CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

atogepant (Qulipta)

(**AbbVie Corporation**)

Indication: The prevention of migraine in adults who have at least 4 migraine days per month.

December 23, 2023

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings.

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Patient Group Input

Name of Drug: Atogepant

Indication: The prevention of migraine in adults

Name of Patient Group: Canadian Migraine Society

Author of Submission: Maya Carvalho

1. About Your Patient Group

We are a patient advocacy group focused on improving the quality of life of Canadians living with migraine. After living with chronic migraine for 15 years, I founded this group in order to make a difference and have been volunteering 40 hours/week for the past four years because I am so passionate about this cause. We focus on three main pillars: Empathy (offered through two robust online support groups with almost 4,000 members), Education (provided through a patient-centric website) and Empowerment (realized by advocating with various stakeholders such as HCPs, pharmaceutical companies, and government bodies). We support patients seven days a week, twelve hours a day — we are the only group in Canada who offers this level of support. We are patient-led, volunteer-based and fully patient-driven in all of our efforts.

Our website is migrainesociety.ca

Our Chronic Migraine Support Group: https://www.facebook.com/groups/207750743101812

Our Episodic Migraine Support Group: https://www.facebook.com/groups/595871004605966

2. Information Gathering

The perspectives I am sharing on migraine disease come from a few sources:

A.The daily interactions over the past four years with the 3,200 members who comprise my chronic migraine support group (as opposed to the episodic support group). In running these support groups, I hear about all migraine-related issues: effects on lifestyle, access to medications and treatments, disease experience and overall impact of the disease on families and caregivers.

B. My personal experience having lived with chronic migraine for almost 20 years, and which includes trying 20 different preventive medications as well as countless therapies and protocols with several different neurologists.

C. We found 10 Canadians currently on Atogepant in our support groups, and conducted extensive email interviews during the period of November 1st to December 12th, 2023.

3. Disease Experience

Migraine disease is regularly diminished, invalidated and under-treated. The World Health Organization (WHO) classified severe migraine attacks **"as among the most disabling illnesses, comparable to dementia, quadriplegia and active psychosis (*Shapiro & Goadsby, Cephalalgia, 2007*)."** Furthermore, **the WHO classified severe, continuous migraine as more disabling than blindness, paraplegia, angina, or rheumatoid arthritis. (*Harwood, Sayer, & Hirschfield., Bulletin of the World Health Organization, April 2004*)**. Based on what I have seen through the ongoing dialogue with the 3,200 members of my chronic migraine community, the WHO assessment provides a much more accurate picture of migraine disease than is commonly understood by the general public.

From a patient's perspective, migraine, and specifically chronic migraine, affects every single facet of a person's life. 85% of chronic migraine patients are women, and the greatest prevalence of the disease occurs between the ages of 30 to 39 — the most productive years of many women's lives. Chronic migraine means having a migraine attack almost every other day of one's life. The migraine cycle and phases of migraine often last more than a day meaning that people with this level of the disease are almost never without pain.

Chronic migraine has a huge impact on people's careers. It typically peaks during the most important phase of a woman's career and for many women, it cuts their career path short. For many it has meant going on Long Term Disability, Short Term Disability, or CPPD. This is crushing for one's self esteem, not to mention the financial implications of suddenly losing a salary. Furthermore the cost to the Canadian economy is huge — these women are unable to contribute to Canada's GDP, but with proper treatment they could.

People living with chronic migraine need to factor their disease into their family planning. Most require caregivers to help them take care of themselves and for some people, they make the difficult and painful decision to not have children. This is a permanent decision for many, and a heartbreaking one.

Almost everyone with chronic migraine needs help from caregivers. Physical exertion is a very common trigger for migraine. Patients need help to cook and feed themselves, help with transportation to medical appointments, help in the home with household chores, and help to look after their children. This is challenging with an invisible illness like migraine, and the common misunderstanding of migraine as a simple headache rather than a neurological disease. There is sometimes doubt and a lack of sympathy from caregivers and some relationships even end in divorce. For the younger cohort who live with chronic migraine, many do not even have a chance to form partnerships.

Finally, chronic migraine keeps people in such a high level of pain that we see an epidemic of isolation that rivals the national epidemics of loneliness. Because people have attacks every other day, it is extremely difficult to maintain social commitments, and social activities. Eventually people simply find their friendships disappearing, and isolation sets in.

4. Experiences With Currently Available Treatments

The currently available treatments available for migraine are not adequate — this is because the disease is so complex that the same combination of medications and treatments do not work for everyone. Each person living with this disease must endure the trial and error process of testing various permutations and combinations of preventive and acute migraine medications until they find the right fit for them. Furthermore, there is no way to predict which medications and treatments will work for any given patient. For example, some patients don't respond to one CGRP mAbs injection, but they do respond to a different CGRP mAbs even though they are in the same class of medication, with the same mechanism of blocking CGRP. I have seen this more times than I can count.

