Canada's Drug and
Health Technology Agency

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Atogepant (Qulipta)

Indication: The prevention of episodic migraine (< 15 migraine days per month) in adults.

Sponsor: Allergan Inc. (an AbbVie Company)

Recommendation: Reimburse with Conditions

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Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that atogepant be reimbursed for the prevention of episodic migraine (< 15 migraine days per month) in adults only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Three double-blind, randomized controlled trials (RCTs) (ADVANCE, CGP-MD-01, and ELEVATE) consistently demonstrated that treatment with atogepant 10 mg, 30 mg, and 60 mg once daily (QD) resulted in added clinical benefit compared to placebo for patients with episodic migraine who had 4 to 14 migraine days per month for at least 3 months. Across the three studies, patients who received atogepant had a statistically significant reduction in mean monthly migraine days (MMD) at 12 weeks compared to placebo of –1.15 days (95% confidence interval [CI], –1.93 to –0.37) to –1.21 days (95% CI, –1.78 to –0.64) for atogepant 10 mg, –0.91 days (95% CI, –1.55 to –0.27) to –1.38 days (95% CI, –1.94 to –0.82) for atogepant 30 mg, and –0.70 days (95% CI, –1.35 to –0.06) to [redacted] for atogepant 60 mg. The results of the included trials also demonstrated a statistically significant benefit for treatment with atogepant relative to placebo in the proportion of patients achieving a 50% reduction in MMDs from baseline to week 12 (10 mg: 55.6% to 57.6%; 30 mg: 53.3% to 58.7%; and 60 mg: [redacted] to 60.8%), as well as reductions in mean change from baseline in monthly headache days (MHD) ranging from –0.94 days to [redacted] days, and reductions in acute medication use days (MUD) of –1.11 days to [redacted] days across atogepant doses. The ADVANCE and ELEVATE studies also demonstrated improvements in health-related quality of life (HRQoL) using the migraine specific quality of life questionnaire (MSQ), and suggested improvements in 6-item headache impact test (HIT-6) scores over 12 weeks of treatment.

Patients with episodic migraine identified a need for treatments that decrease the frequency, intensity, and symptoms associated with migraines, as well as improve HRQoL. CDEC concluded that atogepant may meet some of the needs identified by patients including the reduction in migraine burden of headache days, however, CDEC noted that the comparative benefit versus other CGRP inhibitors remains uncertain.

The results of the sponsor-submitted network meta-analysis (NMA) for the prevention of migraine in adult patients with episodic migraine suggest that there may be no difference between atogepant and other drugs used to prevent migraine. At the sponsor submitted price for atogepant and publicly listed prices for the comparators, atogepant was more costly than some CGRP inhibitors as well as oral treatments used as preventative treatment for episodic migraine in adults. Given that there is insufficient evidence to support a clinical benefit with atogepant compared to relevant comparators, the total treatment cost of atogepant should not exceed the total treatment cost of the lowest cost CGRP inhibitor reimbursed.

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 episodic migraine with the addition of condition 2 for prescribing.	No robust comparative evidence for atogepant was identified. Therefore, the potential benefit of atogepant vs. other CGRP inhibitors currently reimbursed for the treatment of adult patients with episodic migraine is not known.	—
2. Atogepant should not be reimbursed for use in combination with other CGRP inhibitors for the prevention of migraine in adult patients with episodic migraine.	No evidence was identified to demonstrate whether atogepant offers additional benefit when used in combination with other CGRP inhibitor treatments.	—
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 preventative treatment of episodic migraine in adults.	The sponsor-submitted NMAs suggest there may be no difference between atogepant and other CGRP inhibitors for the prevention of migraine in adult patients with episodic migraine. As such, there is insufficient evidence to justify a cost premium for atogepant over the least expensive CGRP inhibitor reimbursed for the treatment of episodic migraine in adult patients.	—

CDEC = Canadian Drug Expert Committee; CGRP = calcitonin gene-related peptide; ICHD = International Classification of Headache Disorders; MMD = monthly migraine days; RCT = randomized controlled trial.

Discussion Points

- CDEC discussed the unmet therapeutic need in treatment-refractory episodic migraine and acknowledged that, as described by the patient and clinician group input for this review, episodic migraine may lead to poor quality of life, social isolation, and an inability to participate in daily activities. CDEC discussed the patient and clinician input which emphasized that current prophylactic medications do not benefit everyone with episodic migraine and have adverse effects that may make them difficult to tolerate, leading to poor adherence and non-achievement of desired outcomes.
- CDEC noted that there was no evidence supporting the use of atogepant in the population of patients with episodic migraine that experience fewer than 4 migraine days per month as these patients were excluded from the trials. Additionally, CDEC considered that with the 3-month duration of the ADVANCE, CGP-MD-01, and ELEVATE trials, the long-term safety and efficacy of atogepant in patients with episodic migraine remains uncertain. CDEC considered the open-label Study 302 and Study 309 which evaluated the 52-week, and 40-week long term safety of atogepant 60 mg QD, respectively. CDEC noted the methodological limitations of the open-label extension studies, including the absence of a comparator arm, CDEC concluded that uncertainty remains in the long-term safety of atogepant.
- CDEC discussed an NMA submitted by the sponsor comparing atogepant and other medications used to prevent migraine in patients with episodic migraine. CDEC considered the methodological limitations associated with the NMAs including the heterogeneity in patient populations across studies, lack of inclusion of the results from the ELEVATE trial in the analysis evaluating patients with greater than or equal to 2 prior oral prophylactic treatment failures, and the imprecision in the results due to the wide credible intervals for comparisons to CGRP inhibitors and oral preventative medications. As such, no conclusions on the comparative efficacy of atogepant could be drawn by CDEC.
- CDEC discussed the uncertainty in the economic analysis, specifically that in the absence of robust comparative evidence, the incremental difference in QALYs between atogepant and its comparators predicted in CADTH's reanalyses may be overestimated, given that NMAs submitted by the sponsor suggest that there may be no difference between atogepant and relevant comparators in terms of reducing MMDs in patients with episodic migraine. CDEC additionally discussed that the pharmacoeconomic analyses reflect the cost-effectiveness of atogepant among patients with 4 to 14 MMDs, and that the cost-effectiveness of atogepant in the full Health Canada indicated and reimbursement populations, which are not restricted based on having at least 4 MMDs, is thus unknown.

Background

Migraine is a complex neurologic disease, the precise cause of which is not completely understood. Migraine is characterized by recurrent episodes of pulsating headache pain of at least moderate severity. Migraine episodes may last from 4 to 74 hours and can be accompanied by symptoms such as photophobia, phonophobia, nausea, and vomiting. The type of migraine can be refined by the frequency of monthly migraine days (MMDs) and monthly headache days (MHDs). Individuals who experience headaches on 14 or fewer days per month over the previous 3 months, which on some days is migraine, are defined as having episodic migraine (EM). In Canada (2010 to 2011), 9.6% of the population over 18 years of age experienced migraine attacks and is more common in females (13.8%) than males (5.3%). In a longitudinal web-based study of migraine in the US (N = 16,789), 91.2% of patients had EM. An estimated 2.5% of patients with episodic migraine (EM) transition to having chronic migraine (CM). Migraine attacks are associated with missed activities at work, school, and/or at home. Additionally, prevalence is highest during peak productive years (i.e., around 30 to 64 years of age), which maximizes the impact on the sufferer, family, and society.

