Canadian Journal of Health Technologies
August 2023 Volume 3 Issue 8

CADTH Reimbursement Review

Atogepant (Qulipta)

Sponsor: AbbVie

Therapeutic area: Migraine, prevention

Clinical Review
Pharmacoeconomic Review
Stakeholder Input

Table of Contents

Clinical Review

List of Tables

List of Figures

Abbreviations

AE	adverse event
AIM-D	Activity Impairment in Migraine–Diary
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BMI	body mass index
C-SSRS	Columbia-Suicide Severity Rating Scale
CGRP	calcitonin gene–related peptide
CHS	Canadian Headache Society
CI	confidence interval
CM	chronic migraine
CrI	credible interval
DIC	deviance information criterion
ECG	electrocardiogram
EF	emotional function
EM	episodic migraine
EQ-5D-5L	5-Level EQ-5D
EU	European Union
HIT-6	6-item Headache Impact Test
HRQoL	health-related quality of life
ICC	intraclass correlation coefficient
ICHD	*International Classification of Headache Disorders*
ITT	intention to treat
IWRS	interactive web response system
LSM	least squares mean
mAb	monoclonal antibody
MAR	missing at random
MHD	monthly headache day
MID	minimal important difference
MIDAS	Migraine Disability Assessment
mITT	modified intention to treat
MMD	monthly migraine day
MMRM	mixed model of repeated measures

MSQ	Migraine-Specific Quality-of-Life Questionnaire
MUD	medication use day
NMA	network meta-analysis
NSAID	nonsteroidal anti-inflammatory drug
OR	odds ratio
PGI-S	Patient Global Impression–Severity
PGIC	Patient Global Impression of Change
PMM	pattern-mixture model
PRO	patient-reported outcome
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SE	standard error
SF-36	Short Form (36) Health Survey
SLR	systematic literature review
SOC	standard of care
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WDAE	withdrawal due to adverse event
WPAI:Migraine	Work Productivity and Activity Impairment Questionnaire: Migraine

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Table 1: Submitted for Review

Item	Description
Drug product	Atogepant (Qulipta), 10 mg, 30 mg, and 60 mg, oral tablets
Indication	The prevention of episodic migraine (< 15 migraine days per month) in adults
Reimbursement request	For the prevention of episodic migraine in adults with < 15 migraine days per month who have experienced an inadequate response, an intolerance, or a contraindication to at least 2 oral prophylactic migraine medications
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	December 22, 2022
Sponsor	AbbVie Corporation

NOC = Notice of Compliance.

Introduction

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.[1] Migraine episodes may last from 4 hours to 74 hours and can be accompanied by symptoms such as photophobia, phonophobia, nausea, and vomiting.[2] The type of migraine can be refined by the frequency of monthly migraine days (MMDs) and monthly headache days (MHDs).[1] 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).[3] In Canada (2010 to 2011), 9.6% of the population older than 18 years experienced migraine attacks; it is more common in females (13.8%) than males (5.3%).[4] In a longitudinal web-based study of migraine in the US (N = 16,789), 91.2% of patients had EM.[5] An estimated 2.5% of patients with EM transition to having chronic migraine (CM).[6] Migraine attacks are associated with missed activities at work, school, and/or home.[7] Additionally, prevalence is highest during peak productive years (i.e., aged around 30 years to 64 years), which maximizes the impact on the patient, family, and society.[7-10]

There are 2 approaches to treating migraine: management of acute attacks, and prophylaxis. These approaches can be used simultaneously. Comprehensive therapy also includes the management of lifestyle factors and triggers.[2,11] 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.[12] Preventive medications for EM include calcitonin gene–related peptide (CGRP) receptor inhibitors (e.g., galcanezumab, fremanezumab, erenumab, eptinezumab), blood pressure medications (e.g., beta-blockers such as propranolol or metoprolol; calcium channel blockers such as flunarizine or verapamil), antidepressants (e.g., amitriptyline, nortriptyline), serotonin-norepinephrine reuptake inhibitors (e.g., venlafaxine), anticonvulsants (e.g., topiramate, gabapentin, divalproex), and serotonin antagonists (e.g., pizotifen). Only topiramate and the CGRP inhibitors have been approved by Health Canada for the prevention of EM.

Atogepant (Qulipta) is a small-molecule, selective CGRP receptor antagonist that blocks the binding of the CGRP to its receptor, a neuropeptide associated with migraine pathophysiology. The Health Canada indication for atogepant is for the prevention of EM (< 15 MMDs) 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, an intolerance, or a contraindication to at least 2 oral prophylactic migraine medications, which differs from the Health Canada indication.

The objective of the current review is to perform a systematic review of the beneficial and harmful effects of atogepant 10 mg, 30 mg, or 60 mg once daily for the prevention of migraine in adults with EM (< 15 migraine days per month).

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups that responded to CADTH's call for patient input and from clinical expert(s) consulted by CADTH for the purpose of this review.

Patient Input

CADTH received a joint submission from Migraine Canada and Migraine Quebec for the review of atogepant. Both organizations 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 2 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 patients were aged between 30 years and 59 years (68%). Among the respondents to the survey, 19% experience 1 migraine day per month to 6 migraine days per month, 28% experience 8 migraine days per month to 14 migraine days per month, and 52% experience 15 migraine days or more per month (i.e., CM). In a second survey conducted by Migraine Canada, a total of 300 patients living in Canada responded. Of these respondents, 15% experience 1 migraine day per month to 6 migraine days per month, 26% experience 8 migraine days per month to 14 migraine days per month, and 59% have CM. The majority (74%) of respondents were aged between 30 years and 59 years.

