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CADTH Reimbursement Recommendation

# Galcanezumab (Emgality)

**Indication:** Emgality is indicated for the prevention of migraine in adults who have at least 4 migraine days per month.

**Sponsor:** Eli Lilly Canada Inc.

**Final recommendation:** Reimburse with conditions

CADTH

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**Funding:** CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

# Summary

CADTH

## What Is the CADTH Reimbursement Recommendation for Emgality?

CADTH recommends that Emgality should be reimbursed by public drug plans for the prevention of migraine if certain conditions are met.

### Which Patients Are Eligible for Coverage?

Emgality should only be covered to prevent migraine attacks in adult patients who have tried at least 2 other types of oral preventive medications.

### What Are the Conditions for Reimbursement?

Emgality should only be reimbursed if the patient is being cared for by a physician who has experience managing migraine headaches. Emgality will only be reimbursed for 6 months at a time. Emgality should not be more than the least costly drug of the same class used to prevent migraine.

### Why Did CADTH Make This Recommendation?

Evidence from 4 clinical trials demonstrated that Emgality reduced the frequency of migraine headache days, and migraine-related disability. Emgality may also reduce migraine intensity, the use of acute pain medication, and improve daily functioning and health-related quality of life.

- There is no evidence to suggest Emgality is more effective than other reimbursed therapies used to treat patients with migraines. Therefore, Emgality should be priced no more than the lowest cost alternative to ensure cost-effectiveness.
- Economic evidence suggests the price of Emgality must be reduced by approximately 49% to 78% to ensure Emgality is cost-effective at a $50,000 per quality-adjusted life-year (QALY) threshold.
- Based on public list prices, Emgality will cost the public drug plans $80,077,151 over 3 years.

## Additional Information

### What Is Migraine?

Migraine is a neurological disease characterized by recurrent episodes of pulsating headache pain of at least moderate severity, which can be accompanied by symptoms like sensitivity to light, sensitivity to sound, nausea, and vomiting. In Canada, 1 person in 10 experiences migraine attacks, women being more affected than men.

### Unmet Needs in Migraine

Many patients have challenges finding effective treatments that reduce the frequency of headaches and often need to try several medications before experiencing a benefit. Furthermore, conventional medications used to prevent migraines are associated with unwanted side effects.

### How Much Does Emgality Cost?

Treatment with Emgality is expected to cost approximately $7,476 to $8,099 per patient per year.

## Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that galcanezumab be reimbursed for the prevention of migraine in adults only if the conditions listed in Table 1 are met.

## Rationale for the Recommendation

Four randomized controlled trials (RCTs) (EVOLVE-1, EVOLVE-2, REGAIN, and CONQUER) demonstrated that galcanezumab reduced mean monthly migraine headache days (MHD) from baseline compared to placebo after 3 to 6 months in patients with chronic migraine and episodic migraine. The treatment groups who received galcanezumab had a reduction in MHD ranging from 1.92 days in EVOLVE-1 to 3.12 days in CONQUER, when compared with those who received placebo. Similarly, there was a consistent reduction in migraine-related disability score across trials, ranging from 6.29 points in EVOLVE-1 to 17.8 points in CONQUER. An improvement in migraine-specific quality of life was observed with galcanezumab in the EVOLVE-1, EVOLVE-2 and CONQUER trials. Acute headache pain medication was also reduced in patients treated with galcanezumab in EVOLVE-1 and EVOLVE-2. Patients identified the need for a preventive treatment that is administered less frequently reduces migraine frequency and intensity, reduces use of acute pain medication, and improves daily functioning and health-related quality of life, all of which may be met with galcanezumab.

Using the sponsor submitted price for galcanezumab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for galcanezumab when considering patients who had failed at least 2 prior lines of therapy was $273,756 per QALY for episodic migraine patients, and $109,325 per QALY for patients with chronic migraine, compared to no preventive therapy. At these ICERs, galcanezumab is not cost-effective at a $50,000 per QALY willingness-to-pay threshold.

### Table 1: Reimbursement Conditions and Reasons

| Reimbursement condition | Reason |
|---|---|
| **Initiation** | |
| 1. The patient has a confirmed diagnosis of episodic or chronic migraine according to the International Headache Society criteria, defined as either of the following:<br>1.1. Episodic migraine: migraine headaches on at least 4 days per month and less than 15 headache days per month for more than 3 months.<br>1.2. Chronic migraine: headaches for at least 15 days per month for more than 3 months of which at least 8 days per month are with migraine. | All 4 RCTs reviewed provided evidence that galcanezumab is superior to placebo in reducing the mean MHDs in patients with episodic migraine and chronic migraine. |