There are 2 approaches to treating migraine: management of acute attacks, and prophylaxis, which can be used simultaneously. Comprehensive therapy also includes the management of lifestyle factors and triggers. Treatment goals aim to relieve pain, restore function, improve health-related quality of life (HRQoL), reduce headache frequency, and prevent the progression of EM to CM. Preventative medications for EM include calcitonin gene-related peptide (CGRP) receptor inhibitors (galcanezumab, fremanezumab, erenumab, eptinezumab), blood pressure medications (e.g., beta-blockers [e.g., propranolol, metoprolol], calcium-channel blockers [e.g., flunarizine or verapamil]), antidepressants (e.g., amitriptyline or nortriptyline), serotonin-norepinephrine reuptake inhibitors (SNRIs; e.g., venlafaxine), anticonvulsants (e.g., topiramate, gabapentin, or divalproex), and serotonin antagonist (pizotifen). Only topiramate and the CGRP inhibitors have been approved by Health Canada for the prevention of EM.

Atogepant has been approved by Health Canada for the prevention of EM (< 15 migraine days per month) in adults. The sponsor requested reimbursement of atogepant for the prevention of migraine in adults with EM (< 15 migraine days per month), who have experienced an inadequate response, intolerance or contraindication to at least 2 oral prophylactic migraine medications. Atogepant

is a small molecule, selective CGRP receptor antagonist that blocks the binding of the CGRP to its receptor, a neuropeptide associated with migraine pathophysiology. It is available as an oral tablet and the dosage recommended in the product monograph is 10 mg, 30 mg, or 60 mg orally, once daily to a maximum of 60 mg per day.

Sources of Information Used by the Committee

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

- a review of 3 randomized controlled trials in adult patients with EM
- patients perspectives gathered by patient groups, Migraine Canada and Migraine Quebec
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 1 clinical specialist with expertise diagnosing and treating patients with migraine
- input from 1 clinician group, including the Canadian Headache Society
- 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 Quebec for the review of atogepant. Both are not-for-profit organizations that have a mission to support and inform individuals living with migraines and raise awareness about the impact of the disease.

The information used to inform the submission was based on two online surveys, as well as direct input from 8 patients with experience with atogepant. A total of 1,165 patients and caregivers responded to the first survey conducted by Migraine Canada, the majority of which were between the ages of 30 to 59 years (68%). Among the respondents to the survey, 19% experience 1 to 6 migraine days per month, 28% experience 8 to 14 migraine days per month, and 52% experience greater than or equal to 15 migraine days per month (i.e., chronic migraine). A second survey conducted by Migraine Canada had a total of 300 Canadians who responded. Of these, 15% experience 1 to 6 migraine days per month, 26% experience 8 to 14 migraine days per month, and 59% have CM. The majority (74%) of respondents were between the ages of 30 to 59 years.

Respondents to the surveys by Migraine Canada indicated how living with migraine has impacted their HRQoL, sleep, mental health, social relationships, and day-to-day functioning at work and school. The majority (73%) of respondents responded that they live in fear of the next migraine attack and have difficulty with planning ahead. Most (67%) respondents reported regularly needing to change or cancel plans and avoid interacting with people altogether. Over 20% of respondents indicated they are on short- or long-term disability or have retired early due to migraines and 38% reported having their sleep always or regularly disrupted by migraines. Migraines led to the development of moderate to severe depression and/or anxiety that have required counselling and/or medications in 39% of patient, and 31% and 35% of respondents felt they were a burden to others for 16 to 30 and 6 to 15 days per month, respectively.

Most (78%) of the survey respondents indicated they have taken a prescription medication for the prevention of migraines; most commonly topiramate, amitriptyline, and botulinum toxin. In the second survey, 21% and 62% of respondents indicated they have tried 3 to 4 and ≥5 preventative treatments, respectively. According to 66% of respondents, treatment discontinuation was a result of side effects associated with their preventative medication, while 25% of respondents reported they had experienced side effects but tolerated them. Most respondents to both surveys (85% and 73%) indicated there is a need for a new oral daily preventative medication. From the second survey, 30% of respondents indicated they have found a preventative treatment that provides greater than 50% improvement in frequency and/or intensity of migraines with no significant side effects. Further, 25% of respondents indicated the care they have received thus far has led to no improvement in HRQoL, while 49% reported mild improvement and 24% experienced marked improvement. Finally, 57% of respondents did not fill their prescription in the past 6 months due to cost and lack of coverage. A total of 8 patients (2 Canadians and 6 Americans) provided direct input on their experience with atogepant. Of these,

75% of patients reported improvement in the frequency and/or intensity of their migraines and 66% reported experiencing some side effects but were either slight and/or improved/stopped over time.

According to all survey respondents, the most valuable outcomes for preventative medications are improvement in HRQoL, and decrease in headache intensity, frequency, and symptoms other than pain such as sensitivity to light, sound, nausea, and brain fog. Overall, patients living with migraines indicated that there is a need to have access to new treatment options that will address the gaps in the currently available treatment options, many of which are not effective and associated with intolerable side effects.

Clinician Input

Input from Clinical Expert Consulted by CADTH

The clinical expert consulted by CADTH emphasized that currently available treatments for patients with migraine have several issues; notably that not all patients respond to current treatments, and that – in the case of monoclonal antibodies (mAbs) for migraine prevention – patients become refractory to treatment, requiring a change of treatment. Migraine attacks are treated with abortive agents, as well as preventative strategies. Monoclonal antibodies (fremanezumab or galcanezumab) are used following the failure of prior prophylactic migraine prevention therapy such as anti-depressants, anti-hypertensives, or anticonvulsants. The clinical expert noted that atogepant is not a cure, rather reduces symptomatic events of EM.

The expert noted that patients with higher migraine headache frequency and major functional disability are more likely to receive atogepant, though it likely wouldn't be considered the first choice for most patients and would likely be considered in patients who have not responded to or are intolerant of anti-CGRP mAbs. The clinical expert noted that identifying patients who would have better response to atogepant was unlikely, though patients least likely to benefit from atogepant are those with a history of poor compliance. Aside from intolerability due to side effects or poor compliance, the clinical expert stated that failure to reach a 50% reduction in MMD, without any improvements in HRQoL are the main reasons to discontinue treatment with atogepant.

The clinical expert noted that clinicians concentrate on what can be quickly quantified and understood from similar metrics used in studies, with 50% reduction in MMD, coupled with change in consumption of abortive medications. The expert did note that change in MMD is not a perfect metric as some patients have no change in daily frequency but may have significant reductions in severity or duration of migraine.

The clinical expert highlighted that no specialized settings are required, and that neurologists or other experts (pain clinic specialists, family medicine with expertise) with headache expertise should prescribe atogepant.

Clinician Group Input

One clinician group, the Canadian Headache Society (CHS), consisting of 5 headache specialists, provided input to CADTH for the review of atogepant. The CHS is a scientific society of health care professionals dedicated to research, education of residents and physicians, and promotion of better care for patients suffering from headache disorders.