Respondents to the surveys by Migraine Canada narrated 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 indicated 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. More than 20% of respondents indicated that they are on short-term 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 required counselling and/or medications in 39% of patients, and 31% and 35% of respondents felt that they were a burden to others for 16 days per month to 30 days per month and 6 days per month to 15 days per month, respectively.

Most (78%) of the survey respondents indicated that 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 that they have tried 3 to 4 preventive treatments and 5 or more preventive treatments, respectively. According to 66% of respondents, treatment discontinuation was a result of side effects associated with their preventive medication, while 25% of respondents reported that they had experienced side effects but tolerated them. Most respondents to both surveys (85% for the first survey and 73% for the second survey) indicated there is a need for a new oral daily preventive medication. From the second survey, 30% of respondents indicated they have found a preventive treatment that provides greater than 50% improvement in frequency and/or intensity of migraines with no significant side effects. Further, 25% of respondents indicated that the care they have received thus far has led to no improvement in HRQoL, while 49% of respondents reported mild improvement and 24% of respondents experienced marked improvement. Finally, 57% of respondents had not filled their prescription in the past 6 months due to cost and lack of coverage. Eight patients (2 in Canada and 6 in the US) 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% of patients reported experiencing some side effects, but these were either slight and/or improved or stopped over time.

According to all survey respondents, the most valuable outcomes for preventive medications are improvement in HRQoL, and decreases in headache intensity, frequency, and symptoms other than pain such as sensitivity to light and 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 are 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, not all patients respond to current treatments and, 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 drugs as well as preventive strategies. mAbs (fremanezumab or galcanezumab) are used following the failure of prior prophylactic migraine prevention therapy such as antidepressants, antihypertensives, or anticonvulsants. The clinical expert noted that atogepant is not a cure — rather, it 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 MMDs 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 a 50% reduction in MMDs, coupled with change in consumption

of abortive medications. The expert did note that change in MMDs 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 with headache expertise (e.g., pain clinic specialists, family medicine practitioners with 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. CHS is a scientific society of health care professionals dedicated to research, the education of residents and physicians, and the promotion of better care for patients experiencing 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 unmet needs similar to those identified by the clinical expert consulted by CADTH — notably, that current treatments are not effective for all patients (response rate of 40% to 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 and territory, particularly for triptans, onabotulinumtoxin A, 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 that its place in therapy will be determined in part by its cost; thus, could be considered before other CGRP antibodies. Moreover, the clinician group 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 a last-line treatment or used in specific circumstances such as nonresponse, intolerance, or a contraindication to, and where risks outweigh the benefits in patients of child-bearing potential 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 onabotulinumtoxin A.

Drug Program Input

The drug programs identified the following jurisdictional implementation issues: relevant comparators, considerations for the initiation of therapy, considerations for the continuation or renewal of therapy, considerations for the discontinuation of therapy, considerations for the prescribing of therapy, generalizability, and care provision. Refer to Table 4 for more details.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

A total of 3 studies were included in this review: Study 301 (ADVANCE), the CGP-MD-01 study, and Study 304 (ELEVATE). The ADVANCE and CGP-MD-01 studies were provided to CADTH 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 the ADVANCE trial were required to have a 1-year history of migraine consisting of 4 migraine days per month to 14 migraine days per month, with or without aura, and migraine onset before aged 50 years. A total of 910 patients were randomized 1:1:1:1 to atogepant 10 mg once daily (n = 222), atogepant 30 mg once daily (n = 230), atogepant 60 mg once daily (n = 235), or placebo (n = 223). The primary outcome of the ADVANCE trial was change from baseline in mean MMDs, with key secondary end points of change from baseline in MHDs, change from baseline in acute medication use days (MUDs), a 50% or greater reduction in a 3-month average of MMDs, change from baseline in the Migraine-Specific Quality-of-Life Questionnaire (MSQ) version 2.1 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 US. There were no Canadian investigative sites included. No interim analyses were conducted.

The CGP-MD-01 study was a phase II/III, double-blind RCT evaluating the safety and tolerability of 10 mg once daily, 30 mg once daily, 30 mg twice daily, 60 mg once daily, and 60 mg twice daily dosage regimens of atogepant for the prevention of EM. Included patients for the CGP-MD-01 trial were similar to those in the ADVANCE trial, though diagnosis of migraine was based on *International Classification of Headache Disorders* (ICHD) 2013. In total, 834 patients were randomized to 1 of 6 different groups in a 2:1:2:1:2:1 randomization sequence of placebo (n = 186), atogepant 10 mg once daily (n = 94), atogepant 30 mg once daily (n = 185), atogepant 30 mg twice daily (n = 89), atogepant 60 mg once daily (n = 187), or atogepant 60 mg twice daily (n = 93). Only Health Canada–approved dosages are summarized in this report; thus, results for the atogepant 30 mg twice daily and atogepant 60 mg twice daily dosages are not discussed. The primary outcome of the CGP-MD-01 study was the same as the ADVANCE study: the change from baseline in mean MMDs, with 3 secondary end points of change from baseline in mean MHDs; the proportion of patients with at least a 50% reduction in mean MMDs; and the change from baseline in mean monthly acute MUDs. The CGP-MD-01 study was conducted at 78 sites in the US. 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 once daily for the prevention of migraine in adult patients with EM who have previously failed 2 classes to 4 classes of oral medications for the prophylaxis of migraine. A total of 315 patients were randomized 1:1 to atogepant 60 mg once daily (n = 157) or placebo (n = 158). The primary and key secondary outcomes of the ELEVATE study were identical to those of 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 study = 86.1% to 90.5%, CGP-MD-01 study = 82.8% to 90.7%, ELEVATE study = [redacted]), white

(ADVANCE study = 81.1% to 89.2%; CGP-MD-01 study = 71.5% to 79.2%, ELEVATE study = [redacted]), and the median age ranged from 38.5 years to 42.0 years in the ADVANCE study, 38.0 years to 40.5 years in the CGP-MD-01 study, and [redacted] years 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 the ADVANCE trial receiving prior migraine therapy, and only 25.1% to 31.2% of patients receiving prior migraine therapy in the CGP-MD-01 trial, while all patients in the ELEVATE trial received prior migraine therapy.

