTrials.gov NCT02638103.

Classification of evidence: This study provides Class IV evidence that long-term fremanezumab treatment is safe, well tolerated, and effective at sustaining reductions in monthly migraine and headache days.

Kuruppu DK, Tobin J, Dong Y, Aurora SK, Yunes-Medina L, Green AL. Efficacy of galcanezumab in patients with migraine who did not benefit from commonly prescribed preventive treatments. *BMC Neurol*. 2021;21(1):175. doi: 10.1186/s12883-021-02196-7.

Galcanezumab is a calcitonin gene-related peptide (CGRP) monoclonal antibody (mAb) indicated for the preventive treatment of migraine. While galcanezumab has demonstrated efficacy in patients who did not respond to prior preventive medications in general, its efficacy in patients who did not benefit from individual, commonly prescribed preventive treatments due to inadequate efficacy or safety/tolerability remains unknown.

Lipton RB, Goadsby PJ, Smith J, et al. Efficacy and safety of eptinezumab in patients with chronic migraine: PROMISE-2. *Neurology*. 2020;94(13):e1365-e1377. doi: 10.1212/wnl.0000000000009169.

OBJECTIVE: To evaluate the efficacy and safety of eptinezumab, a humanized anti-calcitonin gene-related peptide monoclonal antibody, in the preventive treatment of chronic migraine (CM).

METHODS: The Prevention of Migraine via Intravenous ALD403 Safety and Efficacy-2 (PROMISE-2) study was a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Adults with CM were randomly assigned to receive IV eptinezumab 100 mg, eptinezumab 300 mg, or placebo administered on day 0 and week 12. The primary endpoint was change from baseline in mean monthly migraine days (MMDs) over weeks 1 to 12.

RESULTS: Among treated participants (n = 1,072), baseline mean number of MMDs was ≈16.1 across groups. Treatment with eptinezumab 100 and 300 mg was associated with significant reductions in MMDs across weeks 1 to 12 compared with placebo (placebo -5.6, 100 mg -7.7, $p < 0.0001$ vs placebo; 300 mg -8.2, $p < 0.0001$ vs placebo). Treatment-emergent adverse events (TEAEs) were reported by 43.5% (100 mg), 52.0% (300 mg), and 46.7% (placebo) of patients. Nasopharyngitis was the only TEAE reported for >2% of eptinezumab-treated patients at an incidence of >2% over placebo; it occurred in the 300 mg eptinezumab arm (eptinezumab 9.4%, placebo 6.0%).

CONCLUSION: In patients with CM, eptinezumab 100 and 300 mg was associated with a significant reduction in MMDs from the day after IV administration through week 12, was well tolerated, and demonstrated an acceptable safety profile.

CLASSIFICATION OF EVIDENCE: This study provides Class I evidence that for patients with CM, a single dose of eptinezumab reduces MMDs over 12 weeks of treatment.

CLINICALTRIALSGOV IDENTIFIER: NCT02974153.

Reuter U, Ehrlich M, Gendolla A, et al. Erenumab versus topiramate for the prevention of migraine – a randomised, double-blind, active-controlled phase 4 trial. 2021; https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3791424. Accessed July 26, 2021.

Background: Migraine prophylaxis with oral medications is often compromised by intolerable side effects. We compared the tolerability and efficacy of erenumab, a monoclonal antibody binding to the calcitonin gene-related peptide (CGRP) receptor, to topiramate for migraine prophylaxis in adults.

Methods: HER-MES was a 24-week, randomised, double-blind, double-dummy, controlled trial conducted in 82 sites in Germany. Patients with ≥ 4 migraine days per month who were naïve to study drugs were randomly assigned (1:1) to either subcutaneous erenumab (70 or 140 mg/month) or oral topiramate at highest tolerated dose (50–100 mg/day). Randomisation and allocation were done via an interactive response system. Randomisation was stratified by monthly migraine days (MMD: 4–7, 8–14, ≥ 15). Masking was achieved by administration of matching placebo. Patients, investigators, and the sponsor were blinded to treatment. The primary endpoint was the proportion of patients who discontinued study medication due to an adverse event during the double-blind phase. Secondary efficacy endpoints included the proportion of patients that achieved at least a 50% reduction from baseline in MMD. The full analysis set (FAS) included all participants who received at least one dose of study drug. The HER-MES study is registered with ClinicalTrials.gov (NCT03828539).