Most daily oral preventive medications, like Topamax, Propranolol, and Amitryptiline, were not designed specifically for migraine, they have simply been used off-label for migraine. The side effects include weight gain, depression, anxiety, brain fog, dizziness, numbness and tingling, to name a few. Botox has a high success rate but for many, the 31 injections are not tolerable, and in terms of cost it is only available on three provincial formularies. CGRP mAbs like Aimovig, Emgality, Ajovy and Vyepti have been designed specifically to treat migraine and have been life-changing for many. In terms of side effects, CGRP mAbs have a lower side effect profile but due to the long half-lives remain in a patient's system for an average of 5–6 months after cessation. Monthly injections can be hard for some and IV infusions can be very hard to access in smaller communities.

We polled our membership to learn about the number of preventives that have been tried thus far without success: 30% of respondents had tried between 10–20 preventive medications without success — this is why we need new drugs. Each medication typically requires a 3–6 month trial so it can take many years for a patient to go through this trial and error process before finding the right fit.

5. Improved Outcomes

I believe that CADTH should take a nuanced approach to outcomes. The desired outcome should be an increase in quality of life. Again, the issue is that people living with migraine need as many medications to be available as possible, because a different medication will work for each person and there is no way to predict that. Instead of using a single metric of frequency, both migraine frequency **and/or** intensity should be evaluated equally when assessing efficacy. For example, some people on the high end of the chronic migraine spectrum may not get a dramatic decrease in the frequency, but the intensity may be much lower, allowing their acute medications to be more effective. For most people living with chronic migraine, taking a shower, feeding themselves, doing basic domestic activities can be challenging. As mentioned previously, for many people, work becomes impossible.

By definition chronic migraine is 15+ headache days per month, and if each of these attacks last 4 to 72 hours, it becomes nearly impossible to maintain a work schedule. If Atogepant is successful in decreasing frequency or intensity, this means that people living with migraine can rely less on their caregivers (who are usually depleted from having to finance the household), they could regain

independence and spend more time with their children and they could get back to work! Anxiety and depression have a high comorbidity with migraine, however when polling my membership, 80% of members stated that their depression and/or anxiety would decrease or even be eliminated if they could go from chronic migraine to episodic migraine.

6. Experience With Drug Under Review

Patients accessed Atogepant through private insurance, the patient support program provided by Abbvie, or an 80/20% combination of the two. Each person living with migraine disease responds differently to each medication, so the main benefit is that for many people it works! Atogepant works much more quickly than other preventives, it is much easier to take than an injection or IV, and by reducing migraine frequency, patients are able to significantly lower their risk of Medication Overuse Headache/Rebound headaches from needing to treat so many attacks with acute medications. Many of our members had tried several other preventive medications but Atogepant was the only one that was effective for them.

The oral daily preventives that are commonly used for migraine (Topamax, Propranolol, Amitriptyline etc.) often come with serious side effects. The side effects of Atogepant seem to be much better tolerated as they are typically fatigue, nausea, and constipation which patients felt were more easily managed. The main disadvantage of Atogepant is the high cost — for the 35% of patients without health insurance — the cost was about $650/month ($7,800/year).

An important difference between Gepants and CGRP mabs, is that Gepants are oral tablets, small molecule CGRP blockers so they are processed through the liver and kidneys. If patients decide to stop the medication, Atogepant will be out of their system in a few days. The CGRP mabs are large molecule medications so there is a benefit in that they are not processed through the liver and kidneys, but the trade off is that they stay in the system for 5–6 months. Atogepant can take effect quickly, and be assessed quickly — two huge benefits. The lives of patients and their caregivers and families were greatly impacted by having a preventive medication that actually worked from them. Patients told me that they were able to be more productive at work and at home. They have been able to rely less on their caregivers for household chores and have become much more independent. This takes an enormous burden off the entire household not just in terms of workload but in terms of the worry and stress experienced by caregivers. Patients told me it improved their marriages, their social connections, and allowed them to be more present and involved with their children — an immeasurable value.

We interviewed Canadian patients who have personal experience with Qulipta and these were some of the comments we received:

- “Atogepant was more effective than any other preventive medication I have taken in my 35 years as a migraine patient”
- “I had tried two other preventive medications which did not stop or even reduce my migraines and also gave me horrible side effects. So when I started Atogepant and immediately had 100% relief from migraines with no side effects, it was a miracle!”
- “The benefit of this medication was that it worked….and it worked within the first month!”
- “It’s life changing not to constantly have a migraine. I have been able to make and keep plans this month…I could never do that before and it was hard on me and others”
- “This has been the single greatest thing to happen to me”
- “None of the other preventive medications I tried ever worked to stop or even reduce my migraines. They also came with extensive side effects like heart palpitations, insomnia, confusion, irritability. I spent decades of my life trying to figure out how to stop getting migraines — I analyzed every dietary and environmental trigger, did extensive massage therapy and chiropractic adjustments, started counselling to reduce stress and so much more. I have not had a single migraine since starting taking Atogepant which I never thought I would say in my life. It has been the greatest blessing to ever happen to me.”
- “When I combined Botox with Atogepant, almost 100% of my migraines were eradicated. Unfortunately I could not get both meds covered. I will have to choose between eating and migraines — its a tough financial situation to be in.”
- “Qulipta has been life-changing for me in severely reducing migraine and headache events, allowing me to be a better employee, mother and wife. It is the only preventive medication that has worked after trying dozens since age 12 — I am 44.”
- “Within a few weeks I had fewer episodes and less pain. I have had chronic migraine for over 20 years. Less reliance on pain medication and medication overuse. Reduced disability, increased independence, increased ability to contribute to home, society, and work.”