Efficacy Results

The primary efficacy end point of the included studies was change from baseline in MMDs to week 12. In all trials, atogepant resulted in statistically significant differences compared with placebo in the reduction of mean MMDs across the 12-week treatment period. In the ADVANCE trial, the least squares mean (LSM) difference in mean change from baseline in MMDs at 12 weeks compared to placebo was −1.21 days (95% confidence interval [CI], −1.78 to −0.64 days; P < 0.0001) for the atogepant 10 mg group, −1.38 days (95% CI, −1.94 to −0.82 days; P < 0.0001) for the atogepant 30 mg group, and −1.72 days (95% CI, −2.28 to −1.15 days; P < 0.0001) for the atogepant 60 mg group. In the CGP-MD-01 trial, the LSM difference for mean change from baseline in MMDs at 12 weeks compared to placebo was −1.15 days (95% CI, −1.93 to −0.37 days; P = 0.0039) for the atogepant 10 mg group, −0.91 days (95% CI, −1.55 to −0.27 days; P = 0.0056) for the atogepant 30 mg group, and −0.70 days (95% CI, −1.35 to −0.06 days; P = 0.0325) for the atogepant 60 mg group. In the ELEVATE trial, the LSM difference in mean change from baseline in MMDs between atogepant 60 mg once daily 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 results similar to the primary analysis, though the mean difference from placebo was higher in the subgroup of patients with 2 or more prior treatment failures, and results were consistent with those of the ELEVATE study.

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

Results for secondary outcomes of MHDs and acute MUDs were consistent with the primary analysis for all studies, demonstrating statistically significant efficacy compared to placebo. In the ADVANCE study, the LSM

difference in change from baseline in MHDs and acute MUDs compared to placebo was −1.42 days (95% CI, −2.03 to −0.81 days; P < 0.0001) and −1.31 days (95% CI, −1.81 to −0.82 days; P < 0.0001) for the atogepant 10 mg group, −1.53 days (95% CI, −2.13 to −0.92 days; P < 0.0001) and −1.33 days (95% CI, −1.82 to −0.83 days; P < 0.0001) for the atogepant 30 mg group, and −1.71 days (95% CI, −2.32 to −1.10 days; P < 0.0001) and −1.50 days (95% CI, −2.00 to −1.01 days; P < 0.0001) for the atogepant 60 mg group, respectively. In the CGP-MD-01 study, the LSM difference in change from baseline in MHDs and acute MUDs compared to placebo was −1.38 days (95% CI, −2.23 to −0.54 days; P = 0.0014) and −1.30 days (95% CI, −1.99 to −0.60 days; P = 0.0002) for the atogepant 10 mg group, −1.24 days (95% CI, −1.94 to −0.55 days; P = 0.0005) and −1.44 days (95% CI, −2.01 to −0.87 days; P < 0.0001) for the atogepant 30 mg group, and −0.94 days (95% CI, −1.64 to −0.24 days; P = 0.0087) and −1.11 days (95% CI, −1.68 to −0.54 days; P = 0.0001) for the atogepant 60 mg group, respectively. In the ELEVATE study, the LSM difference in change from baseline in MHDs and acute MUDs compared to placebo was [redacted], respectively.

Change from baseline at week 12 in the MSQ version 2.1 role function-restrictive domain score was a key secondary end point of the ADVANCE and ELEVATE studies. In the ADVANCE study, the LSM difference in change from baseline versus placebo was statistically significant in favour of atogepant with a mean difference of 9.90 points (95% CI, 5.45 points to 14.36 points; P < 0.0001) for the atogepant 10 mg group, 10.08 points (95% CI, 5.71 points to 14.46 points; P < 0.0001) for the atogepant 30 mg group, and 10.80 points (95% CI, 6.42 points to 15.18 points; P < 0.0001) for the atogepant 60 mg group. In the ELEVATE study, the LSM difference in change from baseline versus placebo was [redacted].

Change from baseline in the 6-item Headache Impact Test (HIT-6) total score was an additional efficacy outcome end point of the ADVANCE, CGP-MD-01, and ELEVATE studies. In the ADVANCE study, the LSM difference change from baseline in the HIT-6 total score compared to placebo at week 12 was [redacted] for the atogepant 10 mg group, [redacted] for the atogepant 30 mg group, and [redacted] for the atogepant 60 mg group. 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 group ([redacted]), 30 mg group ([redacted]), and 60 mg group ([redacted]) compared to placebo ([redacted]). In study CGP-MD-01, the LSM difference change from baseline in HIT-6 scores was greater for all atogepant doses compared to placebo at all time points. Over 12 weeks, the LSM difference versus placebo was [redacted] for the atogepant 10 mg group, [redacted] for the atogepant 30 mg group, and [redacted] for the atogepant 60 mg group. In the ELEVATE study, the LSM difference change from baseline in HIT-6 scores was [redacted] in favour of the atogepant 60 mg once daily group 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 1 TEAE experienced by 52.9%, 52.2%, 53.7%, and 56.8% of patients with the atogepant 10 mg group, the atogepant 30 mg group, the atogepant