Findings: The study was conducted from February 22, 2019 to July 29, 2020. 777 patients were randomised and 95·1% completed the study. The FAS comprised 776 patients (388 in each group) of which 59·1% were naïve to prophylaxis. In the erenumab group, 10·6% discontinued medication due to adverse events compared to 38·9% in the topiramate group (odds ratio, 0·19; 95% confidence interval [CI] 0·13 to 0·27; p<0·001). Significantly more patients achieved a ≥ 50% reduction in MMD from baseline with erenumab (55·4% vs. 31·2%). No new safety signals occurred.

Interpretation: Erenumab demonstrated a favourable tolerability and efficacy profile compared to topiramate.

Takeshima T, Sakai F, Hirata K, et al. Erenumab treatment for migraine prevention in Japanese patients: efficacy and safety results from a phase 3, randomized, double-blind, placebo-controlled study. *Headache*. 2021;61(6):927-935. doi: 10.1111/head.14138.

OBJECTIVES: Erenumab is a human anti-calcitonin gene-related peptide receptor monoclonal antibody approved for migraine prevention. Global studies have demonstrated its efficacy in chronic and episodic migraine (EM). Here we report the outcomes from a Phase 3 study of erenumab in Japanese patients with chronic migraine (CM) or EM.

METHODS: Japanese patients with EM (<15 headache days/month, including ≥4 migraine days/month) or CM (≥15 headache days/month, including ≥8 migraine days/month) were randomized 1:1 to placebo or erenumab 70 mg once monthly for a 24-week double-blind treatment phase (DBTP). The primary endpoint of change from baseline in mean monthly migraine days (MMD) over months 4, 5, and 6 of the DBTP was compared between erenumab and placebo groups. Secondary efficacy and safety endpoints were also assessed.

RESULTS: A total of 261 patients were randomized to placebo (n = 131) or erenumab 70 mg (n = 130); all patients were included in the efficacy and safety analyses. The mean (standard deviation) MMD at baseline was 11.84 (5.70) for the placebo group and 12.40 (5.99) for erenumab 70 mg. The mean (standard error) change in MMD was -1.98 (0.38) for the placebo group (n = 131) and -3.60 (0.38) for erenumab 70 mg (n = 130). The difference in MMD reduction between groups was -1.67 (95% CI: -2.56, -0.78, p < 0.001) for EM and -1.57 (95% CI: -3.39, 0.24, p = 0.089) for CM. Adverse events (AEs) were consistent with earlier studies. The most frequent AEs (placebo, erenumab) were nasopharyngitis (28.2% and 26.9%, respectively), back pain (4.6% and 5.4%), and constipation (0.8% and 4.6%).

CONCLUSION: Treatment with erenumab 70 mg once monthly demonstrated favorable efficacy and safety findings in Japanese patients with EM or CM.

Tatsuoka Y, Takeshima T, Ozeki A, Matsumura T. Treatment satisfaction of galcanezumab in japanese patients with episodic migraine: a phase 2 randomized controlled study. *Neurol Ther*. 2021;10(1):265-278. doi: 10.1007/s40120-021-00236-5.

INTRODUCTION: This analysis evaluated the treatment satisfaction of Japanese patients receiving galcanezumab (GMB) as a preventive medication for episodic migraine (4-14 monthly migraine headache days).

METHODS: This phase 2, randomized, double-blind, placebo-controlled study enrolled patients aged 18-65 years at 40 centers in Japan. Patients were randomized 2:1:1 to receive monthly subcutaneous injections of placebo (PBO, n = 230), GMB 120 mg (n = 115), or GMB 240 mg (n = 114) for 6 months. Patients' experience with treatment was measured using the Patient Global Impression of Severity (PGI-S), Patient Global Impression of Improvement (PGI-I), and Patient Satisfaction with Medication Questionnaire-Modified (PSMQ-M) scales. PGI-S was administered at baseline and months 1-6, PGI-I at months 1-6, and PSMQ-M at months 1 and 6. Prespecified analyses were differences between GMB and PBO in PGI-I and the change from baseline in PGI-S, and evaluating positive responses for the PGI-I and PSMQ-M.