- “I haven’t had success with any other preventive medications until using Atogepant. I was spending most days either disabled with a migraine or attempting to recover from migraines. Atogepant has lowered the frequency of my migraines, also I noticed that the daily brain fog and cranial pressure was gone after 12 hours after the first dose.”
- “I’ve been able to start working again after being on disability for 7 years — I am able to participate more in all aspects of my life.”
- “Prior to Atogepant, I was fighting to live my life with migraines too often, for too many years. Atogepant has given me relief that I have never had before and I believe that I will require Atogepant to live a decent quality of life”
- “I am no longer stressed about a migraine taking me down and not being able to parent my children, or assist my husband, or missing work”
- “I don’t feel foggy all the time from migraines or medication side effects. I never need to take sick days at work for migraine, and I don’t have to cancel plans with friends and family. I have been more productive and capable at work and at home in these past 6 weeks than I have been for years. I feel happy and more contented in my life, marriage, and with my friends. It has honestly been the best thing to ever happen to me.”

Summary Statement: An effective preventive medication such as Atogepant can give patients their lives back. Patients who have spent years of their life in near constant agony, can reduce their migraine frequency and intensity and start gaining control of their lives. It is important that this medication takes effect quickly, so that patients do not need to wait six months to judge efficacy. It is important that this medication is incredibly easy to take because it is a daily oral pill. It is important that it has minimal side effects, and it is important that is reduces the need for reliance on acute medications, thus reducing the high risks of Medication Overuse/ Rebound headaches in the chronic migraine community. The overall effect is a marked improvement in quality of life and a marked improvement in one’s ability to be a productive member of society.

7. Companion Diagnostic Test

N/A

8. Anything Else?

The most salient piece of input I can offer is this: chronic migraine patients need access to **as many new medications as possible** (both preventive and acute) because everybody who lives with migraine does not respond to the same medication or treatment. Canadians living with chronic migraine are completely debilitated by continuous pain and symptoms. We need to find the right medications, to reduce our migraine frequency and intensity, and finally start living our lives again.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

1. No
2.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

3. No
4.

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Lundbeck	X			

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Maya Carvalho
Position: Founder
Patient Group: Canadian Migraine Society
Date: December 15, 2022

Clinician Group Input

The Canadian Headache Society

CADTH Project Number: SR0817-000

Generic Drug Name (Brand Name): Atogepant

Indication: Migraine, prevention

Name of Clinician Group: Canadian Headache Society

Author of Submission: Dr. Elizabeth Leroux, Dr. Alexander Melinyshyn, Dr. Danny Adel Monsour, Dr. William Kingston.

1. About Your Clinician Group

The Canadian Headache Society (CHS) is a scientific society of healthcare professionals dedicated to Headache Medicine. The CHS was created in 1988. Our goals include research, education of residents and physicians, and promotion of better care for patients suffering from headache disorders.

https://headachesociety.ca/

2. Information Gathering

The information is gathered from published clinical evidence and expert opinions from Headache specialists in Canada and internationally.

3. Current Treatments

Therapies available for migraine management include the following:

Non-Pharmacological Treatments:

- **Behavioral Therapies:** Cognitive behavioral therapy, relaxation therapy, and biofeedback
- **Neuromodulation Devices:** External trigeminal nerve stimulation device, and non-invasive vagus nerve stimulator.
- **Lifestyle Strategies and therapeutic education:** Regular diet/sleep, hydration, stress management, aerobic exercise, pacing, trigger management.
- **Supplements:** magnesium, riboflavin, coenzyme q10, *Petasites hybridus* are supported by evidence. Feverfew, melatonin and others are sometimes used with limited evidence.
- **Alternative approaches:** patients often use therapies such as osteopathy, chiropractic treatments, acupuncture, massotherapy, psychotherapy, naturopathy, physiotherapy to manage their symptoms. Research on these approaches is difficult due to methodology limitations and therefore evidence is limited. Patients often pay for these treatments out-of-pocket, often waiting for appropriate medical care.

- **Other devices:** patients often buy numerous devices to manage migraine and associated neck pain including pillows, TENS machines, cold and warm devices.

Pharmacological Therapies:

Acute Treatments recommended: NSAIDs, acetaminophen, triptans, dihydroergotamine, neuroleptic, gepants

Acute treatments: the guidelines on the acute therapy for migraine are published. The goal of acute therapy is a return to function as quickly as possible and with no or minimal side effects. Triptans are specific to migraine. Access to triptans does vary from one province to the other, with some provinces requiring an Exceptional Access Program. In some patients with frequent attacks, the regular use of acute treatments can lead to medication-overuse headache, a complication of migraine. This is relevant to the discussion of preventive therapy. Some patients do use opioids and cannabinoids to relieve migraine attacks. Both have been linked to a risk of chronification and deterioration of migraine, in addition to other well-known health risks.