| Reimbursement condition | Reason |
|---|---|
| 2. The patient has experienced an inadequate response, intolerance, or contraindication to at least 2 oral prophylactic migraine medications of different drug classes. | The CONQUER trial included adults with episodic migraine or chronic migraine who had documented inadequate response to at least 2 prior preventive treatments. |
| 3. The physician must provide the number of headache and migraine days per month at the time of initial request for reimbursement. | See Initiation Condition 1 and Renewal Condition 5. |
| 4. The maximum duration of initial authorization is 6 months. | Authorization of funding for 6 months provides flexibility to accommodate the practical challenges of assessing clinical response after 3 months of treatment. The 6-month-long maximum duration of authorization is consistent with the duration recommended for other migraine prophylactic medications reviewed previously by CDEC. |
| **Renewal** | |
| 5. The physician must provide proof of beneficial clinical effect when requesting continuation of reimbursement, defined as a reduction of at least 50% in the average number of migraine days per month at the time of first renewal compared with baseline. At subsequent renewals the physician must provide proof that the initial 50% reduction in the average number of migraine days per month has been maintained. | 50% reduction in the number of monthly MHDs was a predefined secondary end point in each of the included RCTs. |
| 6. The maximum duration of subsequent authorizations following the initial authorization is 6 months. | Patients should be assessed every 6 months to ensure the medication is still providing benefit.<br>See Initiation Criterion 4. |
| **Prescribing** | |
| 7. The patient should be under the care of a physician who has appropriate experience in the management of patients with migraine headaches. | Accurate diagnosis of migraine and assessment of prior treatment failures are important to ensure that galcanezumab is prescribed to the appropriate patients. |
| **Pricing** | |
| 8. Galcanezumab should not exceed the drug program cost of treatment with the least expensive CGRP inhibitor for the treatment of migraine. | Results of indirect treatment comparisons suggest that galcanezumab is generally similar to other CGRP inhibitors in terms of efficacy and discontinuation rates. There is insufficient evidence to justify a cost premium for galcanezumab over the least expensive CGRP inhibitor reimbursed for prevention of migraine. |

CGRP = calcitonin gene-related peptide pathway.

## Implementation Guidance

Issues that may impact the drug plan's ability to implement a recommendation as identified by CDEC and the drug plans are summarized in Table 2.

## Table 2: Implementation Guidance From CDEC

| Condition number | Implementation considerations and guidance |
|---|---|
| 2 | Inadequate response to oral prophylactic therapies is defined as less than a 30% reduction in frequency of headache days to an adequate dose of at least 2 prophylactic medications, which must be of a different class. Patients should be within the therapeutic range for at least 8 weeks before ascertaining treatment effect.<br>At least 1 of the 2 prophylactic medications previously used must have been discontinued because of lack of therapeutic effectiveness.<br>Oral prophylactic therapies to be considered include:<br>• beta blockers<br>• tricyclic antidepressants<br>• verapamil or flunarizine<br>• sodium valproate (or divalproex sodium)<br>• topiramate<br>• gabapentin.<br>A list of previously tried oral prophylactic medications, including doses and duration, and reasons for discontinuance, should be provided by the requesting physician.<br>There is no evidence to support the combination of galcanezumab with onabotulinumtoxinA; therefore, these drugs should not be used together |
| 5 | Some jurisdictions may want to include a reduction of at least 30% in the number of headache days per month and an improvement of at least 5 points in the HIT-6 score, compared with baseline, as an alternative criterion for renewal of reimbursement. Jurisdictions that choose to include this criterion should also request that the physician provide the score obtained on the HIT-6 at the time of initial request for reimbursement. This advice is consistent with previous implementation guidance on CGRP inhibitors. |

CGRP = calcitonin gene-related peptide pathway.

# Discussion Points

- Migraine is a common and debilitating neurologic disease that may lead to poor quality of life, social isolation, and an inability to participate in daily activities. CDEC discussed patient and clinician input that current prophylactic medications do not benefit everyone with migraine and have adverse effects that may make them difficult to tolerate, leading to poor adherence and non-achievement of desired outcomes.
- CDEC discussed the unmet therapeutic need in treatment-refractory episodic migraine (EM) and chronic migraine (CM) CDEC noted that conventional oral medications are associated with notable side effects limiting their usefulness in practice.
- Comparative evidence was limited to indirect treatment comparisons of galcanezumab with other medications used to prevent migraines. The limitations with the indirect evidence, such as the misalignment with the reimbursement request, clinical heterogeneity, and small trial sizes, mean there were no statistically robust analyses to determine the comparative effects of galcanezumab.
- CDEC noted the lack of evidence regarding combination use of galcanezumab with onabotulinumtoxinA and other medications used for prevention of migraines is an

important gap in evidence. CDEC also noted the lack of evidence on sequencing multiple calcitonin gene-related peptide pathway (CGRP) inhibitors.

