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DERP VI Surveillance: Calcitonin Gene-Related Peptide Inhibitors for Migraine Prophylaxis

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OHSU

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Objectives

The purpose of this Drug Effectiveness Review Project (DERP) surveillance report is to preview the volume and nature of new research and relevant clinical information that has emerged since the previous surveillance document on calcitonin gene-related peptide (CGRP) inhibitors for migraine prophylaxis (Table 1). The literature search for this report focuses on new randomized controlled trials (RCTs); prospective cohort studies; and actions taken by the U.S. Food and Drug Administration (FDA) since the last surveillance document, 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 update review or another research product type for this topic. Comprehensive searches might identify additional eligible studies.

Topic History

Table 1. Topic History and Search Dates

Document Type	Date Presented	Search Dates
Surveillance	March 2019	July 2018 to February 1, 2019
Systematic Review	October 2018	Date of database inception to July 2018

Key Questions

1. What is the efficacy and effectiveness of CGRP inhibitors for migraine prophylaxis?
2. What is the frequency of adverse events with CGRP inhibitors for migraine prophylaxis?
3. Are there subgroups of patients based on demographics (e.g., age, racial groups, gender), comorbidities (e.g., drug-disease interactions), or other medications for which CGRP inhibitors differ in efficacy, effectiveness, or frequency of adverse events?
4. What are the characteristics of ongoing studies of CGRP inhibitors?

Populations

Adults with episodic or chronic migraines with no previous treatment history or adults who have not responded to other migraine prophylaxis therapies

Interventions

Table 2. Included Interventions

Generic Name (Developmental Names)	Brand Name	Dosage Form	Date of FDA Approval
Erenumab (AMG 334)	Aimovig	Subcutaneous injection	May 17, 2018
Fremanezumab (TEV-48125, LBR-101)	Ajovy	Subcutaneous injection	September 14, 2018
Galcanezumab (LY2951742)	Emgality	Subcutaneous injection	September 27, 2018
Eptinezumab (ALD403)	No brand name	Intravenous infusion	Not approved

Abbreviations. FDA: U.S. Food and Drug Administration.

Comparators

- CGRP inhibitors compared to each other (head-to-head)
- Other migraine prophylaxis (i.e., selected antidepressants [amitriptyline and venlafaxine], anticonvulsants [divalproex, topiramate, valproic acid and derivatives], beta blockers [propranolol and metoprolol], and onabotulinumtoxinA)
- Sham or placebo

Outcomes

- Migraine events including frequency, intensity, and duration
- Pain including intensity and duration
- Other symptoms (e.g., nausea, vomiting, photophobia, and phonophobia)
- Functional ability including cognitive ability
- Disability
- Quality of life
- Other patient-reported outcomes (e.g., depression, anxiety, and difficulties in interpersonal relationships)
- Employment-related outcomes (e.g., unemployment, work productivity loss, and absenteeism)
- Use of rescue therapies
- Number of emergency department and/or primary care provider visits
- Tolerability
- Adverse events including total adverse events, treatment-related events, and events that are likely not related to treatment
- Serious adverse events (i.e., death, life-threatening events, events requiring initial or prolonged hospitalization, events resulting in persistent or significant disability or that required intervention to prevent permanent impairment or damage, congenital anomalies or birth defects, other events that do not fit any of the previous categories but that may jeopardize the patient or require medical or surgical intervention and are considered significant by the investigator)
- Withdrawals or discontinuations due to adverse events

Study Designs

- RCTs
- Prospective cohort studies

Methods

Using the PICOS outlined above, we searched for eligible RCTs and prospective cohort studies in ClinicalTrials.gov, the ISRCTN Registry, and the FDA website. Using relevant clinical trial numbers and other identifiers, we then searched Ovid MEDLINE including Ovid MEDLINE In-Process & Other Non-Indexed Citations and Epub Ahead of Print from February 1, 2019 to August 5, 2019 and used the Google search engine to identify studies published since February 1, 2019. 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 or warnings (e.g., boxed warnings) for included interventions. To identify new drugs, we used Google and searched CenterWatch, a privately owned database of clinical trials information.

Findings

New Drugs or Formulations

During this surveillance period, we identified no new drugs or formulations for any therapies in the CGRP class for prevention of migraine. Eptinezumab, which is included in this surveillance document, has still not been approved by the FDA for migraine prevention.

New Indications

All 3 FDA-approved CGRP inhibitors were initially approved for the prevention of migraine in adults.[1-3] However, in June 2019, galcanezumab received an additional indication for treatment of episodic cluster headache in adults.[3] Although cluster headache was not part of the scope of this topic, we identified 1 new RCT of galcanezumab that evaluated this indication.[4]

New Serious Harms or Warnings

In March 2019, the FDA added a new warning of hypersensitivity reactions to the drug label for erenumab.[2] The FDA advises all patients who have a serious hypersensitivity reaction with erenumab to discontinue use of the drug.[2] This warning was already included in the FDA label for fremanezumab[1] and galcanezumab.[3]

Randomized Controlled Trials

We identified 1 new RCT by Dodick et al.[5] assessing eptinezumab for prevention of chronic migraine. This is the first published study we identified of eptinezumab for chronic migraine (Table 3).