60 mg group, and the placebo group, respectively, in the ADVANCE study; 65.6%, 62.8%, 57.5%, and 49.5% of patients with the atogepant 10 mg group, the atogepant 30 mg group, the atogepant 60 mg group, and the placebo group, respectively, in the CGP-MD-01 study; and [redacted] of patients in the atogepant 60 mg and placebo groups, respectively, in the ELEVATE study. The most frequently reported TEAEs in the ADVANCE study 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 group, the atogepant 30 mg group, the atogepant 60 mg group, and the placebo group, respectively. The most frequently reported TEAEs in the CGP-MD-01 study were [redacted] 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 the atogepant 10 mg group, the atogepant 30 mg group, the atogepant 60 mg group, and the placebo group, 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 the ADVANCE, CGP-MD-01, and ELEVATE trials were infrequent, occurring in only 2 (0.9%) patients in the atogepant 10 mg and placebo groups in the ADVANCE study, and | SAEs occurring in 7 patients in the CGP-MD-01 study (1 [1.1%] patient with the atogepant 10 mg group, 2 [1.1%] patients with the atogepant 30 mg group, 2 [1.1%] patients with the atogepant 60 mg once daily group, and 2 [1.1%] patients with the placebo group), and in 4 [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%) atogepant-treated patients to 9 (4.1%) atogepant-treated patients and 6 (2.7%) patients in the placebo group. In the CGP-MD-01 study, WDAEs were more common in the atogepant groups (4.3%, 6.0%, and 3.2% for the atogepant 10 mg group, the atogepant 30 mg group, and the atogepant 60 mg group, respectively) than in the placebo group (2.7%). In the ELEVATE study, [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 behaviour 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 the CGP-MD-01 trial, no patients reported suicidal behaviour during the study; however, 1 patient in the placebo group reported suicidal ideation limited to a “wish to be dead” during the double-blind treatment period. In the ELEVATE study, [redacted] patients in the atogepant and placebo groups reported suicidal behaviours during the study, respectively.

Table 2: Summary of Key Results From Pivotal and Protocol-Selected Studies

Outcome	ADVANCE study				CGP-MD-01 study				ELEVATE study	
	Atogepant 10 mg q.d. (N = 214)	Atogepant 30 mg q.d. (N = 223)	Atogepant 60 mg q.d. (N = 222)	PBO (N = 214)	Atogepant 10 mg q.d. (N = 92)	Atogepant 30 mg q.d. (N = 182)	Atogepant 60 mg q.d. (N = 177)	PBO (N = 178)	Atogepant 60 mg q.d. (N = [redacted])	PBO (N = [redacted])
Migraine frequency										
CFB in MMDs										
LSM CFB (SE)	−3.69 (0.210)	−3.86 (0.206)	−4.20 (0.206)	2.48 (0.210)	−4.00 (0.32)	−3.76 (0.23)	−3.55 (0.23)	−2.85 (0.23)	[redacted]	[redacted]
LSM difference vs. PBO (SE)	−1.21 (0.291)	−1.38 (0.287)	−1.72 (0.288)	Reference	−1.15 (0.40)	−0.91 (0.33)	−0.70 (0.33)	Reference	[redacted]	Reference
95% CI for difference vs. PBO	−1.78 to −0.64	−1.94 to −0.82	−2.28 to −1.15	Reference	−1.93 to −0.37	−1.55 to −0.27	−1.35 to −0.06	Reference	[redacted]	Reference
P value	< 0.0001	< 0.0001	< 0.0001	Reference	0.0039	0.0056	0.0325	Reference	[redacted]	Reference
50% responders										
Responders, n (%)	119 (55.6)	131 (58.7)	135 (60.8)	62 (29.0)	53 (57.6)	97 (53.3)	92 (52.0)	72 (40.4)	[redacted]	[redacted]
OR[a] vs. PBO (95% CI)[b]	3.06 (2.05 to 4.56)	3.53 (2.37 to 5.26)	3.82 (2.56 to 5.71)	Reference	1.50 (0.98 to 2.31)	1.46 (1.02 to 2.08)	1.42 (1.00 to 2.03)	Reference	[redacted]	Reference
P value	< 0.0001	< 0.0001	< 0.0001	Reference	0.0617	0.0369	0.0512	Reference	[redacted]	Reference
CFB in MHDs										
LSM CFB (SE)	−3.94 (0.225)	−4.04 (0.221)	−4.23 (0.221)	−2.52 (0.225)	−4.31 (0.35)	−4.17 (0.25)	−3.86 (0.25)	−2.93 (0.25)	[redacted]	[redacted]
LSM difference vs. PBO (SE)	−1.42 (0.311)	−1.53 (0.307)	−1.71 (0.309)	Reference	−1.38 (0.43)	−1.24 (0.36)	−0.94 (0.36)	Reference	[redacted]	Reference