- CDEC recognized the multidimensional nature of migraine and the importance of capturing improvements in functional aspects relevant for patients when formulating renewal criteria. If possible, assessment should take into consideration migraine intensity, frequency, and impact on patients, as typically measured by migraine-specific scoring tools such as HIT-6 and MIDAS.

## Background

Galcanezumab has a Health Canada indication for the prevention of migraine in adults who have at least 4 migraine days per month. Galcanezumab is a monoclonal antibody that binds to CGRP and prevents its activity. It is available as subcutaneous injections of 120 mg and the Health Canada–approved dose is a loading dose of 240 mg (administered as 2 consecutive injections) followed by once monthly doses of 120 mg (1 injection).

## Sources of Information Used by the Committee

To make their recommendation, CDEC considered the following information:

- A systematic review that included 4 RCTs in adults with migraine.
- Patients' perspectives gathered by patient groups, Migraine Canada and Migraine Québec.
- Input from public drug plans and cancer agencies that participate in the CADTH review process.
- One clinical specialist with expertise diagnosing and treating patients with migraine.
- A review of the pharmacoeconomic model and report submitted by the sponsor.

## Stakeholder Perspectives

### Patient Input

CADTH received a joint submission from Migraine Canada and Migraine Québec.

Migraine Canada and Migraine Québec identified the following as key impacts on the lives of those living with migraines and their families: inability to work resulting in financial stress and relying on a spouse or family members to compensate, childcare and needing additional help, restricted social activities and difficulties with relationships, and lack of understanding from others. Patients described how their spouse and/or family often must bear the burden of household and financial responsibilities, how families miss out on spending time together, difficulties with starting new relationships and stress on existing relationships, and the lack of support available for caregivers.

Patients indicated that it is important to control the frequency and severity of migraines as well as reduce or eliminate the need for acute medications (i.e., triptans and opioids). Patients indicated that they wanted a preventive medication that allowed them to be more productive at work and home. They also felt it was important that a new medication would allow them to fully participate daily life, work, improve family and social relationships, and reduce exhaustion and side effects. In general, survey respondents felt that nearly any degree of relief would be a successful outcome for a preventive therapy. When asked about methods of administration, 73% of participants stated they would prefer a monthly injection to a daily pill.

## Clinician Input

Per the clinical expert consulted by CADTH, the most important goal of treatment is to reduce the frequency of headache. In the clinical expert's experience, a trial of 2 to 3 oral preventive medications is often required before a patient experiences benefit. The older preventive medications have important side effects that often limit their use and impact adherence to treatment.

If the cost of the patient's prescription drugs is reimbursed, they will typically be tried on 2 or 3 oral preventive medications before receiving either onabotulinumtoxinA (if they have CM) or an anti-CGRP monoclonal antibody.

Patients with a diagnosis of migraine with or without aura, more than 4 headache days per month, and failure on 2 or more daily preventers used at an appropriate dose for an appropriate period of time, and no contraindication to the use of an anti-CGRP monoclonal antibody would be suitable for galcanezumab. In the clinical expert's opinion, patients with frequent EM without medication overuse could be most likely to respond to an anti-CGRP monoclonal antibody and patients with CM may realize the greatest benefit. The clinical expert thought that patients least suitable for treatment with galcanezumab would include patients contemplating pregnancy, and there may be hesitancy to prescribe it (or any anti-CGRP monoclonal antibody) to patients with known active peripheral vascular, cardiovascular, or cerebrovascular disease. In addition, use of this family of medications in patients with Raynaud's phenomenon who were taking triptans may be associated with digital ischemia leading to digit amputation, and therefore caution is needed in that area.

Reduction in frequency and/or severity of headaches, reduced use of abortive medications, improved function and quality of life are important measures of treatment response. The clinical expert reported that the goal is to reduce the frequency of headache, ideally to less than 4 headache days per month. A 50% or greater reduction in headache frequency is also considered successful. A reduction in the severity of the headaches, as measured by MIDAS or HIT-6 scores even though the frequency of headache remains unaltered would also be considered successful by the clinical expert. The clinical expert reported that patients should be assessed for response to galcanezumab treatment at 2 to 3 weeks after their third injection, and those who have not shown improvement at that time should be assessed 2 to 3 weeks after their sixth injection. If there is no improvement after 6 injections, then treatment would be discontinued. The clinical expert indicated that development of intolerable side effects, comorbidities that preclude the patient being on treatment (e.g., stroke, heart attack), or pregnancy would also lead to discontinuation of treatment.

The clinical expert thought that galcanezumab could be prescribed by headache specialists, general neurologists, family doctors on the advice of a neurologist, and family doctors who have gained experience with the use of the medication in other patients. The clinical expert

cautioned against requiring patients to be supervised by a headache specialist due to few specialists in Canada.

## Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for galcanezumab:

- considerations for initiation of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

## Table 3: Responses to Questions From the Drug Programs

| Implementation issues | Advice from CADTH |
|---|---|
| **Considerations for initiation of therapy** | |
| The reimbursement request specifies patients having tried at least 2 prophylactic migraine medications. It would be helpful to jurisdictions for this to be defined further, for example, at least 2 prophylactic medications of different classes, and clarification of the optimal dose/duration of the trials. | CDEC notes that in past reviews of CGRP inhibitors, inadequate response to oral prophylactic therapies was defined as less than a 30% reduction in frequency of headache days to an adequate dose and duration of at least 2 prophylactic medications, which must be of a different class.<br>CDEC further agrees with the clinical expert that for an adequate trial, patients are ideally in the therapeutic range for at least 8 weeks before deciding failure of a treatment. |
| Outline whether failure or intolerance to 1 or more CGRP inhibitor would exclude patients from coverage of galcanezumab. | The clinical expert reported that, currently, there is no RCT evidence on patients who experienced failure or intolerance to 1 or more CGRP inhibitor and proceeded to receive treatment with another CGRP inhibitor such as galcanezumab. |
| **Considerations for prescribing of therapy** | |
| The drug programs noted that there is potential for galcanezumab to be used in combination with onabotulinumtoxinA in some jurisdictions. Can the Committee please comment on combination use? | The clinical expert noted that anti-CGRP monoclonal antibodies work to inhibit CGRP activity on different nerves from those affected by onabotulinumtoxinA. Therefore, the clinical expert thought there may be reason to consider using both medications at the same time in some patients.<br>CDEC noted that no evidence supporting combination use is available to date, and as a result, the safety, efficacy, and cost-effectiveness of such use is unknown. |

| Implementation issues | Advice from CADTH |
|---|---|
| **Generalizability** | |
| The pivotal studies (EVOLVE-1, EVOLVE-2, and REGAIN) excluded patients who had failed to respond to 3 or more classes of adequately dosed migraine preventive treatments. CONQUER excluded patients who had failed more than 4 migraine preventive medications categories.<br>Although the reimbursement request specifies failure of at least 2 prophylactic agents, it would be helpful to clarify if there is a maximum number of prophylactic agents that would be accepted before consideration of coverage. | In the clinical expert's experience, approximately 10% to 20% of patient have not tried any preventive medications when referred to their clinic, 40% have tried 1 to 2 medications (but could be an inadequate trial), and most others have tried 2 to 3 medications. Only a small proportion of patients have tried ≥ 4 preventive medications, in the clinical expert's experience. CDEC agrees with the clinical expert that a maximum number of prophylactic agents would not be necessary. |

# Clinical Evidence

## Description of Studies

Four phase III, multinational, double-blind, randomized, placebo-controlled trials were identified and included in the systematic review: the EVOLVE-1, EVOLVE-2, REGAIN, and CONQUER trials. In all trials, galcanezumab and matching-administration placebo were supplied as an injectable solution in 1 mL pre-filled, manual syringes designed to deliver 120 mg of galcanezumab each. The injections were administered by study site personnel once monthly at dosing visits. The primary outcome in all trials was the overall mean change from baseline in the number of monthly MHDs during double-blind treatment.

The EVOLVE-1 (N = 862) and EVOLVE-2 (N = 922) trials were identically designed studies conducted in patients with EM. In both studies, patients were randomized in a 2:1:1 ratio to placebo, galcanezumab 120 mg (loading dose of 240 mg), or galcanezumab 240 mg. The double-blind treatment phase of the studies was 6-months in duration. The EVOLVE-1 and EVOLVE-2 trials excluded patients that had previously failed at least 3 classes of migraine preventive treatments. Key secondary outcomes controlled for multiplicity included the Migraine-Specific Quality of Life Questionnaire (MSQ) v2.1 Role Function-Restrictive (RF-R) domain and monthly MHDs with acute headache pain medication intake.

The REGAIN trial (N = 1,117) was conducted in patients with CM. Patients were randomized in a 2:1:1 ratio to placebo, galcanezumab 120 mg (loading dose of 240 mg), or galcanezumab 240 mg. The study had a 3-month long double-blind treatment phase. The REGAIN trial excluded patients that had previously failed at least 3 classes of migraine preventive treatments. Key secondary outcomes controlled for multiplicity included the MSQ v2.1 RF-R domain and monthly MHDs with acute headache pain medication intake.

The CONQUER trial (N = 463) was conducted in patients with EM or CM that had a documented history of 2 to 4 migraine preventive medication category failures due to inadequate efficacy or tolerability in the past 10 years. Patients were randomized in a 1:1 ratio to placebo or galcanezumab 120 mg (loading dose of 240 mg). The study had a 3-month double-blind treatment phase. The key secondary outcome of interest to the systematic review was the MSQ v2.1 RF-R domain.