The clinician group emphasized that migraine is often underdiagnosed and undertreated, with limited access to specialized care for migraine in Canada. Along with similar unmet needs to those identified by the clinical expert consulted by CADTH notably that current treatments are not effective for all patients (response rate of 40-50% for oral medications) and may lose effectiveness over time, the clinician group also highlighted difficulties in access due to limited coverage, and regional variation in funding by province, particularly for triptans, onabotulinumtoxinA, and CGRP mAbs.

The clinician group indicated that atogepant could be used as a first line treatment option for the prevention of migraines but noted its place in therapy will be determined in part by its cost, thus could be considered prior to other CGRP antibodies. Moreover, the clinician groups emphasized that atogepant could be provided in primary care, increasing access to patients in need. In contrast, the clinical expert consulted by CADTH indicated atogepant would be considered as last line or used in specific circumstances such as non-response, intolerance, or contraindication to, and where risks outweigh the benefits in women of child-bearing age with other first line treatment options (i.e., monoclonals). The clinician group and clinical expert consulted by CADTH considered the potential for concurrent use of atogepant with mAbs or onabotulinumtoxinA.

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 atogepant:

- relevant comparators
- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- care provision issues

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	
Atogepant was not compared to a relevant comparator drug but was compared to placebo in the pivotal clinical studies.	Comment from the drug programs to inform CDEC deliberations.
Considerations for initiation of therapy	
Per the CDEC recommended initiation criteria for fremanezumab: *1. The patient has a confirmed diagnosis of episodic or chronic migraine according to the International Headache Society criteria, defined as:* *a. Episodic migraine: migraine headaches on at least 4 days per month and less than 15 headache days per month for more than 3 months.* *b. Chronic migraine: headaches for at least 15 days per month for more than 3 months of which at least eight days per month are with migraine.* *2. The patient has experienced an inadequate response, intolerance, or contraindication to at least 2 oral prophylactic migraine medications.* *3. The physician must provide the number of headache and migraine days per month at the time of initial request for reimbursement.* *4. The maximum duration of initial authorization is 6 months.* *Other than for the initiation criteria 1b, should initiation criteria of atogepant be aligned with that of fremanezumab?*	*Given the similarities in the groups highlighted in the initiation criteria for fremanezumab, CDEC and the clinical expert agreed that the initiation criteria for atogepant should be aligned with the initiation criteria for fremanezumab for patients with episodic migraine.*
The ADVANCE study did not enroll patients below the age of 18. Should patients <18 years of age be treated with atogepant? *The clinical studies for atogepant did not include a sufficient number of patients aged 65 years and over. Should patients ≥ 65 years be treated with atogepant?*	*The clinical expert was uncertain regarding whether prescribers would be comfortable using atogepant in patients less than 18 years of age.* CDEC recommended that *atogepant be reimbursed for the prevention of episodic migraine in adult patients only.* *CDEC and the clinical expert noted that the upper age limit for the mAbs in migraine is 70 years based on clinical trial inclusion criteria, thus, the expert*

Implementation issues	Response
	expected that patients greater than 65 years would be eligible to receive atogepant.
The sponsors reimbursement request is for patients who have received at least 2 prophylactic migraine medications. Should patients be required to have intolerance, inadequate response, or failure to at least 2 oral prophylactic migraine medications?	*CDEC and the clinical expert agreed that patients should exhaust all options including lifestyle management and prophylactic treatments to ensure that the patients are educated on the treatment options available to them prior to initiating atogepant.*
If a patient has success on fremanezumab, should they be transitioned to oral therapy with atogepant?	*CDEC and the clinical expert noted that the main reason to transition to oral therapy would be patient preference, lack of efficacy, or intolerable side effects. Thus, if a patient has success on other CGRP inhibitors, they would not be switched until one of the reasons outline above was observed. Moreover, CDEC noted that there is no evidence of benefit in patients failing other CGRP inhibitors.*
The pivotal trial for atogepant does not include patients with Chronic Migraine (i.e., ≥ 15 migraine days per month). Should patients with Chronic Migraine be treated with atogepant? Should other CGRP inhibitors be used first?	*The clinical expert considered that atogepant could be used in patients with chronic migraine, however, noted that other CGRP inhibitors should be used first. CDEC also emphasized that the current evidence only supports the use of atogepant in patients with 4 to 14 MMDs.* *The clinical expert also clarified that the ICHD-3 definition for chronic migraine consists of ≥ 8 days per month for 3 months of migraine days with or without aura, as well as ≥ 15 headache days per month for 3 months.*
Considerations for continuation or renewal of therapy	
CDEC recommended renewal criteria for fremanezumab is as follows: *1. 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.* *2. The maximum duration of subsequent authorizations following the initial authorization is 6-months.* *Should renewal criteria of atogepant be aligned with that of fremanezumab?*	*CDEC agreed with the clinical expert that renewal criteria for atogepant should be aligned with that of fremanezumab. It was highlighted that 6-months is sufficient to observe any clinical changes, and also to observe any wearing-off effects in the CGRP mAbs. Moreover, the expert stated that this aligns with general timelines for patient follow-up after initiation of treatment.*
Considerations for discontinuation of therapy	
CDEC recommendation for fremanezumab indicated that patients who do not achieve 50% in the average number of migraine days per month should discontinue treatment. Should similar discontinuation criteria be considered for atogepant?	*CDEC agreed with the clinical expert that response to treatment would be observed early in migraine, and that discontinuation criteria for atogepant should be similar to fremanezumab. CDEC and the clinical expert agreed that in some patients, significant improvements may be noted in other outcomes such as the duration of migraine or headache hours or intensity, but not the overall migraine/headache days, thus, should be considered when discussing discontinuing treatment.*

Implementation issues	Response
Considerations for prescribing of therapy	
There are 3 doses of atogepant approved by Health Canada (10 mg daily, 30 mg daily, or 60 mg daily). The maximum recommended daily dose is 60 mg. Please advise on how dosage would be selected.	*CDEC and the clinical expert noted the uncertainty on the selection of the appropriate dose given that the results for different dosages in the pivotal trials were not distinctly different.*
Prescribing criteria for other CGRP inhibitors are limited to prescribers with experience in migraine therapy. Given the oral route of atogepant, should this be consistent with other CGRP inhibitors?	*CDEC and the clinical experts agree that atogepant represents a new class of medications and should only be prescribed by physicians with experience in treating patients with migraine.* *CDEC and the clinical expert expressed concern that atogepant may be used in general practice, which would be inappropriate given the complexity in patient education and treatment paradigm.*
Generalizability	
Should patients currently receiving CGRP inhibitors be eligible to switch to atogepant?	*The clinical expert noted that when migraine patients find a treatment that works, it is difficult to get them to switch to other options. Thus, the clinical expert noted that patient desire to switch is unlikely for these patients. CDEC agreed with the expert that non-responders to CGRP mAbs would be candidates for switching to atogepant, however, CDEC did note that there is no evidence for benefit in switching non-responders, and no evidence to support the use of atogepant in patients with prior CGRP inhibitor use.*
Care provision issues	
Compared to other CGRP inhibitors, atogepant is orally administered and can be initiated as outpatient therapy.	Comment from the drug programs to inform CDEC deliberations.