Outcome	ADVANCE study				CGP-MD-01 study				ELEVATE study	
	Atogepant 10 mg q.d. (N = 214)	Atogepant 30 mg q.d. (N = 223)	Atogepant 60 mg q.d. (N = 222)	PBO (N = 214)	Atogepant 10 mg q.d. (N = 92)	Atogepant 30 mg q.d. (N = 182)	Atogepant 60 mg q.d. (N = 177)	PBO (N = 178)	Atogepant 60 mg q.d. (N = [redacted])	PBO (N = [redacted])
95% CI for difference vs. PBO	−2.03 to −0.81	−2.13 to −0.92	−2.32 to −1.10	Reference	−2.23 to −0.54	−1.94 to −0.55	−1.64 to −0.24	Reference	[redacted]	Reference
P value	< 0.0001	< 0.0001	< 0.0001	Reference	0.0014	0.0005	0.0087	Reference	[redacted]	Reference
CFB in acute MUDs										
LSM CFB (SE)	−3.66 (0.183)	−3.68 (0.180)	−3.85 (0.180)	−2.35 (0.184)	−3.71 (0.29)	−3.86 (0.20)	−3.53 (0.21)	−2.42 (0.21)	[redacted]	[redacted]
LSM difference vs. PBO (SE)	−1.31 (0.254)	−1.33 (0.251)	−1.50 (0.252)	Reference	−1.30 (0.35)	−1.44 (0.29)	−1.11 (0.29)	Reference	[redacted]	Reference
95% CI for difference vs. PBO	−1.81 to −0.82	−1.82 to −0.83	−2.00 to −1.01	Reference	−1.99 to −0.60	−2.01 to −0.87	−1.68 to −0.54	Reference	[redacted]	Reference
P value	< 0.0001	< 0.0001	< 0.0001	Reference	0.0002	< 0.0001	0.0001	Reference	[redacted]	Reference
CFB in MSQ version 2.1, role function-restrictive domain score										
LSM (SE)	30.35 (1.639)	30.53 (1.593)	31.25 (1.591)	20.45 (1.617)	NR	NR	NR	NR	[redacted]	[redacted]
LSM difference vs. PBO (SE)	9.90 (2.270)	10.08 (2.229)	10.80 (2.231)	Reference	NR	NR	NR	NR	[redacted]	Reference
95% CI for difference vs. PBO	5.45 to 14.36	5.71 to 14.46	6.42 to 15.18	Reference	NR	NR	NR	NR	[redacted]	Reference
P value	< 0.0001	< 0.0001	< 0.0001	Reference	NR	NR	NR	NR	[redacted]	Reference
HIT-6 total score										
LSM (SE)	−8.41 (0.545)	−8.09 (0.528)	−9.20 (0.529)	−5.24 (0.537)	−8.0 (0.9)	−9.1 (0.6)	−7.6 (0.6)	−6.3 (0.6)	[redacted]	[redacted]

Outcome	ADVANCE study				CGP-MD-01 study				ELEVATE study	
	Atogepant 10 mg q.d. (N = 214)	Atogepant 30 mg q.d. (N = 223)	Atogepant 60 mg q.d. (N = 222)	PBO (N = 214)	Atogepant 10 mg q.d. (N = 92)	Atogepant 30 mg q.d. (N = 182)	Atogepant 60 mg q.d. (N = 177)	PBO (N = 178)	Atogepant 60 mg q.d. (N = [redacted])	PBO (N = [redacted])
LSM difference vs. PBO (SE)	−3.17 (0.755)	−2.85 (0.740)	−3.96 (0.743)	Reference	−1.7 (1.1)	−2.8 (0.9)	−1.3 (0.9)	Reference	[redacted]	Reference
95% CI for difference vs. PBO	−4.66 to −1.69	−4.30 to −1.40	−5.42 to −2.50	Reference	−3.8 to 0.4	−4.6 to −1.0	−3.0 to 0.5	Reference	[redacted]	Reference
P value[c]	< 0.0001	0.0001	< 0.0001	Reference	0.1152	0.0021	0.1545	Reference	[redacted]	Reference
Harms, n (%) (safety population)										
AEs	117 (52.9)	119 (52.2)	124 (53.7)	126 (56.8)	61 (65.6)	115 (62.8)	107 (57.5)	92 (49.5)	[redacted]	[redacted]
SAEs	2 (0.9)	0 (0.0)	0 (0.0)	2 (0.9)	1 (1.1)	2 (1.1)	2 (1.1)	2 (1.1)	[redacted]	[redacted]
WDAEs	9 (4.1)	4 (1.8)	6 (2.6)	6 (2.7)	4 (4.3)	11 (6.0)	6 (3.2)	5 (2.7)	[redacted]	[redacted]
Notable harms, n (%)										
Constipation	17 (7.7)	16 (7.0)	16 (6.9)	1 (0.5)	2 (2.2)	10 (5.5)	9 (4.8)	4 (2.2)	[redacted]	[redacted]
Suicidal ideation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	[redacted]	[redacted]
ALT or AST ≥ 3 × ULN[d]	2 (0.9)	2 (0.9)	1 (0.4)	4 (1.8)	2 of 92 (2.2)	1 of 180 (0.6)	3 of 181 (1.7)	3 of 179 (1.7)[e]	[redacted]	[redacted]
Hy's law cases	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	[redacted]	[redacted]

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CFB = change from baseline; CI = confidence interval; HIT-6 = 6-item Headache Impact Test; LSM = least squares mean; MHD = monthly headache day; MMD = monthly migraine day; MUD = medication use day; NR = not reported; OR = odds ratio; PBO = placebo; q.d. = once daily; SAE = serious adverse event; SE = standard error; ULN = upper limit of normal; vs. = versus; WDAE = withdrawal due to adverse event.

[a]The OR (95% CI) and P value are based on logistic regression with treatment group, baseline value, and prior exposure (yes or no) to a migraine prevention medication with proven efficacy as explanatory variables.