This review only reports the results for the galcanezumab 120 mg treatment arms because it is the Health Canada–approved dose. The results for the galcanezumab 240 mg treatment arms are not reported.

In all trials, most patients were female and White, and the mean age of patients was between 39 and 46 years. Most patients (> 60%) had received prior preventive treatment in the EVOLVE and REGAIN studies, and all patients in the CONQUER study. Mean baseline MIDAS total score was 33.2 and 33.0 in the EVOLVE-1 and EVOLVE-2 studies, respectively, which reflects severe disability. In the REGAIN trial, 29.5% had failed 2 or more such treatments due to lack of efficacy in the past 5 years, and the mean baseline MIDAS total score was 67.2, which reflects very severe disability.[12] Overall, 15.5% of patients in the REGAIN trial had concurrent prophylaxis use with topiramate or propranolol. In the CONQUER trial, most patients had 2 (58.2%) or 3 (30.1%) prior medication category failures and mean baseline total MIDAS score was 50.93, which reflects very severe disability.[12] During the baseline period, the mean number of monthly MHDs was 9.1 in both the EVOLVE-1 and EVOLVE-2 studies. In the REGAIN trial, patients had an average of 21.4 headache days per month in the baseline period, of which an average of 19.4 were MHDs. During the baseline period in the CONQUER trial, patients had an average of 15.0 headache days per month, of which an average of 13.2 were MHDs.

## Efficacy Results

### Migraine-Specific Quality of Life Questionnaire Version 2.1

The mean change from baseline in the MSQ RF-R domain score was a key secondary outcome in the trials and controlled for multiplicity. In the EVOLVE-1 trial, the mean change from baseline in the MSQ RF-R domain score during months 4 to 6 of double-blind treatment was 7.74 points (95% CI, 5.20 to 10.28; P < 0.001) greater in the galcanezumab 120 mg group compared with placebo. Similarly, in the EVOLVE-2 trial, the mean change from baseline in the MSQ RF-R domain score during months 4 to 6 was 8.82 points (95% CI, 6.33 to 11.31; P < 0.001) greater in the galcanezumab 120 mg group compared with placebo. In the REGAIN trial, the least squares (LS) mean change from baseline was 5.06 points (95% CI, 2.12 to 7.99) numerically greater in the galcanezumab 120 mg arm compared with the placebo arm, however the difference could not be tested for statistical significance based on the predefined multiple testing procedure. In the CONQUER trial, the mean change from baseline in MSQ RF-R domain score at month 3 was 12.53 points (95% CI, 9.19 to 15.87; P < 0.0001) greater in the galcanezumab group compared with placebo.

### MHDs With Symptoms

The overall change from baseline in number of monthly MHDs with symptoms (nausea and/or vomiting, photophobia and phonophobia, aura, and prodromal symptoms other than aura) during the double-blind treatment phase was an exploratory outcome in all pivotal trials. These outcomes were not controlled for multiplicity within the trials' multiple testing procedures. The LS mean change differences in the galcanezumab 120 mg arm versus placebo arm indicated a numerically greater reduction with galcanezumab treatment in the number of monthly MHDs with all types of symptoms in all trials.

### Migraine Disability Assessment

Change in MIDAS total score was a secondary outcome in all pivotal trials. This outcome was not controlled for multiplicity within the trials' multiple testing procedures. In the EVOLVE-1 trial, the mean change from baseline to end of double-blind treatment phase (month 6) was −6.29 points (95% CI, −9.45 to −3.13) numerically greater reduction in the galcanezumab

120 mg arm compared to the placebo arm. In the EVOLVE-2 trial, the mean change from baseline to end of double-blind treatment phase (month 6) was −9.15 points (95% CI, −12.61 to −5.69) numerically greater reduction in the galcanezumab 120 mg arm compared to the placebo arm. In the REGAIN trial, the mean change from baseline to last observation carried forward (LOCF) end point was −8.74 points (95% CI, −16.39 to −1.08) numerically greater reduction in the galcanezumab 120 mg arm compared to the placebo arm. In the CONQUER trial, the mean change from baseline to LOCF end point was −17.8 points (95% CI, −25.6 to −10.0) numerically greater reduction in the galcanezumab 120 mg arm compared to the placebo arm.

### Number of Monthly MHDs

The overall change from baseline in the number of monthly MHDs during the double-blind treatment phase was the primary outcome in each of the pivotal trials. Galcanezumab 120 mg showed a statistically significant greater reduction in the overall LS mean change from baseline in the number of monthly MHDs during the double-blind treatment phase compared to placebo in all studies.

