Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Atogepant (Qulipta)

Indication: For the prevention of migraine in adults who have at least 4 migraine days per month

Sponsor: AbbVie Inc.

Recommendation: Reimburse with Conditions

Version: 1.0
Publication Date: June 2024
Report Length: 18 Pages

Single Technology

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that Atogepant be reimbursed for the prevention of migraine in adults with chronic migraine only if the conditions listed in **Error! Reference source not found.** are met.

Rationale for the Recommendation

One randomized placebo-controlled trial (PROGRESS) demonstrated that the use atogepant 60 mg once daily (QD) in patients who had previously failed two or more migraine prevention medications with different mechanism of actions (2+ TF population; N=[redacted]) resulted in added clinical benefit when compared to placebo. The evidence from the trial showed that after 12 weeks of treatment, atogepant reduced monthly migraine days (MMDs) and monthly headache days (MHDs). In the full set analysis of the primary endpoint of the PROGRESS trial, the reduction in MMD from baseline was higher for patients treated with atogepant 60 mg QD than those who received placebo, with least squares mean difference (LSMD) of -1.82 (95% CI, -2.89 to -0.75 days). In the 2+TF population of the PROGRESS study, the reduction in MMD from baseline was higher for patients treated with atogepant 60 mg QD than those who received placebo, with LSMD in change from baseline in mean MMD of [redacted] days (95% CI, [redacted] to [redacted] days). In the same group, the proportion of patients experiencing at least a 50% reduction in MMDs was greater with atogepant 60 mg QD than with placebo ([redacted] versus [redacted] respectively). The odds of achieving at least a 50% reduction in MMD was higher with atogepant 60 mg QD than with placebo (OR =[redacted]; 95% CI, [redacted] to [redacted]).

Patients and clinical experts identified the need for different treatment options. CDEC concluded that atogepant 60 mg QD met some of the needs identified by patients, including reduction in the mean number of migraine days, headaches, and medication use days per month, improvement in function, and the convenience of an oral medication with ease of administration.

At the sponsor submitted price for atogepant and publicly listed price for all comparators, atogepant was less costly than fremanezumab, eptinezumab, and galcanezumab, and more costly than onabotulinumtoxinA. Given that there is insufficient evidence to support a clinical benefit with atogepant compared to relevant comparators, the total drug cost of atogepant should not exceed the total drug cost of the lowest cost CGRP inhibitor reimbursed for the prevention of chronic migraine in the reimbursement request population.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation, renewal, and prescribing		
1. Eligibility for reimbursement of atogepant should be based on the criteria used by each of the public drug plans for initiation, renewal, and prescribing of other CGRP inhibitors currently reimbursed for the prevention of migraine in adult patients with chronic migraine, with the addition of condition 2 for prescribing.	There is no evidence that atogepant should be held to a different standard than other CGRP inhibitors currently reimbursed when considering initiation, renewal, and prescribing. The clinical expert noted that the place in therapy for atogepant is comparable to other CGRP inhibitors.	—
2. Atogepant should not be reimbursed for use in combination with other CGRP inhibitors for the prevention of migraine in adult patients with chronic migraine.	No evidence was identified to demonstrate whether atogepant offers additional benefit when used in combination with other CGRP inhibitor treatments.	—

Reimbursement condition	Reason	Implementation guidance
Pricing		
3. Atogepant should be negotiated so that it does not exceed the drug program cost of treatment with the least costly CGRP inhibitor reimbursed for the treatment of chronic migraine.	There is insufficient clinical evidence to justify a cost premium for atogepant over the least expensive CGRP inhibitor reimbursed for chronic migraine.	—

CGRP = calcitonin gene-related peptide.

Discussion Points

- CDEC noted that the PROGRESS trial did not conduct a calculation to determine the sample size needed to detect statistically significant differences in effects estimate in the 2+TF population that is the focus of the reimbursement request. However, the committee discussed that the consistent and larger effects of atogepant in this subgroup compared with the full set analysis across all main endpoints, and with the GRADE assessment showing moderate certainty for both the main population and the subgroup, indicated the likelihood that atogepant has a beneficial clinical effect in the 2+TF population of patients with migraine.
- CDEC noted that the PROGRESS trial did not compare atogepant 60 mg QD to other available active interventions. The committee observed that the effect estimates from the sponsor-submitted indirect treatment comparisons (ITC) of atogepant to other interventions available in Canada (galcanezumab, fremanezumab, erenumab, Botox, or eptinezumab) had uncertainties due to highly imprecise estimates (wide credible intervals) that limit the ability to draw conclusions. Therefore, the committee concluded that there was insufficient evidence to determine the comparative effectiveness of atogepant to other interventions for migraine currently reimbursed in Canada.
- The committee observed that the results from the PROGRESS study suggested that treatment with atogepant 60 mg QD may improve disability and function scores and HRQoL measures, while reducing MHDs, monthly acute medication use days, and the impact of migraine on daily functioning. CDEC concluded that although atogepant does not impact the underlying cause of migraine, it is a new oral option that addresses some unmet needs and may improve control and reduce the burden of migraines for patients and their caregivers.
- CDEC discussed the uncertainty in the economic analysis, notably that a cost-minimization approach is predicated on the assumption of clinical similarity between atogepant and relevant comparators. If atogepant confers differential efficacy or safety compared to the other CGRP inhibitors, the cost-effectiveness of atogepant relative to other CGRP inhibitors used in the reimbursement request population is unknown.