CDEC = Canadian Drug Expert Committee; CGRP = calcitonin gene-related peptide; mAb = monoclonal antibodies; MMD = monthly migraine days; ICHD = International Classification of Headache Disorders.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

A total of 3 studies were included in this review: ADVANCE, CGP-MD-01, and ELEVATE. Two studies; ADVANCE and CGP-MD-01 were provided when the submission was initially provided by the sponsor, while the ELEVATE study was provided to CADTH during the later stages of the review. ADVANCE was a phase III, double-blind, randomized controlled trial (RCT) evaluating the safety and tolerability of atogepant for the preventive treatment of migraine in patients with EM. Patients in ADVANCE were required to have a 1-year history of migraine consisting of 4 to 14 migraine days per month, with or without aura, and migraine onset prior to 50 years of age. A total of 910 patients were randomized 1:1:1:1 to atogepant 10 mg once daily (QD) (n = 222), atogepant 30 mg QD (n = 230), atogepant 60 mg QD (n = 235), or placebo (n = 223). The primary outcome of the ADVANCE trial was change from baseline in mean MMD, with key secondary endpoints of change from baseline in MHD, change from baseline in acute medication use days (MUD), ≥ 50% reduction in 3-month average of MMD, change from baseline in Migraine-Specific Quality of Life Questionnaire (MSQ) v2.1 Role Function Restrictive domain score, and change from baseline in the Performance of Daily Activities domain score and mean monthly Physical Impairment domain score of the Activity Impairment in Migraine–Diary (AIM-D). The ADVANCE trial was conducted at 136 sites in the United States. There were no Canadian investigative sites included. No interim analyses were conducted.

Study CGP-MD-01 was a phase II/III, double-blind RCT evaluating the safety and tolerability of 10 mg QD, 30 mg QD, 30 mg twice daily (BID), 60 mg QD, and 60 mg BID dose regimens of atogepant for the prevention of EM. Included patients for CGP-MD-01 were

similar to ADVANCE, though diagnosis of migraine was based on International Classification of Headache Disorders (ICHD) 2013. A total of 834 patients were randomized to one of six different arms in a 2:1:2:1:2:1 randomization sequence of placebo (n = 186), atogepant 10 mg QD (n = 94), atogepant 30 mg QD (n = 185), atogepant 30 mg BID (n = 89), atogepant 60 mg QD (n = 187), or atogepant 60 mg BID (n = 93). Only Health Canada-approved dosages are summarized in this report, thus any results for the atogepant 30 mg BID and atogepant 60 mg BID doses are not discussed. The primary outcome of CGP-MD-01 was the same as ADVANCE; change from baseline in mean MMD, with 3 secondary endpoints of change from baseline in mean MHD, proportion of patients with at least a 50% reduction in mean MMD and change from baseline in mean monthly acute MUD. CGP-MD-01 was conducted at 78 sites in the United States. There were no Canadian investigative sites included. No interim analyses were conducted.

ELEVATE was a phase III randomized, double-blind, placebo-controlled study. The objective of the ELEVATE study was to evaluate the efficacy and safety of atogepant 60 mg QD for the prevention of migraine in adult patients with EM who have previously failed 2 to 4 classes of oral medications for the prophylaxis of migraine. A total of 315 patients were randomized 1:1 to atogepant 60 mg QD (n = 157) or placebo (n = 158). The primary and key secondary outcomes of the ELEVATE study were identical to the ADVANCE study. A total of 73 sites in North America and Europe screened patients for eligibility, and 6 patients were included from Canada. No interim analyses were conducted.

Demographic and baseline characteristics in all studies were well balanced. Most patients were female (ADVANCE: 86.1% to 90.5%, CGP-MD-01: 82.8% to 90.7%, ELEVATE: [redacted]), White (ADVANCE: 81.1% to 89.2%; CGP-MD-01: 71.5% to 79.2%, ELEVATE: [redacted]), and the median age ranged from 38.5 to 42.0 years in ADVANCE, 38.0 to 40.5 years in CGP-MD-01, and [redacted] in the ELEVATE study. The included studies differed in the proportion of patients who had received prior migraine prevention medicine, with [redacted] of patients in ADVANCE receiving prior migraine therapy, and only 25.1% to 31.2% of patients receiving prior migraine therapy in CGP-MD-01, while all patients in ELEVATE received prior migraine therapy.

Efficacy Results

The primary efficacy endpoint of the included studies was change from baseline in MMD to week 12. In all trials, atogepant resulted in statistically significant differences compared with placebo in the reduction of mean MMD across the 12-week treatment period. In the ADVANCE trial, the least squares mean difference (LSMD) in mean change from baseline in MMDs at 12 weeks compared to placebo was –1.21 days (95% CI, –1.78 to –0.64) for the atogepant 10 mg group, –1.38 days (95% CI, –1.94 to –0.82) for the atogepant 30 mg, and –1.72 days (95% CI, –2.28 to –1.15) for the atogepant 60 mg (all $P < 0.0001$). In the CGP-MD-01 trial, the LSMD for mean change from baseline in MMDs from baseline at 12 weeks compared to placebo was –1.15 days (95% CI, –1.93 to –0.37; $P = 0.0039$) for the atogepant 10 mg group, –0.91 days (95% CI, –1.55 to –0.27; $P = 0.0056$) for the atogepant 30 mg group, and –0.70 days (95% CI, –1.35 to –0.06; $P = 0.0325$) for the atogepant 60 mg. In the ELEVATE trial, the LSMD in mean change from baseline in MMDs between atogepant 60 mg QD and placebo at 12 weeks was [redacted]. Results for the subgroup analyses of the ADVANCE study in patients with or without prior exposure to migraine prevention therapy were consistent with the primary analysis. A post-hoc subgroup analysis of the ADVANCE trial by number of prior preventive treatment failures exhibited similar results to the primary analysis, though the mean difference from placebo was higher in the subgroup of patients with greater than 2 prior treatment failures, and results were consistent with the ELEVATE study.

Results for key secondary outcomes were in line with the primary endpoint, with atogepant demonstrating statistically significantly greater efficacy compared to placebo. In ADVANCE, a greater proportion of patients achieved a greater than or equal to 50% reduction in mean MMD with atogepant (55.6%, 58.7%, and 60.8% for atogepant 10 mg, 30 mg, and 60 mg groups, respectively) compared to placebo (29.0%). In CGP-MD-01, a greater proportion of patients achieved a greater than or equal to 50% reduction in mean MMD with atogepant (57.6%, 53.3% and 52.0% in the atogepant 10 mg, 30 mg, and 60 mg groups, respectively) compared to placebo (40.4%). In ELEVATE, a greater proportion of patients achieved a greater than or equal to 50% reduction in mean MMD with atogepant 60 mg QD ([redacted]) compared to placebo ([redacted]). Post-hoc subgroup analysis from ADVANCE for patients with greater than or equal to 2 prior treatment failures were [redacted] for the proportion of patients achieving at least a 50% reduction in mean MMD with atogepant (ranging from [redacted] across atogepant treatment groups) compared to a lower placebo group rate ([redacted]).