RESULTS: Average change ± SE from baseline across months 1-6 was - 0.09 ± 0.05 (PBO), - 0.17 ± 0.07 (GMB 120 mg, p = 0.33), and - 0.30 ± 0.07 (GMB 240 mg, p = 0.013) for PGI-S. Average PGI-I across months 1-6 was 3.39 ± 0.05 (PBO), 2.55 ± 0.07 (GMB 120 mg, p < 0.05), and 2.71 ± 0.07 (GMB 240 mg, p < 0.05). Reductions of 2.8-3.0 monthly migraine headache days corresponded to 25-31% higher positive PGI-I response rates with GMB compared with PBO. Positive PSMQ-M response rates for satisfaction and preference were statistically significantly higher for GMB compared with PBO (odds ratio [95% confidence interval], all p < 0.05 vs. PBO): satisfaction GMB 120 mg (3.142 [1.936-5.098]) and GMB 240 mg (3.924

[2.417-6.369]), and preference GMB 120 mg (3.691 [2.265-6.017]) and GMB 240 mg (3.510 [2.180-5.652]).

CONCLUSION: Japanese patients with episodic migraine receiving preventive treatment with GMB are significantly more satisfied than those receiving PBO.

Wang SJ, Roxas AA Jr, Saravia B, et al. Randomised, controlled trial of erenumab for the prevention of episodic migraine in patients from Asia, the Middle East, and Latin America: the EMPOwER study. *Cephalalgia*. 2021:3331024211024160. doi: 10.1177/03331024211024160.

OBJECTIVE: EMPOwER, a double-blind, randomised, phase 3 study, evaluated the efficacy and safety of erenumab in adults with episodic migraine from Asia, the Middle East, and Latin America.

METHODS: Randomised patients (N = 900) received monthly subcutaneous injections of placebo, erenumab 70 mg, or 140 mg (3:3:2) for 3 months. Primary endpoint was change from baseline in monthly migraine days at Month 3. Other endpoints included achievement of ≥50%, ≥75%, and 100% reduction in monthly migraine days, change in monthly acute migraine-specific medication treatment days, patient-reported outcomes, and safety assessment.

RESULTS: At baseline, mean (standard deviation) age was 37.5 (9.9) years, 81.9% were women, and monthly migraine days was 8.2 (2.8). At Month 3, change from baseline in monthly migraine days (primary endpoint) was -3.1, -4.2, and -4.8 days for placebo, erenumab 70 mg, and erenumab 140 mg, respectively, with a statistically significant difference for erenumab versus placebo (P = 0.002 [70 mg], P < 0.001 [140 mg]). Both erenumab doses were also significantly superior to placebo on all secondary endpoints, including the proportion of patients achieving ≥50% reduction from baseline in monthly migraine days, change from baseline in monthly acute migraine-specific medication treatment days and change from baseline in the Headache Impact Test-6™ scores. The safety profile of erenumab was comparable with placebo; no new safety signals were observed.

CONCLUSIONS: This study of erenumab in patients with episodic migraine from Asia, the Middle East, and Latin America met all primary and secondary endpoints. A consistent numerical benefit was observed with erenumab 140 mg versus erenumab 70 mg across all efficacy endpoints. These findings extend evidence of erenumab's efficacy and safety to patients under-represented in previous trials.

ClinicalTrials.gov identifier: NCT03333109.

Winner PK, McAllister P, Chakhava G, et al. Effects of intravenous eptinezumab vs placebo on headache pain and most bothersome symptom when initiated during a migraine attack: a randomized clinical trial. *JAMA*. 2021;325(23):2348-2356. doi: 10.1001/jama.2021.7665.