Background

Migraine is a multifactorial, disabling neurological disease affecting 8% of the population of Canada, characterized by recurrent and often debilitating headaches of moderate to severe intensity accompanied by neurological symptoms. Migraine is commonly categorized according to the frequency of attacks as episodic migraine (EM) or chronic migraine CM. People with migraine who have <15 migraine headache days (MHDs) are commonly referred to as having EM. CM has been defined as headaches occurring on 15 or more days per month for more than 3 months, of which at least 8 days per month have the features of migraine attacks. As attack frequency or severity increases, migraine management requires the use of both acute and preventive treatments. Multiple pharmacologic options for migraine prevention are currently available in Canada for patients with CM including established oral preventive treatments, injectable onabotulinumtoxinA, or self-injectable and infusion calcitonin gene-related peptide monoclonal antibodies (CGRP mAbs).

Atogepant is a CGRP receptor antagonist that has been approved by Health Canada (NOC on May 2, 2024) for the prevention of migraine in adults who have at least 4 migraine days per month. Atogepant is available as tablets 10 mg, 30 mg, and 60 mg, oral, and the dosage recommended in the product monograph is 60 mg once daily.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of one randomized controlled trial in patients with chronic migraine; one long-term extension study; and one systematic review with indirect treatment comparisons.
- patients' perspectives gathered by two patient groups, one from the Canadian Migraine Society and a second from Migraine Canada & Migraine Quebec.
- input from public drug plans that participate in the CADTH review process.
- One clinical specialist with expertise diagnosing and treating patients with chronic migraine.
- input from two clinician groups, the Atlantic Neurology Society Group (ANSG) and the Canadian Headache Society (CHS).
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

CADTH received 2 patient group submissions. One from the Canadian Migraine Society and a second from Migraine Canada & Migraine Quebec. Data was gathered by Canadian Migraine Society from 3 perspectives: experience from support groups with 3,200 members, personal disease experience, and email interviews with 19 patients currently on atogepant conducted from November 1 to December 12, 2023. The information provided by Migraine Canada & Migraine Quebec was collected through a Quality of Life (QoL) online survey that was launched in late fall of 2021. In total, 1,165 adults living in Canada with migraine and their caregivers responded to the online survey. Migraine Canada launched an additional survey in November of 2023 to gather further insights to seek input from patients with experience with atogepant. In total, 230 adults with migraine responded to the survey.

Most of the patients from the two patient groups shared similar symptoms and acknowledged the impact of symptoms on their day-to-day lives and employment. The Canadian Migraine Society reported that migraine, —and especially chronic migraine— affects every single facet of a person's life. In both surveys conducted by Migraine Canada & Migraine Quebec, the three outcomes reported to be most valuable to patients when trying a preventative treatment were: effects in headache intensity, headache frequency, and symptoms other than pain such as sensitivity to light, sound, nausea, brain fog, etc. Canadian Migraine Society further stated that the desired outcome should be an increase in quality of life.

Both groups agreed that patients with chronic migraine need access to different options for effective medications (both preventive and acute), because patients with migraine do not respond equally to the same medication or treatment. Migraine Canada & Migraine Quebec also highlighted that considering the opioid crisis, that new medications should play a role in a national plan to better manage pain and alleviate the need for opioids.

Clinician Input

The clinical expert consulted by CADTH identified several unmet needs in the treatment of chronic migraine, including poor adherence to medication, often due to common side effects even when treatments are effective. Additionally, accessibility issues, such as the requirement for specialized administration of certain medications like onabotulinumtoxinA, contribute to the need for treatments that are more easily accessible. The expert considered that in their opinion atogepant shows promise as a first-line treatment option due to its effectiveness and low side-effect profile, but cost considerations may limit its initial prescription, potentially restricting it to patients who have already tried multiple medications.

The clinical expert advised caution for patients with certain medical histories, such as stroke or cardiac disease, as well as special considerations that are necessary for patients of childbearing age.

According to the clinical expert, assessing treatment response relies on reductions in headache frequency or severity, with no standardized criteria for discontinuing an established treatment, though a minimum trial period of six months was recommended before considering the discontinuation of atogepant.

The clinical expert also mentioned that atogepant offers potential benefits for migraine patients, particularly reduction in migraine and headache frequency in those with treatment-resistant or frequent episodic migraine and can be prescribed by primary care providers without requiring specialized monitoring. However, cost considerations and the need for further research into long-term efficacy and discontinuation criteria remain significant factors in its clinical use.

Clinician Group Input

CADTH received 2 clinician group submissions from the Atlantic Neurology Specialist Group (ANSG) and Canadian Headache Society (CHS). ANSG held two professional meetings to discuss the migraine treatment landscape, identify barriers to treatment access, and the role of atogepant in fulfilling unmet patient needs on October 5 and December 18, 2023. CHS gathered information from published clinical evidence and expert opinions from Headache specialists in Canada and internationally. ANGS identified what they termed the top 3 unmet treatment needs for migraine in Canada: 1) adverse events and inadequate response to acute and preventive treatments, 2) general practitioners (GPs) depend on specialists for prescribing preventive treatments, and 3) restrictive reimbursement criteria that prevent patient access to the care that they need. CHS also found similar treatment gaps and some additional ones such as wearing off in effectiveness of current available treatments, contraindication to some patient populations, and patients' preference for oral formulations over injectables. ANGS stated that atogepant is the first oral small-molecule CGRP antagonist approved for the preventive treatment of migraine in Canada. CHS also commented that atogepant could be combined with drugs with a different mechanism though evidence to support the effectiveness of such combinations is lacking. ANSG believed that specialists, GPs, and nurse practitioners with experience diagnosing migraine could prescribe the product and monitor the patients. CHS further stated that atogepant prescription should not be restricted to neurologists or specialists due to the belief that it is well tolerated and safe compared to many other drugs prescribed in primary care.