Results for secondary outcomes of MHD and acute MUD were consistent with the primary analysis for all studies, demonstrating statistically significant efficacy compared to placebo. In ADVANCE, the LSMD in change from baseline in MHD and acute MUD compared to placebo was –1.42 days (95% CI, –2.03 to –0.81) and –1.31 days (95% CI, –1.81 to –0.82) for atogepant 10 mg, –1.53 days (95% CI, –2.13 to –0.92) and –1.33 days (95% CI, –1.82 to –0.83) for atogepant 30 mg, and –1.71 days (95% CI, –2.32 to –1.10) and –1.50 days (95% CI, –2.00 to –1.01) for atogepant 60 mg, respectively (all P < 0.0001). In CGP-MD-01, the LSMD in change from baseline in MHD and acute MUD compared to placebo was –1.38 days (95% CI, –2.23 to –0.54; P = 0.0014) and –1.30 days (95% CI, –1.99 to –0.60; P = 0.0002) for atogepant 10 mg, –1.24 days (95% CI, –1.94 to –0.55; P = 0.0005) and –1.44 days (95% CI, –2.01 to –0.87; P < 0.0001) for atogepant 30 mg, and –0.94 days (95% CI, –1.64 to –0.24; P =0.0087) and –1.11 days (95% CI, –1.68 to –0.54; P = 0.0001) for atogepant 60 mg, respectively. In ELEVATE, the LSMD in change from baseline in MHD and acute MUD compared to placebo was [redacted], respectively.

Change from baseline at Week 12 in MSQ v2.1 Role Function-Restrictive domain score was a key secondary endpoint of the ADVANCE and ELEVATE studies. In ADVANCE, the LSMD in change from baseline versus placebo was statistically significant in favour of atogepant with mean difference of 9.90 points (95% CI, 5.45 to 14.36) for atogepant 10 mg, 10.08 points (95% CI, 5.71 to 14.46) for atogepant 30 mg, and 10.80 points (95% CI, 6.42 to 15.18) for atogepant 60 mg (all P < 0.0001). In ELEVATE, the LSMD in change from baseline versus placebo was [redacted]

Change from baseline in the Headache Impact Test (HIT-6) total score was an additional efficacy outcome endpoint of ADVANCE, CGP-MD-01, and ELEVATE studies. In the ADVANCE study, the LSMD change from baseline in HIT-6 total score compared to placebo at week 12 was [redacted] for atogepant 10 mg, [redacted] for atogepant 30 mg, and [redacted] for atogepant 60 mg. Higher proportions of HIT-6 responders (defined as patients who had at least a 5-point improvement [decrease] from baseline in the HIT-6 total score) were observed for the atogepant 10 mg ([redacted]), 30, mg ([redacted]), and 60 mg ([redacted]) groups compared to placebo ([redacted]). In study CGP-MD-01, the LSMD change from baseline in HIT-6 scores was greater for all atogepant doses compared to placebo at all timepoints. Over 12 weeks, the LSMD versus placebo was [redacted] for atogepant 10 mg, [redacted] for atogepant 30 mg, and [redacted] for atogepant 60 mg. In the ELEVATE study, the LSMD change from baseline in HIT-6 scores was [redacted] in favour of atogepant 60 mg QD over 12 weeks compared to placebo.

Harms Results

The incidence of treatment emergent adverse events (TEAEs) was generally consistent between atogepant and placebo-treated patients, as well as across trials with at least one TEAE experienced by 52.9%, 52.2%, 53.7%, and 56.8% with atogepant 10 mg, 30 mg, 60 mg, and placebo, respectively, in ADVANCE, 65.6%, 62.8%, 57.5%, and 49.5% with atogepant 10 mg, 30 mg, 60 mg, and placebo, respectively in CGP-MD-01, and [redacted] of patients in the atogepant 60 mg and placebo groups, respectively in the ELEVATE study. The most frequently reported TEAEs in ADVANCE were constipation (7.7 %, 7.0%, 6.9%, and 0.5%), nausea (5.0%, 4.4%, 6.1%, and 1.8%), and upper respiratory tract infections (4.1%, 5.7%, 3.9%, and 4.5%), in the atogepant 10 mg, 30 mg, 60 mg, and placebo groups, respectively. The most frequently reported TEAEs in CGP-MD-01 were nausea (5.4%, 7.1%, 11.8%, and 4.8%), upper respiratory tract infection (6.5%, 7.7%, 5.4%, and 8.1%), nasopharyngitis (3.2%, 6.0%, 7.5%, and 2.2%), and constipation (2.2%, 5.5%, 4.8%, and 2.2%) for atogepant 10 mg, 30 mg, and 60 mg, compared to placebo, respectively. The most frequently reported TEAEs in the ELEVATE study were [redacted]. In all studies, most TEAEs were mild to moderate in severity.

Serious adverse events (SAEs) in ADVANCE, CGP-MD-01, and ELEVATE were infrequent, occurring in only 2 (0.9%) of patients in the atogepant 10 mg and placebo groups, each in ADVANCE, and [redacted] SAEs occurring in 7 patients in CGP-MD-01 (1 [1.1%] with atogepant 10 mg, 2 [1.1%] with atogepant 30 mg, 2 [1.1%] with atogepant 60 mg QD group, and 2 [1.1%] with placebo), and in [redacted] patients in the atogepant and placebo groups of the ELEVATE study, respectively.

In the ADVANCE study, the incidence of withdrawals due to adverse events (WDAEs) was similar across treatment groups, occurring in 4 (1.8%) to 9 (4.1%) atogepant-treated patients and 6 (2.7%) patients in the placebo group. In CGP-MD-01, WDAEs were more common in the atogepant groups (4.3%, 6.0%, and 3.2%) than in the placebo group (2.7%). In ELEVATE, [redacted] patients in the atogepant and placebo groups had WDAEs. There were no deaths reported during any of the included studies.

In the ADVANCE study, 1 patient in the placebo group reported suicidal behavior during the double-blind treatment period. No patients reported suicidal ideation with intent to act via their Columbia-Suicide Severity Rating Scale (C-SSRS) assessments. In CGP-MD-01, no patients reported suicidal behavior during the study, however, 1 patient in the placebo group reported suicidal ideation limited to “wish to be dead” during the double-blind treatment period. In the ELEVATE study, [redacted] and [redacted] patients in the atogepant and placebo groups reported suicidal behaviours during the study, respectively.