Acute treatments, used but non recommended: opioids, cannabinoids

The use of opioids and cannabinoids persists despite recommendations to avoid them or keep them as last resort. Patients might not respond to, or have contraindications to, other therapies.

Preventive Treatments:

The Canadian Headache Society guidelines were published in 2010 and are therefore outdated. An update based on a systematic literature review is ongoing and the publication is planned for 2024. Options for migraine prevention available in 2023 include:

1. Oral preventives including anti-hypertensives, anti-epileptics and anti-depressants. These are considered non-specific to migraine because they were initially used for other conditions. Their mechanism of action is usually not well understood.

2. Onabotulinumtoxin type A has been approved in Canada in 2011 for the prevention of chronic migraine. The use of onabotulinumtoxin type A for migraine was observed initially in the cosmetic world, then demonstrated in randomized controlled trials. The mechanism of action of the toxin for migraine is now better understood.

3. CGRP monoclonal antibodies have been approved in 2018 (erenumab), 2019 (galcanezumab),2020 (fremanezumab), and 2021 (eptinezumab).

The concept of CGRP blockade for migraine treatment is supported by a robust corpus of evidence, and these treatments are considered specific to migraine. The role of CGRP in migraine pathophysiology has been well demonstrated over 30 years and lead to the attribution of the Brain Prize to key researchers in 2021. It is fair to say that CGRP blockade for migraine is a breakthrough in neurology.

https://www.theguardian.com/science/2021/mar/04/scientists-discovered-migraine-mechanism-win-brain-prize

The International Classification of Headache Disorders has separated migraine in episodic and chronic subforms with an arbitrary limit of 15 monthly headache days as the key criterion. Chronic migraine was defined to represent the more severe end of the spectrum that was often excluded from clinical trials. Chronic migraine as currently defined is

associated with more burden, more comorbidities and a worse prognosis than episodic migraine. Still, migraine frequency and severity is a continuum, not a binary variable. Patients often fluctuate from one month to the other. It is expected that the episodic/chronic categories will be challenged and redefined in the future. Migraine is a chronic disease in all its forms, even if it is not listed as such in Canada. Therefore, even if the current definitions still stand by the ICHD-3, it is to be kept in mind that episodic and chronic migraine are on a continuum.

In Canada, for cost-effectiveness reasons, patients suffering from episodic migraine or chronic migraine are required to try non-specific therapies prior to onabotulinumtoxinA and CGRP antibodies. Access to onabotulinumtoxinA and CGRP antibodies varies significantly between provinces depending on public coverage policies. For example, onabotulinumtoxinA is accessible through a Patient of Exception form in Quebec, publicly covered in Ontario and Alberta, and not covered in British Columbia. Fremanezumab is now covered nationwide. Erenumab did not reach an agreement with PcPA and therefore is not likely to be covered publicly. Galcanezumab is covered in the provinces of British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, New Brunswick, Newfoundland and Labrador, and Nova Scotia. Eptinezumab is covered in the provinces of Ontario, Alberta, Quebec, New Brunswick, Nova Scotia, Northwest Territories, and the Non-Insured Health Benefits Program (NIHB). Criteria for coverage also vary from one province to the other even for the same product.

Atogepant became the second FDA-approved oral gepants for migraine prevention, gaining approval on September 28, 2021 in the USA. Atogepant has demonstrated efficacy in the preventive treatment of both episodic and chronic migraine. It received Health Canada approval for the episodic indication in January of 2023, and FDA approval for the chronic indication in April of 2023, allowing for treatment of migraine across the spectrum of frequencies. According to the FDA label, the recommended dose is 10mg, 30mg, or 60mg once per day.

Atogepant is a calcitonin gene-related peptide receptor antagonist (CGRP).

4. Treatment Goals

The treatment goals of atogepant for migraine prevention include the following:

- Improve health related quality of life
- Improve function and reduce disability
- Reduce headache attack frequency, severity, duration, and disability
- Reduce inter-ictal symptoms that also contribute to the migraine burden
- Improve responsiveness to acute treatment
- Decrease the need for acute medications and the risk of medication-overuse headache
- Decrease the use of opioids and cannabinoids in patients who use them as treatments
- Reduce indirect costs associated with migraine (absenteeism and presenteeism)
- Reduce some comorbidities of migraine such as anxiety and depression
- Enable patients to manage their own disease to enhance a sense of personal control

- Decrease out-of-pocket costs for patients
- Decrease the impact of migraine on the person's network (partner, children, friends, co-workers).
- Decrease overall health care utilization costs (reduced visits for migraine, reduced ED visits).