Drug Program Input

Input from the drug plans identified factors pertaining to relevant comparators, considerations for initiation and discontinuation of therapy, generalizability, care provision issues, and system and economic considerations. CDEC weighed evidence from the body of evidence and input from the clinical experts consulted by CADTH, which provided advice on the potential implementation issues raised by the drug programs.

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

Table 2: Responses to Questions from the Drug Programs

Implementation issues	Response
Relevant comparators	
The PROGRESS trial compared Qulipta 30mg BID to 60 mg QD to placebo over 12 weeks. There are no head-to-head comparisons of the relevant comparators in migraine prevention.	This is a comment from the drug programs to inform CDEC deliberations.
Not all plans cover Botox for migraine prevention, but some do. The place in therapy is important to clarify. Injectable CGRP inhibitor medications are listed in many jurisdictions. If needed and applicable, the initiation criteria for atogepant should be aligned with other CGRP inhibitor medications for this indication.	The Committee acknowledged that applicable criteria and place in therapy will be like other CGRP inhibitors. Also added that Botox may have a slightly different place in therapy, despite evidence of effectiveness.
Considerations for initiation of therapy	

Implementation issues	Response
The number and type of prophylactic medications tried before initiation should be discussed. As above, the criteria for atogepant should align with other similar recommendations, if feasible.	The Committee and clinical expert agreed that criteria for atogepant should be aligned with other CGRP inhibitors currently reimbursed in Canada.
Prior therapies: *considering Botox and other CGRP inhibitor medications before initiating atogepant, how many of these (prophylactic) medications should be tried first? Can it be specified as to which medications should be tried?*	The Committee acknowledged the need to consider the same listing criteria as other CGRPs. According to the clinical expert, there is no evidence for establishing a specific order of medications. For example, some patients may need Botox first due to their initial symptoms. The clinical expert mentions that any drug tried before atogepant will be adequate to include in the considerations for initiation.
Eligibility to re-treatment: *Can patients be re-treated? i.e., If patients discontinue the therapy due to benefit and then relapse with symptoms, can the drug be given again? If so, what would be the appropriate timing of re-treatment?*	The clinical expert in agreement with the Committee explained that there are no compelling reasons why clinicians and patients would not consider or try this manoeuvre. No specific timing can be addressed with certainty, but the clinical expert would recommend observing patients during the first 3 months off-therapy, which is the time symptoms may come back.
Consistency with initiation criteria associated with other drugs reviewed by CADTH in the same therapeutic space: Consider alignment with other CGRP inhibitor recommendations for this indication.	The Committee acknowledged the need to aligning atogepant with other CGRP inhibitors for the initiation of therapy for the indication.
Considerations for continuation or renewal of therapy	
Consistency with renewal criteria associated with other drugs reviewed by CADTH in the same therapeutic space: Consider alignment with other CGRP inhibitor recommendations for this indication.	The Committee acknowledged the need to aligning atogepant with other CGRP inhibitors for the continuation or renewal of therapy for the indication.
Considerations for discontinuation of therapy	
Consider alignment with other CGRP inhibitor recommendations for this indication.	The Committee acknowledged the need to aligning atogepant with other CGRP inhibitors for the discontinuation of therapy for the indication.
Considerations for prescribing of therapy	
In the pivotal trial, the 30mg BID and 60mg QD dose schemes were studied. However, the 60mg QD is the only dose recommended for this indication (based on the monograph). • *Is 30mg BID an option? Other dosing options?* *Is 60 mg the daily maximum dose recommended. Can it be exceeded in certain situations*?	The Committee and the clinical expert agreed on focusing on the 60 mg QD dose as this is the one accepted dosage in the HC indication and in the most recent version of the product monograph. The clinical expert mentions the lack of evidence for going over 60 mg daily, hence there is uncertainty in this regard. Also mentions how the 30 mg BID is not needed in clinical practice as the 60 mg is more acceptable and feasible as it provides the same level of efficacy and with easier delivery and possibly better adherence to treatment.
Consider "prescriber with experience in migraine therapy" to align with other recommendations and improve access in areas where neurologists may be difficult to access.	The Committee agreed to aligning atogepant with other CGRP inhibitors and that a prescriber with clinical experience in migraine therapy will be considered in the prescribing conditions.
Comments on *combining atogepant with Botox and possibly with other injectable CGRP inhibitor medications.*	The Committee would prefer avoiding combinations. According to the clinical expert, these interventions can be combined by the treating physician if there is an adequate, close clinical monitoring. In the clinical expert's experience, using Botox with monoclonal antibodies is common in practice. If there are no specific contraindications or drug interactions the combination is allowed.
Generalizability	

Implementation issues	Response
Populations of interest match the indication but with insufficient data: Pediatric patients and Patients who have tried and failed over 4 prophylactic meds – these were excluded from trial	The Committee agreed that pediatric populations are out of scope for this drug as it is not approved by HC. Furthermore, there is insufficient data to address the use of atogepant in patients with over 4 medications, as these were excluded from the pivotal trial. Other CGRPs inhibitors currently reimbursed in Canada do not mention this sub population.
Patients on active treatment with a time-limited opportunity to switch to the drug(s) under review: *If patients are currently on an injectable CGRP inhibitor, can they switch to atogepant? If yes, is there a recommended switching regimen?*	The Committee and clinical expert agreed that it would be feasible for patients to switch from one CGRP inhibitor to another, and no specific regimen would be needed to accomplish this strategy.
System and economic issues	
Presence of confidential negotiated prices for comparators: All injectable CGRP inhibitor medications for this indication and this one for the indication of episodic migraine have achieved negotiated prices.	This is a comment from the drug programs to inform CDEC deliberations.