Detke et al.[6] published first on the effect of galcanezumab for chronic migraine (REGAIN) in December 2018. This study was captured in the last surveillance document. Since that time, other publications on REGAIN have also been published (secondary analyses).[7,8] Secondary analyses of already published studies are not considered original, new studies, so we do not provide additional details on these studies.

Table 3. Published RCT of CGRP Inhibitors for Migraine Prophylaxis

Author, Year NCT Number	Population Sample Size (N)	Treatment Groups	Outcomes
Dodick et al., 2019[5]	Participants with chronic migraines N = 665	• Eptinezumab 300 mg • Eptinezumab 100 mg • Eptinezumab 30 mg • Eptinezumab 10 mg • Placebo	• Migraine responder • Adverse events

Ongoing Studies

We identified 20 ongoing studies across the class of CGRP inhibitors.[9-28] Of these 20 studies, 2 are evaluating eptinezumab,[9,10] 9 are evaluating erenumab,[11-19] 6 are evaluating fremanezumab,[20-25] and 3 are evaluating galcanezumab[26-28] (Table 4). Although the scope of the DERP systematic review and this surveillance document focused on adults, we identified 2 ongoing studies that plan to analyze children and adolescents.[29,30] Because this population is out of scope, we do not provide full details on those ongoing studies.

The largest body of evidence with publications potentially upcoming is for erenumab. Of the 9 ongoing studies we identified for this drug, 2 are head-to-head studies.[13,18] Both have large sample sizes (600 and 700 participants) and are expected to be completed in 2020 (Table 4).

Table 4. Ongoing Studies of CGRP Inhibitors for Migraine Prophylaxis

NCT Number	Treatment Groups Conditions	Primary Outcomes	Estimated Enrollment (N)	Estimated Completion Date
Eptinezumab				
NCT02559895[9]	Dose level 1 (not defined) Dose level 2 (not defined) Dose level 3 (not defined) Placebo Episodic migraines	Change in frequency of migraine days at 12 weeks	N = 900	December 2017 Preliminary results have been reported[31-34]
NCT02974153[10]	Dose level 1 (not defined) Dose level 2 (not defined) Placebo Chronic migraines	Change in frequency of migraine days at 12 weeks	N = 1,121	April 2018 Preliminary results have been reported[31,35,36]
Erenumab				
NCT02630459[11]	Dose level 1 (not defined) Dose level 2 (not defined) Dose level 3 (not defined) Placebo Episodic migraines	Change in mean monthly migraine days from baseline to 24 weeks	N = 475	June 2019
NCT03333109[12]	Dose level 1 (prefilled syringe) Dose level 2 (prefilled syringe) Placebo Episodic migraines	Change in mean monthly migraine days from baseline to 12 weeks	N = 880	February 2020

NCT Number	Treatment Groups Conditions	Primary Outcomes	Estimated Enrollment (N)	Estimated Completion Date
NCT03828539[13]	**70 mg every 4 weeks** **140 mg every 4 weeks** **Topiramate 50 to 100 mg/day (highest tolerated dose)** **Episodic migraine**	**Adverse events** **At least a 50% reduction in mean monthly migraine days at 12 and 24 weeks**	**N = 700**	**June 2020**
NCT03977649[14]	140 mg every 4 weeks Placebo Episodic migraine	At least a 50% reduction in mean monthly migraine days at 3 and 6 months	N = 120	November 2020
NCT03912337[15]	Dose not defined every 4 weeks Placebo Episodic migraine	Change in MIDAS from baseline to 6 months	N = 340	March 2021
NCT03812224[16]	Dose not defined every 4 weeks Placebo Episodic and chronic migraines	Change in mean monthly migraine days from baseline to 67 weeks	N = 256	July 2020
NCT03867201[17]	Prefilled syringe (dose not defined) Placebo Chronic migraine	Change in mean monthly migraine days during the last 4 weeks of the 12-week treatment period	N = 550	February 2022
NCT03927144[18]	**Dose level 1** **Dose level 2** **Oral prophylactic** **Episodic migraine**	**At least a 50% reduction in mean monthly migraine days at 12 months**	**N = 600**	**December 2020**
NCT03971071[19]	70 mg every 4 weeks 140 mg every 4 weeks Placebo Chronic migraine and diagnosed with medication overuse headache	Number of participants with no medication overuse headache at 6 months	N = 687	August 2021