5. Treatment Gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

Some of the currently available treatments:

- Are not effective for all patients (average response rate 40-50% for oral medications which leaves 50-60% not responding, with no documented predictive factors for response)
- May lose their effectiveness over time (wearing off)
- In the case of oral preventives, are not disease specific
- Have significant side effects (profile depends on the drug)
- May be contraindicated in certain patients (profile depends on the drug)
- Are injectable (not ideal for some patients)
- Have long half-lives (antibodies), which limits their use if a pregnancy is planned
- Are difficult to access due to limited coverage

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

- Patients who do not respond to currently available treatments
- Patients who would favor options specific for migraine
- Patients who have significant side effects with current treatments or contrandications to their use
- Patients who prefer oral options
- Women who are planning a pregnancy and need options with short half-lives

6. Place in Therapy

6.1. How would the drug under review fit into the current treatment paradigm?

- Atogepant, as an oral CGRP pathway blocker, could in theory be combined with drugs with a different mechanism (other oral preventives, onabotulinumtoxinA) though evidence to support the effectiveness of such combinations is lacking.

- Atogepant, as an oral CGRP blocker, is the first of his class and provides unique advantages such as an oral intake for patients who prefer a pill over an injection. A once daily dosing is also shown to increase compliance. Primary care physicians, who may be reluctant to prescribe monoclonal antibodies (often seen as «specialist options») may feel confident to prescribe atogepant. This would make atogepant an excellent CGRP blockade option in primary care.
- The combination of atogepant with CGRP antibodies is currently under investigation, since they share a similar mechanism of action. Still, antibodies do not cross the blood-brain barrier and gepants may cross it partially, which could lead to different effects.
- The combination of atogepant with onabotulinumtoxinA is a rational combination, as both target different sensory fibers. OnabotulinumToxinA also has an effect on other peptides released from sensory fibers that could complement CGRP blockade. Please see the CHS letter presenting arguments and references to support this therapeutic combinations.
- Primary care providers and patients are often discouraged by the slow titration and side effects of preventives. In addition, patients are reluctant to use medications that treat diseases that they do not suffer from. From a purely medical perspective, when looking at the effectiveness of atogepant, its tolerability, its safety and the fact that it is a once daily oral migraine specific preventive, it is well-suited for prescription in primary care. Since access to specialized care for migraine is very limited in Canada, this would be a massive advantage from a public health perspective. The economic and social burden of migraine in our society (in the workplace for example) is severely underestimated.
- The place of atogepant in the therapeutic algorithm will be determined in great part by its cost. If the cost leads to restrictions and the need for paperwork, then its use will be limited and primary care physicians might decide not to prescribe it and refer patients who fail non-specific oral preventives to neurology, which would be a missed opportunity to improve our population's health. Headache specialists should dedicate their expertise and skills to treat complex headache cases, not fill forms for a medication that could be used in primary care.

6.2. Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

Considering studies of similar methodology and also acknowledging the lack of head-to-head trials, atogepant would make a suitable first line medication as it compares favorably to other oral preventives for effectiveness, tolerability and mode of administration. The fact that it is a migraine-specific medication, targeting a demonstrated pathophysiologic target, is also a strong consideration for patients who seek to treat the cause of their disease. The opinion of neurologists specialized in headache medicine is quite clear on this.

Realistically, access to treatments is strongly influenced by their cost. In a public health care system, cost-effectiveness is key. Therefore, if the cost of atogepant is significantly higher than the cost of other oral preventives, it would likely be pushed farther along the therapeutic path. Failure of other oral preventives could be required. Would it be 2, or 3 as we see for onabotulinumToxinA and CGRP antibodies? Is it fair to force patients suffering with chronic pain and disability through a year or more of therapeutic trials with low efficacy, side effect prone options when we are aware

of effective and tolerable alternatives? We do not force patients with other conditions like diabetes or syphilis to recapitulate the course of ancient medical treatments before prescribing insulin or penicillin.

The question remains: how many patients would find an effective and tolerated option through these trials? Our experience suggests that most patients are left without adequate relief and discouraged by side effects after many oral trials.

Classically recommended migraine preventives are prone to considerable side effects and harm potential. Weight gain is harmful to health and is commonly seen with tricyclics. This is not easily reversible. Obesity is now recognized as a chronic disease in Canada and is associated with more than 200 complications. Tricyclics have been associated with an increased risk of dementia. Is it reasonable to ask a young patient to take it for years in the presence of an alternative? Cognitive issues and renal calcification are common with topiramate, often causing significant distress and disability to patients. Many patients with migraine are young women with low baseline pressure. Many have a tendency to vagal syncope. How reasonable is it to ask them to try a beta blocker or candesartan? The same reasoning goes for young patients who exercise, a very favorable element of a healthy life. A limitation in exercise capacity is a well-known side effect of beta-blockers. Older options such as valproate, flunarizine and pizotifen carry even higher risks of adverse events including weight gain and depression, not to mention long term risks of parkinsonism and tremor. Many headache specialists now prescribe these only as a last resort.

Atogepant, with its high efficacy and tolerability rates is a reasonable first line treatment from a medical perspective. Only financial arguments justify a second-line place requiring the trial of other oral preventives.

6.3. How would this drug affect the sequencing of therapies for the target condition?

At present, there is no scientifically proven way to predict in advance the response to a migraine treatment;this applies to both acute and preventive medications. The choice of preventives is commonly based on contraindication and selection of the «less harmful» adverse events profile. Strategies for selection can be found in the guidelines. For example, a patient with a normal weight with insomnia and low blood pressure might favor a tricyclic, but an overweight patient with hypertension might be a better candidate for a beta-blocker or candesartan.