BID = twice a day; CDEC = Canadian Drug Expert Committee; CGRP = calcitonin gene-related peptide; QD = once a day

Clinical Evidence

Description of Studies

One pivotal RCT (PROGRESS) was included assessing atogepant for treatment of patients with chronic migraine. The PROGRESS study is a randomized placebo-controlled trial that assessed the effects of atogepant 60 mg QD against placebo in adult patients with chronic migraine. The study included a subgroup of patients who have experienced an inadequate response, intolerance, or contraindication to at least two oral prophylactic migraine medications. There was a prespecified subgroup of patients with 2+TF (N= [redacted] patients). The study assessed efficacy outcomes (monthly migraine days, monthly headache days, and monthly acute medication use), function or disability outcomes (performance of daily activities, missed school- or workdays, and impact of headaches in daily function), HRQoL, health resource utilization, and harms.

Efficacy Results

Change from baseline in mean monthly migraine days.

The primary efficacy endpoint in the PROGRESS study was the change from baseline in mean monthly migraine days (MMDs) across the 12-week treatment period. In patients who had previously failed two or more migraine prevention medications with different mechanism of actions (2+ TF population, n = [redacted]), the LS mean change from baseline as measured by the mean MMDs across the 12-week treatment period was -[redacted] days (95% CI, [redacted] to [redacted] days) for atogepant 60 mg QD compared with [redacted] days (95% CI, [redacted] to [redacted] days) for placebo. The least squares mean difference (LSMD) in change from baseline in mean MMD was -[redacted] days (95% CI, [redacted] to -[redacted] days; P = [redacted]), favouring atogepant 60 mg QD.

Reduction of ≥50% in 3-month average of MMDs

In the 2+ TF population, the proportion of patients that had ≥ 50% reduction in the 3-month average of monthly migraine days with atogepant 60 mg QD was [redacted] compared to [redacted] with placebo. The adjusted absolute between-group difference was [redacted] (95% CI, [redacted] to [redacted]). The odds ratio (OR) for the proportion of patients who demonstrated a ≥ 50% reduction in the 3-month average of monthly migraine days was [redacted] (95% CI, [redacted] to [redacted]; P = [redacted]), favouring atogepant 60 mg QD.

Change from baseline in mean monthly headache days.

In the 2+ TF population, from the LS mean change from baseline in the number of mean monthly headache days across the 12-week treatment period was [redacted] days (95% CI, [redacted] to [redacted] days) with atogepant 60 mg QD compared to [redacted] days (95% CI, -[redacted] to [redacted] days) with placebo. The LSMD in change from baseline in mean was [redacted] days (95% CI, [redacted] to [redacted] days; P = [redacted]), favouring atogepant 60 mg QD.

Change from baseline in mean monthly acute medication use days.

In the 2+ TF population, from the LS mean change from baseline in the number of mean acute medication use days across the 12-week treatment period was [redacted] for atogepant 60 mg QD compared to [redacted] with placebo. The LSMD in change from baseline in mean acute medication use days between atogepant 60 mg QD and placebo was [redacted], favouring atogepant 60 mg QD.

Change from baseline in mean monthly Performance of Daily Activities Domain Score of the AIM-D

In the 2+ TF population, the LS mean change from baseline in the mean monthly Performance of Daily Activities domain score of AIM-D across the 12-week treatment period was [redacted] for atogepant 60 mg QD compared [redacted] for placebo where negative values imply improvements from baseline. The LSMD in change from baseline in mean monthly Performance of Daily Activities Domain Score of AIM-D across the 12-week treatment period was [redacted] favouring atogepant 60 mg QD.

Change from baseline in the Migraine Disability Assessment (MIDAS) total score.

This endpoint was not available for the 2+TF population, hence only assessed in the overall modified intention-to-treat (mITT) population, where the LS mean change from baseline in MIDAS total score at Week 12 was [redacted] for atogepant 60 mg QD (improvement) as compared to [redacted] with placebo. The LSMD in change from baseline was [redacted] favouring atogepant 60 mg QD.

Change from baseline in Headache Impact Test (HIT-6) total score.

In the 2+TF population, the LS mean change from baseline in HIT-6 total score at Week 12 [redacted] for atogepant 60 mg QD (negative numbers implying improvement) and [redacted] in the placebo group. The LSMD in change from baseline was [redacted], favouring atogepant 60 mg QD.

Change from baseline in Migraine Specific Quality of Life Questionnaire (MSQ v2.1) Role Function-Restrictive domain score.

In the 2+TF patient population, the LS mean change from baseline in MSQ v2.1 Role Function-Restrictive domain score at Week 12 was [redacted] higher for atogepant 60 mg QD while the placebo group had an increase of [redacted], where higher values suggest an improvement in patients' functioning with daily social and work-related activities. The LSMD in change from baseline in mean monthly MSQ v2.1 Role Function-Restrictive Domain Score at Week 12 was [redacted] in the atogepant 60 mg QD group when compared to placebo.