In the EVOLVE-1 trial, the overall mean change from baseline in the number of monthly MHDs during the double-blind treatment phase was −1.92 days (95% CI, −2.48 to −1.37; P < 0.001) greater reduction in the galcanezumab 120 mg arm compared to placebo. In the EVOLVE-2 trial, the overall mean change was −2.02 days (95% CI, −2.55 to −1.48; P < 0.001) greater reduction in the galcanezumab 120 mg arm compared to placebo. In the REGAIN trial, the overall mean change was −2.09 days (95% CI, −2.92 to −1.26; P < 0.001) greater reduction in the galcanezumab 120 mg arm compared to placebo. In the CONQUER trial, the overall mean change was −3.12 days (95% CI, −3.92 to −2.32; P < 0.0001) greater reduction in the galcanezumab arm compared to placebo.

### Number of Monthly Headache Days

The overall change from baseline in number of monthly headache days was a secondary outcome in the 4 pivotal trials. This outcome was not included in the trials' multiple testing procedures and thus was not adjusted for multiplicity. In the EVOLVE-1 trial, the mean change difference from placebo for the galcanezumab 120 mg arm was −1.66 days (95% CI, −2.25 to −1.07) numerically greater reduction. In the EVOLVE 2 trial, the mean change difference from placebo for the galcanezumab 120 mg arm was −2.00 days (95% CI, −2.58 to −1.42) numerically greater reduction. In the REGAIN trial, the LS mean change difference from placebo for the galcanezumab 120 mg arm was −1.84 days (95% CI, −2.65 to −1.02). In the CONQUER trial, the mean change difference from placebo for the galcanezumab 120 mg arm was −3.13 days (95% CI, −3.96 to −2.29) numerically greater reduction.

### Acute Headache Pain Medication Intake

In the EVOLVE-1, EVOLVE-2, and REGAIN trials, the overall change from baseline in monthly MHDs with acute medication use during the double-blind treatment phase was a key secondary outcome and included in the trials' multiple testing procedures. In the EVOLVE-1 trial, the mean change difference from placebo in the galcanezumab 120 mg arm was −1.81 days (95% CI, −2.28 to −1.33; P < 0.001) greater reduction. In the EVOLVE-2 trial, the mean change difference from placebo in the galcanezumab 120 mg arm was −1.82 days (95% CI, −2.29 to −1.36; P < 0.001) greater reduction. In the REGAIN trial, the mean change difference from placebo in the galcanezumab 120 mg arm was −2.51 days (95% CI, −3.27 to −1.76) numerically greater reduction. The difference between the galcanezumab 120

mg and placebo arms could not be tested for statistical significance based on the REGAIN trial's predefined multiple testing procedure. In the CONQUER trial, the overall change from baseline in MHDs with acute medication use during the double-blind treatment phase was a secondary outcome. This outcome was not included in the trial's multiple testing procedure, and therefore is not adjusted for multiplicity. The mean change difference from placebo in the galcanezumab 120 mg arm was −3.40 days (95% CI, −4.14 to −2.65) numerically greater reduction.

### Time to First Loss of Response in the Post-Treatment Phase

Time to the first loss of 50% response in patients who were 50% responders (defined as a ≥ 50% reduction from baseline in monthly MHDs) in the last month of double-blind treatment and entered the post-treatment phase was assessed in the EVOLVE-1, EVOLVE-2, and REGAIN trials. In the EVOLVE-1 and EVOLVE-2 trials, approximately 1/2 of the patients in all treatment groups had first loss of 50% response by 4 months after the end of the double-blind treatment phase. In the REGAIN study, the percentage of patients with first loss of 50% response at month 1 of the post-treatment phase was 24.3%. By month 4 of the post-treatment phase, 48.2% patients had first loss of 50% response.

### Time to Initiation of a Migraine Prevention Treatment in Post-Treatment Phase

Time to initiation of migraine preventive medication during the post-treatment phase was assessed in the EVOLVE-1, EVOLVE-2, and REGAIN trials. In the EVOLVE-1 study, 12 (< 2%) patients initiated treatment with a migraine prevention medication and there were no significant differences between placebo and galcanezumab-treated patients with regard to the time of initiation. In the EVOLVE-2 study, 3.2% of patients in the placebo arm initiated treatment with a migraine prevention medication, compared with 1.4% patients in the galcanezumab 120 mg arm. There were no significant differences between placebo and galcanezumab-treated patients with regard to the time of initiation. In the REGAIN study, 5.7% of patients who entered the post-treatment follow-up phase started a migraine preventive medication during the post-treatment period.

### Health Care Resource Utilization

Health Care Resource Utilization (HCRU) was a secondary outcome in the REGAIN and CONQUER trials. These outcomes were not adjusted for multiplicity. The number of HCRU events were recorded in the baseline period (6-month period before randomization) and the 3-month double-blind treatment periods. Because low rates of HCRU events were observed and because of the different time periods assessed at baseline and post-baseline, rates for the migraine-related events were standardized per 100 patient-years.