As the number of options increases, medical and financial factors complexify the decisions, and add significantly to the paperwork that headache specialists have to fill.

If the cost allows its use as a first line therapy, then other preventives could be used in different sequences based on each patient’s comorbidity profile and preferences, just as we do presently.

If previous trials are required, it could be considered only after 1 or 2 other preventives. Evidence and experience suggest that some patients may respond to CGRP blockade with antibodies even after failing 4 to 11 other preventives. Whether this applies to atogepant or not remains to be demonstrated by future studies in refractory populations and real-world evidence.

Atogepant is priced at $6,735 per patient per year, less than the CGRP antibodies. It could potentially be used prior to CGRP antibodies, considering only financial reasons. From a medical perspective, effectiveness and tolerability are similar across RCTs for chronic migraine for CGRP antibodies and atogepant.

Since onabotulinumtoxinA costs significantly less for the treatment of chronic migraine, this could rationally be considered for trial prior to prescription of atogepant when considering cost alone, however as this is not indicated for episodic migraine, it should not be considered as a requirement for that algorithm.

As a separate note, the longitudinal course of migraine is such that sufferers may convert from episodic to chronic frequency and vice versa in response to external factors such as age, lifestyle factors, inappropriate use of acute medications, and general medical conditions. The traditional dichotomous approach to treatment of episodic and chronic migraine is under scrutiny; the distinction between the two was borne from research criteria. This binarization does not represent the continuum of attack frequency and disability in migraine; the disability experienced by patients on either side of this arbitrary boundary has been shown to overlap considerably.

6.4. Which patients would be best suited for treatment with the drug under review?

Currently, there are no specific biomarkers to identify patients most likely to respond to the medication under review.

Though the need for treatment increases with the attack frequency and severity (see the list of goals for migraine prevention), both eligibility for prevention and the importance of the migraine burden remain underestimated by healthcare providers. For example, some providers might think that only chronic migraine is worth treatment. It is true, and supported by evidence, that the burden of chronic migraine is higher than the one of episodic migraine.

The need for treatment increases with attack frequency and severity (see the list of goals for migraine prevention). Often, the need for prevention and the importance of the migraine burden are underestimated by health care providers as patient encounters represent a brief snapshot in time. For example, some providers might think that only chronic migraine is worth treatment. This belief has been called into question by recent studies demonstrating that use of a 15 headache day per month threshold to distinguish episodic and chronic migraine does not capture the burden of illness nor reflect the treatment needs of patients. The burden of episodic migraine is also worthy of intervention. For example, In the world of epilepsy, the goal is to be seizure-free. The fact that a person is expected to be happy with 6 to 8 migraine attacks per month is only determined by centuries of lowered expectations due to ineffective or poorly tolerated treatments. Expectations for migraine treatment are now revisited in the light of specific, effective therapies and a shift in terms of the possibility of «migraine freedom» has been observed.

From a cost-effectiveness perspective, it is noteworthy that 80% of people with migraine have fewer than 6 migraine days per month. Of course, the frequency is not the only parameter to consider, since severity and response to acute medications are also key to the return to function.

Regarding the stage of disease, migraine is not considered to be a degenerative disease. The majority of patients with migraine do not progress over time and will remain in the «low frequency episodic» migraine category. Still, a subset of patients will “chronify”, or increase their frequency past the arbitrarily defined 15 days per month. Intervention before chronification is thus a therapeutic goal. Factors for chronification have been described. A high baseline frequency is a key factor for chronification. Clinical experience suggests that patients who are successfully treated with a preventive function better on all parameters. Indeed, we often see patients who, due to a neglect of their migraine treatment or limited access to care, have progressed to a severe state and endured significant distress, loss of quality of life, personal life difficulties and even disability.

Therefore, any migraine preventive should be available to patients who present a “high frequency episodic migraine” or a lower frequency but with severe attacks impacting function.

6.5. How would patients best suited for treatment with the drug under review be identified?

The diagnosis of migraine is clinical. There are no specific laboratory testing or diagnostic tools. Imaging is indicated uniquely in presence of red flags or an abnormal neurological examination. The condition is not challenging to diagnose in routine neurology clinical practice.

Evidence suggests underdiagnosis in primary care practice. The absence of a readily available and reliable biomarker imposes on primary care providers a longer questionnaire which is difficult with the limited time they have. Primary care providers receive very limited education on migraine diagnosis and treatment compared to other chronic diseases. Quite often, patients and providers will focus on symptoms or triggers leading to a misdiagnosis («sinus headache», «neck headache», «hormonal headache»).

Migraine is quantified with a headache diary, an essential tool that is underused in primary care because time is limited to perform these initial steps of therapeutic education.

There is currently no evidence that migraine has a pre-symptomatic stage. It does frequently start at a young age and fluctuates over a lifetime depending on very numerous factors. Treatment must be adjusted depending on the current state of the patient, always including the three axes of lifestyle adjustment, acute therapy, prevention of medication overuse and appropriate preventive therapy. Early therapeutic education and patient empowerment is key to avoid learned helplessness.