Change from Baseline in Percent Work Time Missed Assessed by the WPAI: MIGRAINE

This was only evaluated in subset of the overall (mITT) population and no information was provided for the 2+ TF subgroup. In the overall (mITT) population, the LS mean change from baseline in the percent work time missed assessed with the WPAI at Week 12 was [redacted]) for atogepant 60 mg QD (negative values imply improvement) compared to [redacted]) with placebo. The LSMD in change from baseline in percent work time missed at Week 12 was -4.85 points (95% CI, -9.48 to -0.23 points; P = 0.0397), favouring atogepant 60 mg QD.

Harms Results

The most frequently reported AEs (≥ 5% of patients in the safety population) in the atogepant treatment group were constipation (10%) and nausea (9.6%). In the 2+TF population, patients also experienced [redacted].

In the 2+TF population, [redacted] of patients in the atogepant 60 mg QD treatment group and [redacted] of patients in the placebo treatment group. [redacted] of patients in the atogepant 60 mg QD treatment group, and [redacted] of patients in the placebo

treatment group. [redacted] of patients in the atogepant 60 mg QD treatment group, and [redacted] of patients in the placebo treatment group.

[redacted]

AEs leading to treatment discontinuation were infrequent in the atogepant 60 mg QD treatment group and placebo group, [redacted]. All AEs leading to treatment discontinuation in the atogepant 60 mg QD group occurred in <1% of patients.

No deaths were reported in the PROGRESS trial.

Adverse events of special interest (AESIs) were reported at low rates. [redacted]. A total of 3 patients had elevated ALT or AST laboratory value that was ≥ 3 × ULN, which were subject to blinded adjudication by the Adjudication Committee.

Critical Appraisal

The PROGRESS trial is a randomized controlled trial investigating the efficacy and safety of atogepant 60 mg QD (the dose of interest for this review) compared to placebo. The study involved a randomization and allocation concealment process that was judged to be properly implemented, ensuring an overall balanced distribution of participants to either the atogepant 60 mg QD or placebo arms. The number of prior migraine prevention medications failed was a stratification factor in the randomization, which should ensure that the randomization is upheld in the 2+ TF subgroup. Some minor baseline imbalances were observed for the WPAI endpoint, obtained from a subset of the population, with imbalances between groups. However, these were judged to have overall low risk for introducing bias or to have suggested problems in the randomization process. In the study, patients maintained good adherence to the intended intervention. Concomitant medication use was comparable across the placebo and atogepant 60 mg QD treatment groups.

The 2+TF subgroup, which represents [redacted] (n=[redacted]) of the total mITT population, is of interest for this CADTH report because it is the focus of the sponsor's reimbursement request. However, the sample size (power) calculation did not consider this subgroup separately, therefore; it is unknown whether there was enough statistical power to detect any differences in treatment effect between the intervention and comparator arms in this subgroup. However, greater effect sizes for the 2+TF subgroup were consistent across all key clinical endpoints (CFB in MMDs, MHDs, MUDs, reduction in ≥ 50% in 3-month average of MMDs) compared to the mITT population. There were no instances of meaningful missing outcome data, except for [redacted] patients in the atogepant 60 mg and [redacted] in the placebo group for the main outcomes in the mITT population, which was unlikely to significantly affect the results. In the PROGRESS study, measurements of the outcomes were appropriate. The blinding of participants and clinical investigators was kept throughout the conduct of the study, and there is no evidence that patients or personnel became unblinded. The results were reported in accordance with predefined protocols, including the results from the subgroup 2+TF, reducing the likelihood of selective reporting bias.

Overall, the study appears to have minimized risks across all domains assessed for risk of bias for the outcomes addressed when comparing atogepant to placebo.

GRADE Summary of Findings and Certainty of the Evidence

For the pivotal study identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform CADTH's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group:[8,9]

Following the GRADE approach, evidence from RCTs start as high-certainty evidence and can be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effect estimates, and publication bias.

When possible, certainty is rated in the context of the presence of an important effect (i.e., how certain are we that the effect is a non-trivial treatment effect). To determine what an important effect is GRADE suggests using thresholds of clinical importance

(MID); if the threshold is not possible to obtain, the certainty is rated in the context of the presence of any treatment effect, i.e., how certain are we that there is any —beneficial or harmful— effect. In this case, the clinical importance of any effect remains unclear. In all cases, the target of the certainty of evidence assessment is based on the point estimate of each outcome and where it is located relative to the chosen threshold for a clinically important effect (when a threshold is available) or to the null (when there is no threshold).

A GRADE summary of findings for the body of evidence for this review included the evaluation of the main outcomes considered important by clinicians, patient groups, and stakeholders. These assessments are presented in Table 3 for each outcome included.