Critical Appraisal

The ADVANCE, CGP-MD-01, and ELEVATE studies were all double-blind RCTs. Appropriate methods for randomization (via interactive web response system [IWRS]), treatment allocation, and maintenance of blinding to treatment assignment were used in all studies, reducing the possibility for selection, performance, and detection biases. There was a high proportion of screen failures in the ADVANCE, CGP-MD-01, and ELEVATE studies (60%, 53%, and [redacted]), mostly due to patients not meeting eligibility criteria. In study CGP-MD-01, more patients discontinued based on withdrawal of consent or withdrawal by patient in the placebo arm, however, it is unclear how such discontinuations would have affected blinding or the study results. The rate of constipation was more frequent in the atogepant groups across trials, which may have led to unblinding. Given that the overall rates were generally low, it is unclear to what effect this would have on the results. Sensitivity analyses to account for missing data were conducted on the primary endpoint in all studies, and were in line with the primary results, suggesting that missing data had little impact. Acceptable methods to account for multiplicity were used in all trials. In the ADVANCE and ELEVATE studies, the primary endpoint, and 6 key secondary endpoints were controlled for multiplicity using the overall familywise error rate at the 0.05 level. One pre-specified subgroup analysis of the ADVANCE study was conducted which included patients with or without prior migraine prevention medication with proven efficacy. An additional post-hoc subgroup analysis of ADVANCE was submitted to CADTH by request for patients in the ADVANCE study with greater than or equal to 1, and greater than or equal to 2 prior migraine prevention treatment failures, which represents the population for the reimbursement request. Given that this subgroup was conducted post-hoc and was not part of the randomization scheme or statistically powered to detect within-group, or between-group differences, the results from the subgroup analysis may confound the observed results and should only be interpreted as supportive evidence for the overall effect of atogepant. Moreover, missing data was unaccounted for, and the analyses did not adjust for multiplicity. The population for this post-hoc subgroup analysis was the target population for the ELEVATE study, which also included 3 pre-specified subgroups including 2 of interest to this review (prior oral prophylactic treatment failure, and migraine days at baseline).

The inclusion and exclusion criteria for the ADVANCE, CGP-MD-01, and ELEVATE studies were appropriate, and generalizable to the Canadian population according to the clinical expert consulted by CADTH. As part of the inclusion and exclusion criteria for the ADVANCE and CGP-MD-01 studies, patients were required to have an inadequate response to no more than 3 medications prescribed for the prevention of migraine, and patients were excluded who had previous exposure to CGRP mAbs. Conversely, the ELEVATE study enrolled patients that had failed 2 to 4 oral prophylactic migraine medications, and was the only trial that was reflective of the population included in the reimbursement request. One of the major differences between the ADVANCE, CGP-MD-01, and ELEVATE studies was the proportion of patients who had received prior migraine prevention medications, where [redacted] of patients received prior migraine therapy in ADVANCE compared to 25.1% to 31.2% of patients in CGP-MD-01, and [redacted] of patients in ELEVATE. As noted in the post-hoc subgroup analysis for ADVANCE, only 119 patients had failed 2 or more prior preventative migraine treatments, though given that baseline characteristics for this subgroup were not presented, it was unclear if any of these patients had received prior anti-CGRP mAbs. Thus, the full population of the ADVANCE study does not entirely represent the population for the reimbursement request and may not be generalizable to this population in Canada. All included trials were placebo-controlled and did not include an active comparator which allows for adequate evaluation of the treatment effect of atogepant, however, may overestimate the treatment effects. In all studies, there was a high placebo response, impacting the ability to interpret the efficacy of atogepant.

Baseline demographic and clinical characteristics including the average number of MMDs and MHDs days at baseline was noted to be a true reflection of what would be seen in Canadian clinical practice as noted by the clinical expert, however, it is worth noting that patients enrolled in the studies had to have history of 4 to 14 migraine days per month on average in the 3 months prior to the first visit, hence all studies excluded patients with 1 to 3 migraine days per month, and it is uncertain if results from ADVANCE, CGP-MD-01, and ELEVATE are generalizable to patients with fewer than 4 migraine days per month. Outcomes of the ADVANCE and CGP-MD-01 trials were similar to those reported in other clinical trials for migraine and are reflective and important in guiding treatment decisions in Canadian clinical practice.

Indirect Comparisons

Description of Studies

For the purposes of the Canadian submission, the sponsor-submitted NMA included 2 updated analysis scenarios from the original NMA updated to reflect the relevant comparators and reimbursement request:

- **Scenario 2:** CGRP inhibitors and key oral preventives approved in the US as a treatment for EM.
- **Scenario 4:** Global patients who have experienced two or more prior preventive treatment failures, versus CGRP preventives.

The objective of the sponsor-submitted report was to evaluate the relative efficacy, safety, and tolerability of atogepant compared with injectable CGRP inhibitors and key oral preventives approved for the treatment of EM. The sponsor submitted NMA was informed by a systematic literature review (SLR) (updated to August 9, 2021) to identify all existing RCTs assessing the efficacy, safety, and tolerability of preventive treatments for adults with EM compared to other preventive treatments, placebo, or standard care. The analyses were conducted using a Bayesian network meta-analysis (NMA). Selection of both fixed and random effects were conducted. In Analysis Scenario 2, random-effects models for the analyses excluding Japanese studies were selected as the base case analysis given the larger evidence base. In Analysis Scenario 4, fixed-effects models were selected as the base case due to the fewer number of trials and the lower deviance information criterion (DIC). In the updated NMAs, where available, efficacy analyses included 50% response in MMD, between-treatment change from baseline in MMD, and between-treatment change from baseline in monthly migraine MUD. Safety outcomes included all-cause discontinuation, and TEAEs.

Efficacy Results

In Analysis Scenario 2, [redacted]

In Analysis Scenario 4, [redacted]

In Analysis Scenario 2 [redacted]

[redacted]

Critical Appraisal

There were several limitations associated with the sponsor-submitted NMA, particularly the clinical and methodological heterogeneity, which resulted in limited interpretability and generalizability of the results. The SLR and feasibility assessment were generally well conducted, however, the list of treatments for the NMA was narrower than that of the SLR. The NMA did not include valproic acid or candesartan, which, according to the clinical expert consulted by CADTH, could be considered relevant comparators for the treatment of EM. Important outcomes such as HRQoL were not considered based on a low availability of data. Following the submission of the ELEVATE study to CADTH, the SLR and NMA were not updated to include this relevant study in this patient population.

Analysis Scenario 2 evaluated CGRP inhibitors and key oral preventives, while Analysis Scenario 4 evaluated patients who have experienced 2 or more prior preventive treatment failures in only CGRP inhibitors. In Analysis Scenario 2, it is unclear how the number of prior treatment failures as a factor of heterogeneity may have impacted the results, and the direction of bias remains uncertain. In Analysis Scenario 4, trial populations often included small sample sizes, ranging from 19 to 137 patients per treatment arm, with the ADVANCE trial including only 122 patients total in the 2+ treatment failure subgroup, which limits the precision and generalizability of the treatment effect. Follow up duration of the included trials generally varied and was also a significant source of heterogeneity across trials, with treatment periods ranging from 12 to 56 weeks. For the primary efficacy endpoint, the time of assessment of 1 to12 weeks was chosen, as this was the timeframe of the primary efficacy endpoint in ADVANCE. However, other included studies varied on when change from baseline was assessed.

Clinical heterogeneity was assessed visually for baseline characteristics including age, sex, race, body-mass index (BMI), baseline MMD, and baseline MHD, as well as for timepoints and endpoint availability. The sponsors reported that in general the studies were similar, including mostly patients of the same age group, sex, and gender. The sponsor considered the main difference between studies to be with regards to race, whereby Japanese studies were excluded from the base case of the primary analysis in the original NMA, with 2 other Japanese studies excluded in the NMA update due to a lower, or negligible placebo response compared to other studies, potentially due to unaccounted for baseline or study center characteristics that varied. Consideration was given to many baseline characteristics as treatment effect modifiers or prognostic factors; however, it was unclear how this was managed in any statistical analyses. Though not reported, there may have been several differences in study and baseline characteristics across the trials that remain unaccounted for including study design which included RCTs, open-label studies, and crossover studies, as well as varying definitions of MMD and MHD, with some trials not reporting any MMD or MHD inclusion criteria, and as noted by the sponsor, none of the trials published before 2001 reported MMD or MHD inclusion criteria.