6.6. Which patients would be least suitable for treatment with the drug under review?

Special Populations:

Pregnancy:
There is insufficient data on the developmental risk associated with the use of atogepant in pregnant women. CGRP does play a role in pregnancy, and therefore drugs blocking CGRP could be harmful. Still, the shorter half-life of atogepant (5-7h) would be an advantage compared to the long half-life of antibodies (27-31 days) in the case of a woman planning a pregnancy.

Lactation:
There is insufficient data on the presence of atogepant in breastmilk, the effects of atogepant on breastfed infants, and the effects of atogepant on milk production. In lactating rats, oral dosing with atogepant resulted in twice the amount of atogepant in milk than in maternal plasma.

Pediatrics:
Safety and effectiveness in pediatric patients has not been established.

Geriatrics:
Population pharmacokinetic modeling suggests no clinically significant pharmacokinetic differences between elderly and younger subjects. Clinical studies of atogepant contained an insufficient number of patients aged 65 years and over to determine if they respond differently than younger patients. In general, caution should be exercised in dose

selection for an elderly patient, typically starting with the lowest dosage in the dosing range reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Renal Impairment:
The renal route of elimination plays a minor role in the clearance of atogepant. In patients with severe renal impairment (CLcr 15-29 mL/min), and in patients with end-stage renal disease (ESRD) (CLcr <15 mL/min), the recommended dosage of atogepant is 10mg once daily. For patients with ESRD undergoing intermittent dialysis, atogepant should preferably be taken after dialysis. No dose adjustment is recommended for patients with mild or moderate renal impairment.

Hepatic Impairment:
No dose adjustment of atogepant is recommended for patients with mild or moderate hepatic impairment. Avoid use of atogepant in patients with severe hepatic impairment.

Drug Interactions:

CYP3A4 Inhibitors
Coadministration of atogepant with itraconazole, a strong CYP3A4 inhibitor, resulted in a significant increase in exposure of atogepant in healthy subjects. The recommended dosage of atogepant with concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin) is 10mg once daily. No dosage adjustment of atogepant is needed with concomitant use of moderate or weak CYP3A4 inhibitors.

CYP3A4 Inducers
Coadministration of atogepant with steady state rifampin, a strong CYP3A4 inducer, resulted in a significant decrease in exposure of atogepant in healthy subjects. Concomitant administration of atogepant with moderate inducers of CYP3A4 can also result in decreased exposure of atogepant. The recommended dosage of atogepant with concomitant use of strong or moderate CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort, efavirenz, etravirine) is 30mg or 60mg once daily. No dosage adjustment of atogepant is needed with concomitant use of weak CYP3A4 inducers.

OATP Inhibitors
Coadministration of atogepant with single dose rifampin, an OATP inhibitor, resulted in a significant increase in exposure of atogepant in healthy subjects. The recommended dosage of atogepant with concomitant use of OATP inhibitors (e.g., cyclosporine) is 10 mg or 30 mg once daily.

6.7. Is it possible to identify those patients who are most likely to exhibit a response to treatment with the drug under review?

There are no specific identifying factors to determine patients who are most likely to exhibit a response to treatment.

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

Health care providers will usually evaluate the response based on the stated goals of decreasing attack frequency and severity, improving function and quality of life and decreasing distress and comorbidities. The level of detail will vary based on the experience of the clinician and available time in the clinic.

The methodology of migraine preventive trials has evolved over time in parallel with the clinical assessment of patients. Most headache specialists are now aware of the typical research outcomes and evaluate their patients with a similar approach. Questionnaires, scales and other PROs are used in research. Their use and utility in clinical practice varies, but they are now frequently asked by the insurance companies.

The evaluation of patients with migraine in primary care varies greatly. Some physicians will roughly ask if a patient is «doing better, approximately how much% ». Others will ask for frequencies. Few will use a diary. Even fewer will evaluate the impact of migraine on work, sleep and mood.

Still, with episodic migraine patients, the identification of responders (50%) and super-responders (75%) can be relatively easy compared to the complex clinical pictures of patients with chronic migraine. A basic headache diary should be sufficient to ensure a reliable monitoring of outcomes.

6.9. What would be considered a clinically meaningful response to treatment?

The usual key parameter for a response in episodic migraine is a 50% in monthly migraine days (frequency), usually evaluated with a headache diary.

Other clinically meaningful responses supported by evidence to atogepant include the following:

- Improved health related quality of life
- Improved function and reduce disability
- Reduced headache attack frequency, severity, duration, and disability
- Improved responsiveness to acute treatment
- Decreased the need for acute medications and the risk of medication-overuse headache

Clinically meaningful responses not yet demonstrated by evidence include the following

- Reduced inter-ictal symptoms that also contribute to the migraine burden
- Decreased the use of opioids and cannabinoids in patients who use them as treatments
- Reduced indirect costs associated with migraine (absenteeism and presenteeism)
- Reduced some comorbidities of migraine such as anxiety and depression
- Enhanced sense of personal control
- Decreased out-of-pocket costs for patients

The challenge from a clinical perspective is to find a time-effective way to document this and acknowledge what a significant response is for a particular patient. A “quick ’n easy” option is good, but not always sufficient.