Table 3: Summary of Findings for Atogepant 60 mg QD versus placebo for Patients with Chronic Migraine and 2 or more treatment failures.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Atogepant 60 mg	Difference		
Migraines, headaches, and acute medication use							
LS mean change from baseline in MMDs. Follow-up: 12 weeks	[redacted] (1 RCT)	NA	[redacted]	[redacted]	[redacted] fewer ([redacted] fewer)	Moderate [a]	Atogepant 60 mg QD likely results in a clinically important reduction in the mean MMDs when compared to placebo.
Reduction of ≥ 50% of 3-month MMDs. Follow-up: 12 weeks	[redacted] (1 RCT)	OR: [redacted] ([redacted])	[redacted] per 1,000	[redacted] per 1,000 (NR)	[redacted] more per 1,000 ([redacted] more per 1,000)	Moderate [a]	Atogepant 60 mg QD likely results in an increase in the proportion of patients achieving a ≥50% reduction in MMDs when compared to placebo. There is uncertainty about the clinical importance of the increase.
LS mean change from baseline in MHDs. Follow-up: 12 weeks	[redacted] (1 RCT)	NA	[redacted]	([redacted])	[redacted] fewer ([redacted] fewer)	Moderate [a]	Atogepant 60 mg QD likely results in a clinically important reduction in the mean MHDs when compared to placebo.
LS mean change from baseline in Monthly Acute Medication Use Days. Follow-up: 12 weeks	[redacted] (1 RCT)	NA	[redacted]	([redacted])	[redacted] fewer ([redacted] fewer)	Moderate [a]	Atogepant 60 mg QD likely reduces the monthly acute medication use days when compared to placebo. There is uncertainty about the clinical importance of the reduction.
Function or disability							
LS mean change from baseline in mean monthly Performance of Daily Activities Domain Score of the AIM-D (0 [best] to 100 [worst]), points. Follow-up: 12 weeks	[redacted] (1 RCT)	NA	[redacted]	[redacted]	[redacted] lower points ([redacted] lower)	Moderate [b]	Atogepant 60 mg QD likely reduces (improves) the monthly performance of daily activities score of the AIM-D when compared to placebo. There is uncertainty about the clinical importance of the improvement.
LS mean change from Baseline in MIDAS Total Score (0 [no disability] to >40 [very severe disability]), points. Follow-up: 12 weeks	[redacted] (1 RCT)	NA	[redacted]	[redacted]	[redacted] lower points ([redacted] lower to [redacted] lower)	Moderate [c,d]	Atogepant 60 mg QD likely reduces (improves) in the MIDAS total score when compared to placebo. There is uncertainty about the clinical importance of the improvement

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Atogepant 60 mg	Difference		
LS mean change from baseline in Headache Impact Test (HIT-6) total score (36 [best] to 78 [worst]), points. Follow-up: 12 weeks	[redacted] (1 RCT)	NA	[redacted]	[redacted]	[redacted] lower ([redacted] to [redacted] lower)	Moderate [a,e]	Atogepant 60 mg QD likely results in a clinically important reduction (improvement) in the impact of headaches in daily function as measured by the HIT-6 scale, when compared to placebo.
HRQoL							
LS mean change from Baseline in Monthly MSQ v2.1 (RFR domain) (0 [worst] to 100 [best]), points. Follow-up: 12 weeks.	[redacted] (1 RCT)	NA	[redacted]	[redacted]	[redacted] higher [redacted] to [redacted] higher)	Moderate [a,f]	Atogepant 60 mg QD likely results in a clinically important increase in HRQoL (work-related and daily social activities) when compared to placebo.
Resource utilization							
Change from baseline in percent worktime missed: (WPAI: Migraine) (0% [best] to 100% [worst]), % Follow-up: 12 weeks	[redacted] (1 RCT)	NA	[redacted]	[redacted]	[redacted] lower ([redacted] lower to [redacted] higher)	Low [g,h]	Atogepant 60 mg QD may reduce the percent worktime missed. The clinical relevance of the effect size is unclear.
Harms							
AEs, SAEs, WDAEs, Deaths. Follow-up: 12 weeks.	[redacted] (1 RCT)	NA	AEs were overall similar [redacted] Only [redacted] was deemed numerically increased in atogepant [redacted] vs placebo [redacted] SAE were reported by [redacted] in the atogepant group and [redacted] in the placebo group. WDAEs were reported in [redacted] in each group. No deaths were reported in any group.			Moderate [a]	Atogepant 60 mg QD likely results in little to no difference in AEs, SAEs, and WDAEs. Atogepant likely increases the number of mild/moderate constipation cases; the clinical importance is uncertain.

2+TF = 2 or more treatment failure; AE = adverse events; CI = confidence interval; HRQoL = health-related quality of life; LSMD = least square mean difference; MHDs = monthly headache days; MID = minimally important difference; MMDs = monthly migraine days; QD = once a day; RCT = randomized controlled trial; SAE = serious adverse events; WDAE = withdrawals due to adverse events

Note: analyses are unadjusted for multiplicity. The absolute difference (95% CI) in the change from baseline in reduction of ≥ 50% of 3-month MMDs was requested from the sponsor for interpretation purposes.

a. Rated down one level for imprecision. The population is composed by those patients with the reimbursement criteria (2 or more treatment failures); the sample size and optimal information size for this subgroup was not reached. One day was defined as the threshold for a small but important benefit (or harm) for the change from baseline of MMD. For AEs, the number of events was small.

b. Rated down one level for imprecision. No MID is available for this measure, therefore the effect was judged versus the null. The OIS was not reached, but sample size is >30% of the OIS.

c. The information was obtained from the overall 2+TF population. Within group MID (change from baseline) is estimated to be 4.5 points.

d. Rated down one level for imprecision.

e. Within-patient and between-group MID for patients with chronic migraine is estimated to be 6 points and 2.3 points respectively.

f. Within-group MID is estimated to be 11 points. A lenient threshold of 5.5 points would lead to not rate down for imprecision; however, the OIS is not reached, and the imprecision will remain rated down one level.

g. Rated down one level for imprecision. The 95% CI excludes the null but may include an important benefit and a trivial effect. Since there is no threshold of between-group clinical importance, the clinical relevance of the effect remains unclear. Furthermore, the sample size on this outcome did not reach the OIS.

h. Rated down one level due to risk of bias as this outcome was assessed in a subset of the target population; prognostic balanced is not ensured.