NCT Number	Treatment Groups Conditions	Primary Outcomes	Estimated Enrollment (N)	Estimated Completion Date
Fremanezumab				
NCT03303092[20]	225 mg once per month 675 mg in first month, then a monthly placebo Placebo Episodic migraines	Change in mean monthly migraine days from baseline to 12 weeks	N = 330	June 2019
NCT02638103[21]	Dose level 1 (not defined) Dose level 2 (not defined) Placebo Episodic and chronic migraines	Percentage of participants with adverse events at 533 ± 15 days	N = 1,890	December 2018 Preliminary results have been reported[37]
NCT03303079[22]	675 in the first month, then 225 mg/month 675 mg in the first month, then a monthly placebo Placebo Chronic migraine	Change in mean monthly headache days of at least moderate severity from baseline to 12 weeks	N = 540	June 2019
NCT03308968[23]	Dose level 1 per month (not defined) Dose level 2 per 3 months (not defined) Placebo Episodic and chronic migraines	Change in mean monthly migraine days from baseline to 12 weeks	N = 838	June 2019
NCT03303105[24]	225 mg once per month 675 mg once per 3 months Placebo Episodic and chronic migraines	Percentage of participants with adverse events at 562 days	N = 40	February 2020
NCT04041284[25]	225 mg once per month Placebo Migraine and major depressive disorder	Mean change in average number of monthly migraine days	N = 340	April 2021

NCT Number	Treatment Groups Conditions	Primary Outcomes	Estimated Enrollment (N)	Estimated Completion Date
Galcanezumab				
NCT02959177[26]	Dose level 1 (not defined) Dose level 2 (not defined) Placebo Episodic migraines	Change in monthly migraine days from baseline to month 6	N = 451	February 2019
NCT03559257[27]	Dose (not defined) Placebo Episodic or chronic migraines	Change in mean monthly migraine days from baseline to 3 months	N = 420	October 2019
NCT03963232[28]	Dose (not defined) Placebo Episodic migraine	Change in mean monthly migraine days from baseline to 3 months	N = 486	July 2021

Note: Bold text indicates a head-to-head study. Abbreviations. MIDAS: Migraine Disability Assessment.

Summary

Since the completion of the original DERP systematic review in October 2018, we identified the following:

- 3 new RCTs (1 in this surveillance document)
    - Zero head-to-head studies
    - 3 placebo-controlled trials
- 20 ongoing studies
    - 2 head-to-head studies
    - 18 placebo-controlled trials
- 1 new indication (in this surveillance document)
    - Galcanezumab for cluster headache in adults
- 1 new warning for erenumab (in this surveillance document)
    - Hypersensitivity reactions
- No new drugs, formulations, or serious harms
    - Eptinezumab was included in this surveillance document and still has not been approved by the FDA

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

Table 5. Summary and ITS Rating

Clinical Evidence	Yes How many?	No
New Comparative Trial		☒
New Placebo-Controlled Trial	☑ 3	
New Meaningful[a] Study	☑ 2	
Ongoing Study Likely to be Published in the Next Year	☑ 8	
FDA Actions	**Yes Description**	**No**
New Drug or Formulation		☒
New Indication		☒
New Serious Harm or Warning	☑ New warning: Hypersensitivity reactions for erenumab	
ITS Rating: *Maybe*		

Abbreviation. ITS: Is There a There There Scale. Note. [a] *Large studies (≥ 600 participants), studies that have long-term follow-up (≥ 12 months), 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 that is not previously reported in the literature or is clinically important (e.g., mortality) and adds to the body of literature.*

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Appendix A. Abstracts of New Eligible Studies

Dodick DW, Lipton RB, Silberstein S, et al. Eptinezumab for prevention of chronic migraine: a randomized phase 2b clinical trial. *Cephalalgia*. 2019;39(9):1075-1085.

BACKGROUND: Calcitonin gene-related peptide plays an important role in migraine pathophysiology. We evaluated eptinezumab, an intravenous (IV) anti-calcitonin gene-related peptide monoclonal antibody, for the prevention of chronic migraine. OBJECTIVE: To determine the safety, tolerability, and effectiveness of four dose levels of eptinezumab and to inform the phase 3 development program. METHODS: This was a phase 2b, parallel-group, double-blind, randomized, placebo-controlled, dose-ranging clinical trial. Men and women (N = 616) aged 18-55 years were included if they had a diagnosis of chronic migraine, with onset at age </=35 years and history of chronic migraine >/=1 year. During the 28-day screening period, patients must have had >/=15 headache days, including >/=8 migraine days, with >/=5 migraine attacks as recorded in the electronic diary. Patients were assigned in a 1:1:1:1:1 ratio to eptinezumab 300, 100, 30, 10 mg or placebo, administered as a single IV infusion. The primary endpoint was the percentage of patients with a >/=75% decrease in monthly migraine days over weeks 1-12 compared with the 28-day screening period. RESULTS: The >/=75% migraine responder rates over weeks 1-12 for eptinezumab 300, 100, 30, and 10 mg were 33.3%, 31.4%, 28.2%, and 26.8%, respectively, versus 20.7% for placebo (p = 0.033, 0.072, 0.201, 0.294 vs. placebo). Secondary efficacy endpoints (e.g. >/=50% responder rate, change from baseline in frequency of migraine/headache days, and percentage of severe migraines) had results favoring the three higher eptinezumab doses versus placebo. Eptinezumab was well tolerated and adverse event rates were similar to placebo. CONCLUSIONS: The results of this trial demonstrate that eptinezumab appears effective and well-tolerated for the preventive treatment of chronic migraine and justifies the conduct of pivotal phase 3 trials for migraine prevention. TRIAL REGISTRATION: ClinicalTrials.gov identifier: NCT02275117.

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.