The key example, as seen with CGRP antibodies, is the patients who does not reach a 50% improvement in frequency but does see a significant improvement in severity with a functional gain (for example, less presenteeism). The insurance decides not to cover, and the patient is desperate.

We hope that both frequency and severity (as both contribute to quality of life and ability to function) will be considered in the evaluation of response, as this is what we do in clinical practice. The MIDAS or HIT-6 score could be used to monitor benefit and determine whether to continue or alter preventive therapies.

6.10. How often should treatment response be assessed?

Oral preventive therapies can take 3 months at therapeutic dosages to see benefits. Therefore, monitoring at 3-month intervals is recommended when the treatment is initiated. Then, once a patient is stable, yearly visits could be sufficient.

6.11. What factors should be considered when deciding to discontinue treatment?

The following factors should be considered when deciding to discontinue treatment:

- Lack of significant clinical response
- Adverse reactions to the medication
- If a CYP3A4 Inducers, CYP3A4 Inhibitors or OATP Inhibitors are required for long term use
- Patients who develop renal disease or hepatic disease
- A woman who plans a pregnancy
- Any change in the medical situation that would warrant a change in the treatment plan

We would like to stress that therapeutic success (for example a decrease in migraine frequency) should not be seen as a reason to discontinue treatment. In other terms, if a migraine preventive is effective, it should not be stopped.

The decision to discontinue an effective therapy, once demonstrated, after requiring months to years of ineffective medicines lacks rationale and could be seen is often interpreted by patients as cruel. It is well known that the therapeutic effect of migraine preventives wears off if not dosed at the usual frequency. The resultant worsening of headache is entirely predictable and results in unnecessary pain and suffering.

Comparisons to other chronic conditions requiring ongoing therapy foil the absurdity of this situation:

One would not stop a diabetic's insulin because they have achieved good glycemic control and have a HbA1c within normal range. One would not stop a disease modifying drug for multiple sclerosis simply because a patient has not had a relapse in a year. One would not stop a biologic agent for a rheumatologic condition because rashes and joint swelling have abated.

Requiring migraineurs to stop medication to observe a resultant increase in frequency is unconscionable and driven solely by a cost containment strategy. This further stigmatizes migraine as a disease constantly requiring proof, as opposed to other, more accepted illness states.

6.12. What settings are appropriate for treatment with the drug under review?

Physicians treating migraine patients usually work in outpatient clinics (academic or community).

6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?

Atogepant can be prescribed by primary care providers. Atogepant prescription should not be restricted to neurologists or specialists. It is indeed well tolerated and safe compared to many other drugs prescribed in primary care.

7. Additional Information

We would like to emphasize that

1. Migraine is underdiagnosed and undertreated, particularly in primary care, due to a lack of education but also a lack of effective, specific and tolerated options for prevention.
2. Access to specialized care or migraine is extremely limited across country. Atogepant could be a good migraine preventive in primary care, if cost allows. Any limitation with form or criteria will lead to referrals in neurology and a significant limitation in access to care for people with a significant burden.
3. Access to different migraine treatments, both acute and preventives, vary from one province to another, in contradiction to the Canadian law that promotes equity to access to care (Canada Health Act 1984). This is a fact for triptans, onabotulinumtoxinA (drug and injection fee codes) and CGRP antibodies.

8. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict-of-interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

No.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

No.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Danny Adel Monsour, MD, FRCPC

Position: Headache Neurologist

Date: 08/12/2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Miravo (Honoraria)		X		
AbbVie (Honoraria)		X		
Lundbeck (Honoraria)	X			
Teva (Honoraria)	X			
Eli Lilly (Honoraria)		X		
Pfizer (Honoraria)	X			
Novartis (Honoraria)	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Elizabeth Leroux, MD, FRCPC

Position: Headache Neurologist, President - Canadian Headache Society

Date: 16/03/2022

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	**Check appropriate dollar range***

	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Abbvie/Allergan			X	
Eli Lilly			X	
Lin Pharmaceuticals		X		
Lundbeck			X	
McKesson		X		
Miravo		X		
Novartis			X	
Paladin Pharmaceuticals	X			
Teva			X	

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: William Kingston, MD, FRCPC, FAHS

Position: Headache Neurologist, Board member – Canadian Headache Society

Date: 16-03-2022

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Teva			x	
Novartis			x	
AbbVie/Allergan			x	

Eli Lilly			x	
Miravo		x		
Lundbeck		x		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Alexander N. Melinyshyn, BSc, MD, FRCPC (Neurology)

Position: Headache Neurologist

Date: 08 /20 /2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

Company	**Check appropriate dollar range***			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Teva (Honoraria)			X	
Lundbeck (Honoraria)			X	
Eli Lilly (Honoraria)			X	
Novartis (Honoraria)		X		
Miravo (Honoraria)		X		
AbbVie (Honoraria)			X	