Long-Term Extension Studies

Description of Studies

Study 3101-312-002 (Study 312) is a multicenter, open-label, 156-week long-term safety extension study conducted in all eligible patients who completed PROGRESS or ELEVATE, where ELEVATE is a phase 3, multicenter, randomized, double-blind, placebo controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of oral atogepant for the prophylaxis of migraine in participants with episodic migraine who have previously failed 2 to 4 classes of oral prophylactic treatments. The study consists of a 156-week open-label treatment period, and a safety follow-up period of 4 weeks. The primary objective of the study is to assess the safety and tolerability of long-term use of atogepant 60 mg QD treatment in patients with CM or EM. Efficacy endpoints for long-term evaluation were included, however, were they considered exploratory. An interim analysis (November 2023) is presented here including only patients from the PROGRESS study. Patients were instructed to take atogepant 60 mg orally at approximately the same time each day for 156 weeks. Patients were followed for 4 weeks following completion or discontinuation atogepant. All analyses were performed for the full population in the extension study, and no analyses specific to the 2+ TF population were presented.

Efficacy Results

Overall, reductions in mean monthly migraine days, mean monthly headache days, and mean monthly acute medication use days relative to the lead-in study baseline were observed during the open-label treatment period. The proportion of patients with ≥ 50% improvement in monthly migraine days was 41.0% across the 12-week treatment period in the PROGRESS study, 67.0% for Weeks 13-16, and remained similar for Weeks 29-32 and 45-48. The change from baseline in monthly performance of daily activities domain score of the AIM-D remained relatively consistent across weeks 13-16, weeks 29-32 and weeks 45-48. Moreover, the change from baseline in the MSQ v2.1 Role Function Restrictive domain score at Weeks 12, 20, 28, 36, 44, and 52 remained similar across all weeks.

Harms Results

At the time of the interim analysis, [redacted] of patients had completed the study and [redacted] were still ongoing. Of the 325 patients enrolled in Study 312 from PROGRESS, [redacted] discontinued treatment, with [redacted] being the most common reason for discontinuation. Treatment-emergent AEs were reported by 265 (81.5%) patients. The most reported AEs included COVID-19 (30.8%), constipation (10.2%), nasopharyngitis (9.8%), urinary tract infection (6.2%), and insomnia (5.5%). Serious treatment-emergent adverse events (SAEs) were reported by 20 (6.2%) patients. The following SAEs were reported by one patient each: [redacted]. AEs leading to study drug discontinuation were reported in 27 (8.3%) patients. AEs leading to any study drug discontinuation included: [redacted]

Critical Appraisal

Study 312 was limited by its open-label and noncomparative design; since there is no comparator, it cannot be confirmed whether the results observed may be attributable to the effects of the drug or natural history of the condition. Furthermore, the mITT population analyzed excluded [redacted] of patients, and the large missing outcome data (more than [redacted] introduces a risk of bias. The open-label and nonblinding nature of the study increases the risk of bias and because the outcome measures are generally self-reported they are subjective, and it is uncertain if they can be replicated in another population beyond that included in the study. No information was provided on the 2+ TF population (the reimbursement requested population). It is therefore not possible to know whether the effects observed in the full population would be similar in that group. Because the patients who took part in the open-label long-term safety extension phase were originally from the pivotal PROGRESS trial, it is reasonable to expect that the same limitations to generalizability are relevant to the open-label long-term safety extension phase. Given the nature of noncomparative study design, it is not possible to compare the effectiveness and tolerability of atogepant as prophylactic treatment of chronic migraine against other preventive treatment.

Indirect Comparisons

Description of Studies

The ITC submitted is a network meta-analysis (NMA) conducted by the sponsor. The objective of the NMA was to evaluate the efficacy, safety, and tolerability of atogepant compared with CGRP inhibitors, i.e., the comparators of interest that are approved medications for the treatment of CM in Canada (Atogepant, OnabotulinumtoxinA, Eptinezumab, Erenumab, Fremanezumab, or Galcanezumab),

A clinical systematic literature review (SLR) was performed using the population, interventions, comparators, outcomes, and study design criteria previously established for the reimbursement request. [redacted].

Efficacy Results

Baseline characteristics of patients (age, sex, race) involved in all comparisons were overall similar across studies. [redacted] These wide CrI's denote imprecise estimates for any comparison of atogepant 60 mg QD to all active treatments. These wide CrI's were observed whether the analysis was made in the fixed effects (FE) or random effects (RE) models.

[redacted]

[redacted]

[redacted] The effect estimates suffered from wide credible intervals (imprecision) that conveyed important uncertainty to draw definite conclusions for these comparisons.

Harms Results

Within the evidence from the NMA, only the overall CM population was assessed for harms. In this, [redacted]

For the rest of the comparisons, the hazard ratios were also accompanied by wide CrI's that carried uncertainty due to imprecision in the hazard rates between atogepant and all relevant comparators.

Critical Appraisal

The systematic review and NMA aimed to evaluate the efficacy and harms of atogepant 60 mg QD compared to relevant comparators for chronic migraine treatment, identified based on drugs licensed and approved in Canada. While the identification and inclusion of relevant trials for the specific population and comparators were appropriately executed, details regarding the screening process were lacking. Despite well-described study designs, there's a notable absence of information on data extraction and risk of bias assessment procedures. Some head-to-head trials were excluded due to strict criteria, to address this, sensitivity analysis was conducted to address effects based on excluded populations. This ensures the robustness in the final estimates. Some differences, however, were observed between FE and RE models implying possible issues of inconsistencies between the included trials.