[b]Analyses were based on a generalized linear mixed model of repeated measures. The model included treatment group and visit as fixed effects, the baseline value as a covariate, and treatment-group-by-visit and baseline-by-visit as interaction terms, with an unstructured covariance matrix. P values were from the test between the atogepant dose group and the PBO group.

[c]Not adjusted for multiplicity.

[d]Values were n of N1, where N1 = the number of patients with at least 1 nonmissing postbaseline value.

[e]One of these 3 patients had elevated liver function values that were not treatment-emergent values related to pre-existing rhabdomyolysis; as a result, this case was not subject to adjudication.

Sources: ADVANCE Clinical Study Report,[13] CGP-MD-01 Clinical Study Report,[14] and ELEVATE Clinical Study Report.[15]

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 screening failures in the ADVANCE, CGP-MD-01, and ELEVATE studies (60%, 53%, and [redacted], respectively), 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 group; 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 what effect this would have had on the results. Sensitivity analyses to account for missing data were conducted on the primary end point 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 end point and the 6 key secondary end points were controlled for multiplicity using the overall familywise error rate at the 0.05 level. One prespecified subgroup analysis of the ADVANCE study was conducted; it included patients with or without prior exposure to migraine prevention medication with proven efficacy. An additional post hoc subgroup analysis of the ADVANCE study was submitted to CADTH by request for patients in the ADVANCE study with 1 or more prior migraine prevention treatment failures, and with 2 or more 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 were 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 comprised 3 prespecified subgroups, including 2 prespecified subgroups 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 if they had had previous exposure to CGRP mAbs. Conversely, the ELEVATE study enrolled patients who 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 the ADVANCE trial compared to 25.1% to 31.2% of patients in the CGP-MD-01 study, and [redacted] of patients in the ELEVATE trial. As noted in the post hoc subgroup analysis for the ADVANCE trial, only 119 patients had failed 2 or more prior preventive 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. As a result, the trials 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 at baseline, were observed 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 a history of 4 migraine days per month to 14 migraine days per month on average in the 3 months before the first visit. Hence, all studies excluded patients with 1 migraine day per month to 3 migraine days per month, and it is uncertain if results from the ADVANCE, CGP-MD-01, and ELEVATE trials 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 network meta-analysis (NMA) included 2 analysis scenarios from the original NMA that had been updated to reflect the following 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 2 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 NMA. Fixed and random effects were selected. 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, and the variability in the Japanese studies. 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 a 50% response in MMDs, between-treatment change from baseline in MMDs, and between-treatment change from baseline in monthly migraine MUDs. Safety outcomes included all-cause discontinuation and TEAEs.

Efficacy Results

In analysis scenario 2, [redacted].

In analysis scenario 4, [redacted].

Harms Results

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 patients to 137 patients per treatment group, with the ADVANCE trial including only 122 patients in total in the subgroup of 2 or more treatment failures; this limits the precision and generalizability of the treatment effect. The 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 weeks to 56 weeks. For the primary efficacy end point, the time of assessment of 1 week to 12 weeks was chosen, as this was the time frame of the primary efficacy end point in the ADVANCE study. However, other included studies varied on when change from baseline was assessed.

Clinical heterogeneity was assessed visually for baseline characteristics including age, sex, race or ethnicity, body mass index (BMI), baseline MMDs, and baseline MHDs, as well as for time points and end point 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 regard to race or ethnicity, 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 centre 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. This comprised 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. 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, [redacted] 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 [redacted] for atogepant, whereby the atogepant 10 mg dose demonstrated the [redacted], while the atogepant 60 mg dose [redacted] 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 have been 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 EM for up to 40 weeks of treatment. Patients were eligible to enrol in Study 309 if they completed the lead-in ADVANCE study. A total of 685 patients received at least 1 dosage 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 (standard deviation [SD] = 12.3) years. Most (43.9%) patients were diagnosed with migraine without aura and the mean duration of the migraine disorder was 21.6 (SD = 12.8) years. The mean number of MMDs and MHDs 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 EM for up to 52 weeks of treatment. Patients were eligible to enrol in Study 302 if they had completed the lead-in study CGP-MD-01, and new patients who met the eligibility criteria were also eligible to enrol. 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 group only served to provide context for interpreting the safety results of atogepant. A total of 543 patients and 196 patients received at least 1 dosage of atogepant 60 mg once daily and SOC, respectively. The mean age of patients was 42.5 (SD = 12.0) years in the atogepant group and 41.1 (SD = 12.1) years in the SOC group. Most ([redacted] in the atogepant and SOC groups, respectively) patients were diagnosed with migraine without aura. The mean duration of the migraine disorder was [redacted] (SD = [redacted]) years and [redacted] (SD = 12.4) years in the atogepant and SOC groups, respectively. The mean number of MMDs and MHDs in the last 3 months were 7.3 (SD = 2.6) days and [redacted], respectively, in the atogepant group. The mean number of

MMDs and MHDs in the last 3 months were [redacted], respectively, in the SOC group. A total of 373 (68.3%) patients and 136 (68.7%) patients completed the open-label treatment period in the atogepant and SOC groups, 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 group only. The mean number of MMDs decreased at week 49 to week 52 from baseline; mean MMDs at baseline was 7.28 (SD = 2.70) days and LSM change was −5.19 (standard error [SE] = 0.16; 95% CI, −5.50 to −4.87). The proportion of patients who achieved a reduction in 50% or more, 75% or more, or 100% in MMDs at week 49 to week 52 was [redacted] respectively. The mean number of MHDs decreased at week 49 to week 52 from baseline; mean MHDs at baseline was 8.33 (SD = 2.97) days and LSM change was [redacted]. At week 49 to week 52, the LSM change from baseline in the number of monthly moderate to severe headache days and severe headache days was [redacted], respectively. The LSM change from baseline in the number of monthly cumulative headache hours was [redacted] hours at week 49 to week 52. The mean number of MUDs decreased at week 49 to week 52 from baseline; mean MUDs at baseline was [redacted] and LSM change was [redacted]. The LSM change from baseline in the number of monthly triptan use days was [redacted] days at week 49 to week 52. The LSM change from baseline in the MSQ version 2.1 role function-restrictive domain score was [redacted] at week 52. The LSM change from baseline in the AIM-D performance of daily activities domain score was [redacted] at week 49 to week 52. The LSM change from baseline in the AIM-D physical impairment domain score was [redacted] at week 49 to week 52.