All studies included in the NMA were believed to be statistically heterogeneous based on the considerable range of I^2 values, though it is unclear what the source of heterogeneity was, as it was not explored. Though the authors relied on visual inspection of clinical heterogeneity, the observed heterogeneity is likely due to the observed and unobserved differences in patient populations across the included studies, data imputation analysis methods, and the specific prior, or background treatments allowed or received.

In the analyses comparing atogepant to all other treatments, there was generally no difference between atogepant and any of the other treatments in Analysis Scenario 2, or the other CGRP inhibitors in Analysis Scenario 4. Moreover, there were wide credible intervals (CrIs) that crossed the null threshold, further challenging the precision of the results. The general results in Analysis Scenario 2 displayed a reverse-dose-response relationship for atogepant, whereby the atogepant 10 mg dose demonstrated the greatest response, while the atogepant 60 mg dose demonstrated less of a response, which was the opposite of what was seen in the ADVANCE trial. No rationale for this observation was provided, and the reason for this remains uncertain, however, it may be due to the pooling of estimates from the ADVANCE and CGP-MD-01 trials. This effect was not observed in Analysis Scenario 4.

Other Relevant Evidence

Description of Studies

Two studies; Study 309, and Study 302, were included as other relevant evidence for the review of atogepant. Study 309 was a phase III, open label extension study that examined the long-term safety and tolerability of oral atogepant 60 mg once daily in adult patients with episodic migraine for up to 40 weeks of treatment. Patients were eligible to enroll into Study 309 if they completed the lead-in ADVANCE study. A total of 685 patients received at least one dose of atogepant 60 mg once daily and 511 (74.6%) patients completed the study. The mean age of patients in the study was 41.8 years (standard deviation [SD]: 12.3). Most (43.9%) patients were diagnosed with migraine without aura and the mean duration of the migraine disorder was 21.6 years (SD: 12.8). The mean number of migraine and headache days per month in the last 3 months were [redacted]), respectively.

Study 302 was a phase III, randomized, open-label study that examined the long-term safety and tolerability of oral atogepant 60 mg once daily in adult patients with episodic migraine for up to 52 weeks of treatment. Patients were eligible to enroll into Study 302 if they had completed the lead-in study CGP-MD-01 and new patients who met the eligibility criteria. Patients were randomized at Visit 2 to receive atogepant 60 mg once daily or standard of care (SOC) (oral migraine preventive medication) in a 5:2 ratio. The SOC treatment arm only served to provide context for interpreting the safety results of atogepant. A total of 543 and 196 patients received at least one dose of atogepant 60 mg once daily and SOC, respectively. The mean age of patients was 42.5 years (SD: 12.0) in the atogepant arm and 41.1 years (SD: 12.1) in the SOC arm. Most ([redacted] in the atogepant and SOC arms, respectively) patients were diagnosed with migraine without aura. The mean duration of the migraine disorder was [redacted] years (SD: [redacted]) and [redacted] years (SD: [redacted]) in the atogepant and SOC arms, respectively. The mean number of migraine and headache days per month in the last 3 months were 7.3 (SD: 2.6) [redacted], respectively, in the atogepant arm. The mean number of migraine and headache days per month in the last 3 months were [redacted] and [redacted], respectively, in the SOC arm. A total of [redacted] and [redacted] patients completed the open label treatment period in the atogepant and SOC arms, respectively.

Efficacy Results

Study 309 did not evaluate the efficacy of atogepant 60 mg once daily.

Efficacy outcomes in Study 302 were collected daily at home via an electronic diary and at clinic visits via an electronic tablet from patients in the atogepant arm only. The mean number of MMD decreased at weeks 49 to 52 from baseline; mean MMD at baseline was 7.28 (SD: 2.70) and least squares (LS) mean change was –5.19 (SE: 0.16; 95% CI, –5.50 to –4.87). The proportion of patients who achieved a greater than or equal to 50%, 75%, and 100% reduction in MMD at weeks 49 to 52 was [redacted], respectively. The mean number of MDH decreased at weeks 49 to 52 from baseline; mean MHD at baseline was 8.33 (SD: 2.97) and LS mean change was [redacted]. At weeks 49 to 52, the LS mean change from baseline in the number of monthly moderate/severe and severe headache days was [redacted], respectively. The LS mean change from baseline in the number of monthly cumulative headache hours was [redacted] hours at weeks 49 to 52. The mean number of MUD decreased at weeks 49 to 52 from baseline; mean MUD at baseline was [redacted] and LS mean change was [redacted]. The LS mean change from baseline in the number of monthly triptan use days was [redacted] days at weeks 49 to 52. The LS mean change from baseline in the MSQ v2.1 Role Function-Restrictive domain score was [redacted] (SE: [redacted]) at week 52. The LS mean change from baseline in the AIM-D Performance of Daily Activities domain score was –[redacted] at weeks 49 to 52. The LS mean change from baseline in the AIM-D Physical Impairment domain score was [redacted]) at weeks 49 to 52.

Harms Results

In Study 309, TEAEs were reported in 428 (62.5%) patients during open label treatment, included upper respiratory tract infection (5.5%) and urinary tract infection (5.3%). Serious adverse events were reported in 23 (3.4%) patients and no deaths were reported during the open label treatment. Premature discontinuation due to at least one TEAE was reported in 22 (3.2%) patients during the open label treatment. For notable harms, 23 (3.4%) patients reported constipation and 4 (0.6%) patients reported alanine or aspartate aminotransferase greater than or equal to three times the upper limit of normal value. No Hy's law cases and suicidal ideation were reported.

In Study 302, TEAEs were reported in 364 (67.0%) patients during the open label treatment, including upper respiratory tract infection (10.3%), constipation (7.2%), nausea (6.3%), and urinary tract infection (5.2%). For context, TEAEs were reported in 154 (78.6%) patients in the SOC arm. Serious adverse events were reported in 24 (4.4%) and 7 (3.6%) patients during the open label treatment with atogepant and SOC, respectively. Two deaths were reported in the safety population in the atogepant arm (no deaths were reported in SOC arm). Premature discontinuation due to at least one TEAE was reported in 31 (5.7%) and 5 (2.6%) patients during the open label treatment with atogepant and SOC, respectively. Notable harms identified in the atogepant arm included constipation in 39 (7.2%) patients, suicidal ideation in 3 (0.6%) patients, and elevations in alanine or aspartate aminotransferase that were greater than or equal to three times the upper limit of normal value in 13 (2.4%) patients. No Hy's law cases were reported.

Critical Appraisal

The open label study design of the long-term extension study, Study 309, can bias the reporting of endpoints, particularly any subjective measures included in the safety (and efficacy in Study 302) parameters due to the unblinding of the study drug during the treatment period. Since patients were required to have completed the lead-in study without any significant deviations from the protocol (i.e., noncompliance with procedures) and did not experience any adverse events (AEs) that may indicate an unacceptable safety risk per investigator judgement, the resultant population may be more tolerant of atogepant, leading to an underreporting of AEs and are also more likely to have benefits of atogepant, overestimating the efficacy of treatment as those without benefit are unlikely to continue. In the absence of an active comparator or placebo group, the interpretation of the results is limited. This is compounded using descriptive statistics only.