The construction of networks was thorough, assessing model fit, consistency, convergence, and heterogeneity, establishing comparability among populations included in each network and upholding the transitivity assumption. However, there was no formal assessment of publication bias, and imprecise effect estimates for several endpoints posed challenges in drawing definitive conclusions.

Overall, the populations in individual studies were deemed generalizable to the Canadian population, with no significant concerns regarding the applicability of the results detected. However, the NMA did not include several relevant outcomes of interest (e.g., MIDAS, HIT-6, MSQ, WPAI, SAE). Also, of relevance to this submission, there was a short length of follow-up if other long-term assessments are required such as rare AEs, and efficacy beyond 24 weeks. The lack of comparison to Eptinezumab was considered important to note for the Canadian landscape as well as the few comparisons available for the 2+ TF population.

Overall, while the systematic review and NMA effectively synthesized existing evidence; however, some methodological gaps and imprecisions in effect estimates warrant cautious interpretation of the findings.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Information

Component	Description
Type of economic evaluation	Cost minimization analysis
Target population	Adults with >15 headache days per month (among which 8 days are considered to be migraine days) and who have previously failed, are intolerant to, or have a contraindication to at least two migraine preventive therapies.
Treatment	Atogepant: 60 mg[a]
Dose regimen	60 mg once daily
Submitted price	Atogepant: $18.44 per 60 mg tablet
Submitted treatment cost	$6,735 per patient per year
Comparators	• Fremanezumab • Galcanezumab • Eptinezumab • OnabotulinumtoxinA (scenario only)
Perspective	Canadian publicly funded health care payer
Time horizon	5 years
Key data sources	Network meta-analysis, with the effectiveness of atogepant informed by the PROGRESS trial
Costs considered	Drug acquisition costs, drug administration costs, healthcare resource use costs
Key limitations	• The clinical effectiveness of atogepant compared to other preventative migraine treatments is uncertain. There is a lack of direct head-to-head evidence comparing atogepant to CGRP inhibitors and there is high uncertainty in the results of the sponsor's submitted NMA, owing to wide credible intervals that include effect estimates both in favour of and against atogepant compared to other treatments in the reimbursement population. • The timing of assessment of initial treatment response in the sponsor's model is not aligned with clinical practice or with public drug plan renewal criteria for CGRP inhibitors reimbursed for CM. Clinical expert feedback obtained by CADTH indicated that assessment of initial response to treatment would be after a 6-month trial, not 3 months as assumed by the sponsor. There is a lack of comparative clinical evidence at 6 months to support clinical similarity of atogepant to other reimbursed treatments for CM. • The exclusion of onabotulinumtoxinA from the sponsor's base case was inappropriate, based on clinical expert input received by CADTH and its reimbursement for CM in some CADTH participating drug plans. • The submitted model structure does not adequately reflect the management of migraine in clinical practice, in that the cost of subsequent therapies was excluded by the sponsor. The magnitude of impact of this limitation on the estimated costs of treatment is unknown. • Confidential pricing agreements exist for eptinezumab, fremanezumab, and galcanezumab for the prevention of migraine. As such, the cost paid by the participating drug plans for

Component	Description
	comparators may be less than assumed by the sponsor, and the submitted price of atogepant may require a price reduction to avoid incurring additional costs relative to its comparators.
CADTH reanalysis results	• In the CADTH base case, CADTH included onabotulinumtoxinA as a comparator. Results of this analysis suggest that atogepant is associated with higher costs compared to onabotulinumtoxinA (incremental cost: $2,479) and lower costs compared to eptinezumab, galcanezumab, and fremanezumab (range of incremental savings: $15 to $741 per patient). The differences in costs were mainly attributed to differences in drug acquisition costs. • CADTH could not address uncertainty in the clinical evidence, the timing of response assessment, exclusion of costs related to subsequent treatments, and confidential pricing agreements for comparators. Thus, whether the reimbursement of atogepant will be cost saving compared to currently reimbursed treatments for CM is uncertain. Reimbursement of atogepant may lead to additional costs to the healthcare system.

CM = chronic migraine.

[a] Atogepant is additionally available as 10 and 30 mg oral tablets. These strengths were not submitted to CADTH as part of the current review of atogepant for the prevention of chronic migraine.

Budget Impact

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

- The exclusion of onabotulinumtoxinA from the sponsor's base case was inappropriate, given that onabotulinumtoxinA is used in the requested reimbursement population as part of standard of care and is funded in some jurisdictions
- The NIHB population was inappropriately calculated.
- The price of drugs paid by public plans is uncertain as confidential pricing is likely in place.

In the CADTH base case, onabotulinumtoxinA was included as a comparator in jurisdictions where it is funded for the reimbursement population (i.e., Alberta, Ontario). In this analysis, the budget impact of reimbursing atogepant for the prevention of CM in adults who have previously failed to respond, are intolerant to, or have a contraindication to at least two migraine preventive therapies is expected to result in a savings of $994,373 over three years (year 1: $235,229, year 2: $340,637, year 3: $418,507).

Uncertainty remains in the prices paid by public plans for comparators. The presence of confidential prices for comparators may result in the cost savings realized by the drug plans being lower than predicted by the sponsor's and CADTH's base case.

All stakeholder feedback received in response to the draft recommendation is available on the CADTH website.

CDEC Information

Members of the Committee:

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Danyaal Raza, Dr. Edward Xie, and Dr. Peter Zed.

Meeting date: May 22nd, 2024

Regrets:

One expert committee member did not attend.

Conflicts of interest:

None