Intravenous eptinezumab, an anti–calcitonin gene-related peptide antibody, is approved for migraine prevention in adults. It has established onset of preventive efficacy on day 1 after infusion. To evaluate the efficacy of and adverse events related to eptinezumab when initiated during a migraine attack. Phase 3, multicenter, parallel-group, double-blind, randomized, placebo-controlled trial conducted from November 4, 2019, to July 8, 2020, at

47 sites in the United States and the country of Georgia. Participants (aged 18-75 years) with a greater than 1-year history of migraine and migraine on 4 to 15 days per month in the 3 months prior to screening were treated during a moderate to severe migraine attack. Eptinezumab, 100 mg (n = 238), or placebo (n = 242), administered intravenously within 1 to 6 hours of onset of a qualifying moderate to severe migraine. Co-primary efficacy end points were time to headache pain freedom and time to absence of most bothersome symptom (nausea, photophobia, or phonophobia). Key secondary end points were headache pain freedom and absence of most bothersome symptom at 2 hours after start of infusion. Additional secondary end points were headache pain freedom and absence of most bothersome symptom at 4 hours and use of rescue medication within 24 hours. Of 480 randomized and treated patients (mean age, 44 years; 84% female), 476 completed the study. Patients treated with eptinezumab vs placebo, respectively, achieved statistically significantly faster headache pain freedom (median, 4 hours vs 9 hours; hazard ratio, 1.54 [P < .001]) and absence of most bothersome symptom (median, 2 hours vs 3 hours; hazard ratio, 1.75 [P < .001]). At 2 hours after infusion, in the respective eptinezumab and placebo groups, headache pain freedom was achieved by 23.5% and 12.0% (between-group difference, 11.6% [95% CI, 4.78%-18.31%]; odds ratio, 2.27 [95% CI, 1.39-3.72]; P < .001) and absence of most bothersome symptom by 55.5% and 35.8% (between-group difference, 19.6% [95% CI, 10.87%-28.39%]; odds ratio, 2.25 [95% CI, 1.55-3.25]; P< .001). Results remained statistically significant at 4 hours after infusion. Statistically significantly fewer eptinezumab-treated patients used rescue medication within 24 hours than did placebo patients (31.5% vs 59.9%, respectively; between-group difference, −28.4% [95% CI, −36.95% to −19.86%]; odds ratio, 0.31 [95% CI, 0.21-0.45]; P < .001). Treatment-emergent adverse events occurred in 10.9% of the eptinezumab group and 10.3% of the placebo group; the most common was hypersensitivity (eptinezumab, 2.1%; placebo, 0%). No treatment-emergent serious adverse events occurred. Among patients eligible for preventive migraine therapy experiencing a moderate to severe migraine attack, treatment with intravenous eptinezumab vs placebo shortened time to headache and symptom resolution. Feasibility of administering eptinezumab treatment during a migraine attack and comparison with alternative treatments remain to be established.

Appendix B. ITS Ratings and Definitions

The *Is There a There There Scale* (ITS) consists of 3 ratings: *no*, *maybe*, and *yes*. The definitions of these ratings and methods for selection are described below. Center for Evidence-based Policy (Center) researchers will use these definitions to rate each surveillance topic. The assigned rating is offered as guidance and does not require DERP participants to follow this recommendation. Each rating is strictly based on the identified new research and clinical information and is not comprehensive to all aspects of policy decision making, such as competing priorities, budget, contracting, or internal and external state agency needs.

No

- We did not find clinical evidence or information that would indicate a need to update the report or develop a derivative research product.
- A rating of No is typically given when there are few new studies and/or no new meaningful studies, and no new serious harms.

Maybe

- We found some clinical evidence or information that might suggest a need to update the report or develop a derivative research product.
- A rating of Maybe is typically given when there are multiple new comparative trials or at least 1 new meaningful study or serious harm.

Yes

- We found clinical evidence or information that suggests a need to update the report or develop a derivative research product.
- A rating of Yes is typically given when there are multiple new comparative trials and meaningful studies and/or new serious harms, drugs, formulations, or indications.

Suggested citation: Harrod C and Anderson R. *DERP surveillance: calcitonin gene-related peptide inhibitors for migraine and cluster headache*. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2021.

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