Harms Results

In Study 309, TEAEs were reported in 428 (62.5%) patients during open-label treatment, including upper respiratory tract infection (5.5%) and urinary tract infection (5.3%). SAEs were reported in 23 (3.4%) patients and no deaths were reported during the open-label treatment. Premature discontinuation due to at least 1 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 ALT or AST values greater than or equal to 3 times the upper limit of normal (ULN) value. No Hy's law cases or 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 group. SAEs were reported in 24 (4.4%) patients 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 group (no deaths were reported in the SOC group). Premature discontinuation due to at least 1 TEAE was reported in 31 (5.7%) patients and 5 (2.6%) patients during the open-label treatment with atogepant and SOC, respectively. Notable harms identified in the atogepant group included constipation in 39 (7.2%) patients, suicidal ideation in 3 (0.6%) patients, and elevations in ALT or AST values that were greater than or equal to 3 times the ULN 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, could have biased the reporting of end points, particularly any subjective measures included in the safety parameters (and efficacy parameters in Study 302) 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 to have not experienced any adverse events (AEs) that could indicate an unacceptable safety risk per investigator judgment, the resultant population could have been more tolerant of atogepant, leading to an underreporting of AEs, and were also more likely to have benefits of atogepant, overestimating the efficacy of treatment as those patients without benefit were unlikely to continue. In the absence of an active comparator or placebo group, the interpretation of the results was limited. This was compounded using descriptive statistics only.

The limitations could also be applied to Study 302. The enrolment of new patients without prior experience with atogepant and patients who had completed a lead-in study further limited the interpretation of the results. It should be noted that the SOC treatment group only served to provide context for interpreting the safety results of atogepant. The oral migraine preventives were prescribed in a manner that reflected routine clinical practice. A flexible treatment paradigm was used that permitted the discontinuation of, or switching from, 1 drug to an alternative for migraine prevention as needed and per investigator judgment. Regardless of the type of change made, patients in the SOC group were permitted to continue with the study. Thus, AE reporting in the SOC group could have been influenced by investigator choice as the AEs could have differed based on the oral migraine preventive selected.

Conclusions

Three randomized, double-blind studies were included in this review: the ADVANCE, CGP-MD-01, and ELEVATE studies. However, only the population from the ELEVATE study reflected the reimbursement request for patients who have experienced an inadequate response, an intolerance, or a contraindication to at least 2 oral prophylactic migraine medications. In the ADVANCE, CGP-MD-01, and ELEVATE studies, atogepant demonstrated a statistically significant change from baseline compared to placebo in mean MMDs, MHDs, and acute MUDs. Atogepant was also associated with clinically meaningful 50% reductions in average 3-month MMDs. Results for other key secondary end points, including change from baseline in MSQ version 2.1 and AIM-D, were generally in line with the primary outcome. Together, the migraine frequency, HRQoL, and patient-reported efficacy outcomes were appropriate and reflective of clinical practice in Canada; however, there was generally a high placebo response in these outcomes, limiting the interpretability and generalizability of the efficacy of atogepant. Overall, treatment with atogepant was well tolerated over the study period and did not appear to be associated with more TEAEs or SAEs compared to placebo. Known AEs for CGRP inhibitors, including constipation, were more frequent in the atogepant groups; however, there were no concerns.

The sponsor submitted a series of NMAs evaluating atogepant and appropriate comparators in the treatment of EM. However, the results of the indirect evidence on the comparative efficacy and safety of atogepant and relevant treatments was inconclusive, given that there was no difference between atogepant and other active

comparators for important outcomes of interest, including the reduction of migraine frequency, and the results from the ELEVATE study were not included in the analysis.

Overall, the available evidence suggests that treatment with atogepant provides an additional treatment option for patients with EM, reducing the frequency and intensity of migraine headaches compared to placebo, and provides a meaningful clinical response in patients with EM. However, it is worth noting that patients enrolled in the studies had to have a history of 4 migraine days per month to 14 migraine days per month on average in the 3 months before the first visit; hence, all studies excluded patients with 1 migraine day per month to 3 migraine days per month, and it is uncertain if results from the ADVANCE, CGP-MD-01, and ELEVATE studies are generalizable to patients with fewer than 4 migraine days per month.