### Work Productivity and Activity Impairment Questionnaire

The Work Productivity and Activity Impairment questionnaire was assessed in the CONQUER trial. The LS mean change (standard error [SE]) for activity impairment was −20.71% (1.95%) and −8.64% (1.92%) in the galcanezumab and placebo arms, respectively. For presenteeism, the LS mean change (SE) was −12.50% (2.37%) and −2.56% (2.32%) in the galcanezumab and placebo arms, respectively. For overall work impairment, the LS mean change (SE) was −14.31% (2.51%) and −3.46% (2.41%) in the galcanezumab and placebo arms, respectively. For absenteeism, the LS mean change (SE) was −4.22% (1.29%) and −2.90% (1.24%) in the galcanezumab and placebo arms, respectively.

### Adverse Events

During the double-blind treatment period, most patients in the EVOLVE-1 and EVOLVE-2 trials experienced at least 1 treatment-emergent adverse event (AE), with a numerically smaller proportion of patients experiencing at least 1 AE in the placebo arm compared to the galcanezumab 120 mg arm (60% versus 66% in EVOLVE-1; 62% versus 65% in EVOLVE-2). The most frequently reported AEs in the EVOLVE-1 trial were injection site pain and nasopharyngitis. The most frequently reported AEs in the EVOLVE-2 trial were injection site pain and upper respiratory tract infection.

During the double-blind treatment period of the REGAIN trial, 50% of patients in the placebo arm and 58% of patients in the galcanezumab 120 mg arm experienced at least 1 treatment-emergent AE. The most frequently reported AEs were injection site pain and nasopharyngitis.

During the double-blind treatment period of the CONQUER trial, 53% of patients in the placebo arm and 51% of patients in galcanezumab 120 mg arm experienced ≥ 1 treatment-emergent AE. The most frequently reported AEs were nasopharyngitis and influenza.

### Serious Adverse Events

Few patients experienced serious adverse events (SAEs) in the studies, with less than 3% of patients experiencing 1 or more SAEs.

### Withdrawal Due to Adverse Events

As with SAEs, a small percentage of patients (< 4%) discontinued double-blind treatment due to AEs.

### Mortality

No patients died during the trials.

### Notable Harms

**Anaphylaxis and hypersensitivity reactions**: No patients in the trials experienced an anaphylactic reaction. In the EVOLVE trials, 2% to 4% of patients in the placebo arms and 4% to 6% of patients in the galcanezumab 120 mg arms experienced a hypersensitivity event. One patient in the placebo arm experienced angioedema in each of the EVOLVE trials. In the REGAIN trial, 2% and 4% of patients experienced a hypersensitivity event in the placebo and galcanezumab 120 mg arms, respectively, during the double-blind treatment phase. Three patients in the placebo arm and 2 patients in the galcanezumab 120 mg arm experienced angioedema during double-blind treatment. In the CONQUER trial, 3% and 3% of patients experienced a hypersensitivity event in the placebo and galcanezumab 120 mg arms, respectively, during the double-blind treatment phase. One patient in the placebo arm and 0 patients in the galcanezumab 120 mg arm experienced angioedema during double-blind treatment.

**Injection site reactions**: Injection site reactions during double-blind treatment were reported in a numerically greater proportion of patients in the EVOLVE-1 study compared to the other trials. In the EVOLVE-1 trial, injection site reactions were reported by 20% of patients in the placebo arm and 28% of patients in the galcanezumab 120 mg arm. In the other trials, injection site reactions were reported by 9% to 10% and 7% to 18% of patients in the placebo and galcanezumab 120 mg arms, respectively.

**Antibody formation**: During the double-blind treatment periods of the EVOLVE-1, EVOLVE-2, and REGAIN studies, up to 9.4% of patients treated with galcanezumab 120 mg and up to 1.7% of patients treated with placebo were treatment-emergent anti-drug antibody (ADA) positive. The formation of ADAs was not assessed proactively in the CONQUER study and therefore are not reported.

**Vascular events**: In the EVOLVE trials, approximately 2% and 3% of patients in the placebo and galcanezumab 120 mg arms, respectively, experienced a vascular disorder. In the REGAIN trial, 1.79% and 1.10% of patients in the placebo and galcanezumab 120 mg arms, respectively, experienced a vascular disorder during the double-blind treatment phase. The most frequently reported vascular disorders in the EVOLVE-1, EVOLVE-2, and REGAIN studies were hypertension and hot flush. In the CONQUER trial, 2.61% and 0.43% of patients in the placebo and galcanezumab 120 mg arms, respectively, experienced a vascular disorder during the double-blind treatment phase. Hypertension was the only vascular disorder experienced by at least 1 patient (1.30% in the placebo arm, 0.43% in the galcanezumab arm).