The limitations can also be applied to Study 302. The enrollment of new patients without prior experience with atogepant and patients who have completed a lead-in study further limits the interpretation of the results. It should be noted that the SOC treatment arm only served to provide context for interpreting the safety results of atogepant. The oral migraine preventatives were prescribed in a manner that reflected routine clinical practice. A flexible treatment paradigm was used that permitted the discontinuation of or switching from one agent to an alternative for migraine prevention as needed and per investigator judgement. Regardless of the type of change made, patients in the SOC arm were permitted to continue with the study. Thus, AE reporting in the SOC arm could be influenced by investigator choice as the adverse events may differ based on the oral migraine preventative selected.

Economic Evidence

Cost and Cost-Effectiveness

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Semi-Markov model
Target populations	• Health Canada indication population: Adults with episodic migraine (EM) who have <15 monthly migraine days (MMDs) • Reimbursement population: Adults with EM who have < 15 MMDs and an inadequate response, intolerance or contraindication to at least two oral preventative migraine medications (≥2 previous therapies)
Treatment	Atogepant: 10 mg, 30 mg, or 60 mg
Dose regimen	10 mg, 30 mg, or 60 mg once daily
Submitted price	10 mg, 30 mg, or 60 mg: $18.44 per tablet
Treatment cost	$6,735 per patient per year
Comparators	• Health Canada indication population: ○ Best supportive care (BSC; comprised of a basket of acute migraine treatments[a]) ○ Fremanezumab 225 mg ○ Fremanezumab 675 mg ○ Galcanezumab ○ Eptinezumab 100 mg ○ Eptinezumab 300 mg ○ Amitriptyline ○ Propranolol ○ Topiramate • Reimbursement request population: ○ BSC[a] ○ Fremanezumab 225 mg ○ Fremanezumab 675 mg ○ Galcanezumab ○ Eptinezumab 100 mg ○ Eptinezumab 300 mg
Perspective	Canadian publicly funded health care payer
Outcome	QALYs
Time horizon	5 years
Key data source	Network meta-analyses; effectiveness of atogepant informed by the ADVANCE trial, discontinuation of active comparators informed by the LTS-302 study.
Key limitations	• The full Health Canada and reimbursement populations were not modelled. Effectiveness of atogepant was based on the ADVANCE trial, which enrolled patients with 4 to 14 MMDs. The cost-effectiveness of atogepant among patients with less than 4 MMDs is unknown. • The comparative clinical effectiveness of atogepant to other preventative therapies (i.e., galcanezumab, fremanezumab, eptinezumab, oral preventative migraine treatments) is uncertain owing to a lack of head-to-head studies and limitations with the sponsor's NMAs. Indirect evidence submitted by the sponsor suggests that there may be no difference in the effectiveness of atogepant compared to any other active treatment. • The sponsor's model incorporated treatment-specific utility values, such that patients who received BSC were assumed to have lower utility than patients who received any active comparator for the same number of MMDs. Additionally, the sponsor submitted several sets of health state utility values, and scenario analyses submitted by the sponsor indicate that the results are highly sensitive to the chosen utility values.

Component	Description
	• The model structure does not adequately reflect the management of migraine in clinical practice; subsequent therapies after treatment discontinuation were not considered in the model. • The long-term efficacy of atogepant is uncertain owing to the lack of clinical data beyond 12 weeks. Potential waning of effectiveness was not adequately explored.
CADTH reanalysis results	• In CADTH reanalyses, the same health state utility values were assigned for each MMD level regardless of which treatment was received. CADTH was unable to address the lack of head-to-head comparative clinical data, uncertainty in the health state utility values, limitations related to the sponsor's modelling approach, and uncertainty in the long-term effectiveness of atogepant. • CADTH reanalyses for both the Health Canada indication and reimbursement populations reflect the cost-effectiveness of atogepant for patients with between 4 and 14 MMDs. Owing to a lack of clinical data, the cost-effectiveness of atogepant among EM patients with 1 to 3 MMDs is unknown, as is the cost-effectiveness of atogepant in the full Health Canada indication or reimbursement populations (i.e., among patients with 1 to 14 MMDs). • The results of CADTH's reanalyses were generally consistent with those submitted by the sponsor: ○ In the Health Canada indicated population (patients with EM), all doses of atogepant were dominated by propranolol, such that atogepant would not be the optimal treatment strategy in this population regardless of a decision makers' willingness to pay threshold. ○ In the reimbursement population (EM, ≥2 previous therapies), atogepant 10 and 60 were dominated by fremanezumab 225 and 675, respectively, and atogepant 30 was extendedly dominated by a mix of BSC and fremanezumab 225. • There is insufficient clinical evidence to justify a price premium for atogepant over currently available treatments for EM. To ensure cost-effectiveness, atogepant should be priced no more than the lowest cost active comparator used to treat EM that is funded.

BSC = best supportive care; EM = episodic migraine; ICER = incremental cost-effectiveness ratio; MMD = monthly migraine day; QALY= quality-adjusted life-year; WTP = willingness-to-pay threshold.

[a] Includes ibuprofen, Excedrin (acetaminophen, acetylsalicylic acid, caffeine), sumatriptan, and acetaminophen.

Budget Impact

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

- The modeled population does not reflect the reimbursement request.
- Market uptake and comparator displacement do not reflect the Health Canada indication.
- The sponsor's derivation of the eligible Non-Insured Health Benefits (NIHB) population was inappropriately calculated.
- The displacement of galcanezumab by atogepant was overestimated in Year 2.
- The proportion of EM patients receiving preventative migraine therapy may have been underestimated.

CADTH reanalyses included assuming that atogepant would capture market share from oral preventative migraine therapies and increasing the market share of atogepant in the Health Canada indicated population, and increasing the proportion of patients prescribed a preventative migraine therapy in the reimbursement population. In both populations, CADTH corrected NIHB and ODB client eligibility and assumed the anti-CGRP comparators would be displaced proportionally to their market shares in the reference scenario.

CADTH reanalyses suggest that:

- For the Health Canada indicated population, reimbursement of atogepant for the prevention of migraine in adult with EM (<15 MMDs) would be associated with a budgetary increase of $$25,119,733 in Year 1, $50,595,833 in Year 2, and $77,157,179 in Year 3, for a 3-year total incremental cost of $152,872,745.

- For the prevention of migraine in adult patients with EM and ³ 2 prior therapies, where oral CGRP agonists would be displaced, atogepant may be associated with an incremental cost of $40,639 in Year 1, a savings of $140,257 in Year 2, and a cost of $1,183,230 in Year 3, for a 3-year incremental budgetary cost of $1,083,612.

The estimated budget impact of reimbursing atogepant is highly sensitive to assumptions around the displacement of oral preventative migraine therapies in the Health Canada indication population and the uptake of atogepant. In both populations, the estimated budget impact is highly sensitive to the price of atogepant.

CDEC 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, Mr. Morris Joseph, 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: April 26, 2023

Regrets:

One expert committee member did not attend.

Conflicts of interest:

None