# Economic Evidence

## Table 4: Summary of Economic Evaluation

| Component | Description |
|---|---|
| **Type of economic evaluation** | Cost-utility analysis |
| **Target populations** | Adults who have at least 4 migraine days per month and who have a history of at least 2 prior preventive treatment failures owing to a lack of efficacy or tolerability, or both, in 2 populations:<br>• Episodic: 4 to 14 MHD per month, and < 15 headache days per month<br>• Chronic: > 15 headache days per month, at least 8 of which are classified as MHD. |
| **Treatment** | Galcanezumab. 240 mg (administered as 2 consecutive injections of 120 mg), followed by once monthly doses of 120 mg. |
| **Submitted price** | Galcanezumab, 120 mg/mL: $623.00 per single-dose pre-filled pen or syringe |
| **Treatment cost** | $8,099 in the first year, $7,476 in subsequent years. |
| **Comparator** | Best supportive care, consisting of acute medication for migraine as permitted in the CONQUER trial including triptans, NSAIDs, and acetaminophen or acetaminophen combinations, with some restrictions on opioids and barbiturates. |
| **Perspective** | Canadian publicly funded health care payer |
| **Outcome** | QALYs |
| **Time horizon** | 20 years |
| **Key data source** | CONQUER trial |
| **Submitted results** | • EM, ≥ 2 prior preventive therapies: ICER = $39,010 per QALY ($27,524 incremental costs, 0.706 incremental QALYs)<br>• CM, ≥ 2 prior preventive therapies: ICER = $16,594 ($26,101 per QALY incremental costs, 1.573 incremental QALYs) |

| Component | Description |
|---|---|
| **Key limitations** | • The full Health Canada–approved population was not modelled; patients who have not experienced at least 2 previous preventive therapies for migraine were not included in the analysis.<br>• The sponsor's base case did not consider active comparators such as oral preventive therapies currently reimbursed in Canada, onabotulinumtoxinA injections, or the other approved CGRP medications erenumab or fremanezumab.<br>• The reduction in MHDs was stratified by treatment response rather than by treatment group.<br>• The model structure did not adequately reflect the management of migraine in clinical practice. Patients who discontinued galcanezumab therapy received no further preventive treatments for the remainder of the time horizon.<br>• The uncertainty in the long-term treatment effect of galcanezumab was not effectively explored, as it was assumed that patients maintained their response to galcanezumab for the duration of therapy based on limited trial and extension study data, until they discontinued due to adverse events.<br>• Health care resource use was based on a utilization study from the US and may not reflect the management of migraine in Canada.<br>• Utilities were treatment-specific rather than based on the model health states, which is not aligned with CADTH guidelines. Migraine severity and other factors potentially impacting QoL were not appropriately modelled. |
| **CADTH reanalysis results** | In CADTH reanalyses, the time horizon was reduced to 5 years, treatment independent health state utilities were applied, hospital costs were removed, and MHD reductions were not stratified by response. Based on CADTH reanalyses, the ICER for galcanezumab is:<br>• EM, ≥ 2 prior preventive therapies: ICER = $273,560 per QALY (incremental cost: $14,563; incremental QALYs: 0.053) compared with BSC. A 78% price reduction would be required to reduce the ICER below $50,000.<br>• CM, ≥ 2 prior preventive therapies: ICER = $109,325 per QALY (incremental cost: $18,247; incremental QALYs: 0.167) compared with BSC. A 49% price reduction would be required to reduce the ICER below $50,000. |

CM = chronic migraine; EM = episodic migraine; ICER = incremental cost-effectiveness ratio; LY = life-year; MHD = migraine headache days; NSAID = nonsteroidal anti-inflammatory drug; QALY = quality-adjusted life-year; QoL = quality of life.

## Budget Impact

CADTH identified the following key limitations with the sponsor's analysis:

- The sponsor may have underestimated the proportion of patients with migraines who will receiving therapy.
- The sponsor's derivation of the eligible population was overestimated due to including the pediatric population and double counting the Non-insured Health Benefits-eligible population.
- The base case did not consider the reimbursement of other CGRP medications.

CADTH reanalysis included revising the proportion of patients receiving preventive therapy and revising the eligible population. Under these alterations, CADTH reanalyses reported that the reimbursement of galcanezumab for EM and CM patients who have failed 2 or more previous preventive therapies would be associated with a budgetary increase of $$20,379,387 in year 1, $26,224,548 in year 2, and $33,473,217 in year 3, for a 3-year total incremental cost of $80,077,151. In a scenario where erenumab and fremanezumab are already assumed to be reimbursed, the 3-year total incremental cost of also reimbursing galcanezumab would be $2,430,164.

CADTH

# Canadian Drug Expert Committee Information

## Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

**Meeting date**: October 27, 2021

**Regrets**: Two expert committee members did not attend

**Conflicts of interest**: None