Introduction

Disease 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.[1] Migraine episodes may last from 4 hours to 74 hours and can be accompanied by symptoms such as photophobia, phonophobia, nausea, and vomiting.[2] The type of migraine can be refined by the frequency of monthly MMDs and MHDs.[1] A diagnosis of migraine is made using a history, a physical examination, and a neurologic examination.[2]

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 EM.[3]

In Canada (2010 to 2011), 9.6% of the population older than 18 years experienced migraine attacks, with more females (13.8%) than males (5.3%) having had migraine.[4] In a longitudinal web-based panel study of migraine in the US (N = 16,789), 91.2% of patients had EM.[5] An estimated 2.5% of patients with EM transition to having CM.[6]

Among those patients who experienced migraine in Canada (aged ≥ 15 years, 2011), 38.2% reported that migraine at least moderately affected their life and 25.5% reported that the pain prevented them from activities.[7] In a cross-sectional, web-based observational survey of patients with migraine (N = 8,726), it was found that nearly half of all respondents reported moderate or severe disability, with more headache days per month being associated with more severe disability.[16] Among the respondents, 5.7% had CM and 94.3% had EM.[16] Patients with CM reported longer, more painful headaches and more comorbidities than those with EM.[16] Additionally, patients with CM reported worse headache-related disability compared with those with EM, as measured by the Migraine Disability Assessment (MIDAS), which is a validated tool that measures disability in patients with migraine.[16] Migraine attacks are often disabling. Headache disorders are among the 3 highest causes of years lived with a disability worldwide (1990 to 2017), with migraine accounting for 47,245.4 years lived with a disability in 2017.[17]

Migraine attacks are associated with missed activities at work, school, and/or home.[7] Additionally, prevalence is highest during peak productive years (i.e., aged around 30 years to 64 years); this maximizes the impact on the patient, family, and society.[7-10] Migraine reduces productivity, leading to missed work days and substantial economic costs. Loss of productivity accounts for up to 70% of total migraine-related annual costs.[18] In Canada (2011), 34% of individuals with migraine reported limitations in job opportunities due to their disease, 36% of those currently employed reported missing at least 1 day of work in the past 3 months due to migraine, and 18% who had previously been employed reported that they had changed their work activities (hours or type of work, or had stopped work) for 3 months or longer due to migraine.[7]

Standards of Therapy

There are 2 approaches to treating migraine: the management of acute attacks, and prophylaxis. These approaches can be used simultaneously. Comprehensive migraine therapy also includes the management of lifestyle factors and triggers.[2,11] The goals of migraine treatments are to relieve pain, restore function, improve HRQoL, reduce headache frequency, and prevent the progression of EM to CM.[12] CHS has guidelines for the acute treatment of migraine and for preventing attacks.[2]

Migraine prophylaxis is an important part of the overall approach for a proportion of individuals with migraine. Preventive medications for EM include CGRP receptor inhibitors (galcanezumab, fremanezumab, erenumab, and eptinezumab), blood pressure medications (e.g., beta-blockers such as propranolol or metoprolol; calcium channel blockers such as flunarizine or verapamil), antidepressants (e.g., amitriptyline, nortriptyline), serotonin-norepinephrine reuptake inhibitors (e.g., venlafaxine), anticonvulsants (e.g., topiramate, gabapentin, divalproex), and serotonin antagonist (e.g., pizotifen). Only topiramate and the CGRP inhibitors have been approved by Health Canada for the prevention of EM. Of patients with migraine who have received preventive medications, 87% have had an inadequate response to 2 or more preventive therapies.[19]

Drug

Atogepant (Qulipta) is a small-molecule, selective CGRP receptor antagonist that blocks the binding of the CGRP to its receptor, a neuropeptide associated with migraine pathophysiology. Atogepant is available as an oral tablet. The recommended dosage of atogepant is 10 mg, 30 mg, or 60 mg orally once daily to a maximum of 60 mg per day.[20]

The Health Canada indication for atogepant is for the prevention of EM (< 15 migraine days per month) in adults. The Health Canada Notice of Compliance was granted on December 22, 2022. The US FDA had approved atogepant for the preventive treatment of EM in adults on September 28, 2021.

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, an intolerance, or a contraindication to at least 2 oral prophylactic migraine medications; this differs from the Health Canada indication. Atogepant has not previously been reviewed by CADTH.

Table 3: Key Characteristics of Atogepant, Galcanezumab, Fremanezumab, Beta-Blockers, Anticonvulsants, TCAs and SNRIs, CCBs, ACE Inhibitors and ARBs, and Pizotifen

Drug name	Mechanism of action	Indication[a]	Route of administration	Recommended dosage	Serious adverse effects or safety issues	Other
Atogepant	Blocks the binding of the CGRP to its receptor	The prevention of EM (< 15 migraine days per month) in adults	Oral	10 mg, 30 mg, 60 mg orally once daily	None	NA
Galcanezumab	Binds to CGRP ligand	The prevention of migraine in adults who have at least 4 migraine days per month	SC	240 mg loading dose followed by 120 mg monthly	Hypersensitivity reactions	NA
Fremanezumab	Binds to CGRP ligand	The prevention of migraine in patients who have at least 4 migraine days monthly	SC	675 mg quarterly, 675 mg followed by 225 mg monthly (patients with CM), or 225 mg monthly (patients with EM)	Hypersensitivity reactions	NA
Beta-blockers	Beta1-receptor antagonists	• Migraine prophylaxis: Propranolol, timolol • Others: None for migraine • Various cardiovascular indications	Oral	Varies by drug	Rebound syndrome Bronchospasm	Drugs: Propranolol, timolol, nadolol, metoprolol
Anticonvulsants	Multiple mechanisms of action	• Topiramate: Migraine prophylaxis • Topiramate or others: Epilepsy	Oral	Varies by drug	Valproic acid: Hepatotoxicity	Drugs: Topiramate, gabapentin, valproic acid
TCAs and SNRIs	Inhibit reuptake of serotonin, norepinephrine	• None for migraine • Depression • Anxiety	Oral	Varies by drug	Hypertension Serotonin syndrome Conditions that may be exacerbated by anticholinergic effects (TCA mainly)	Drugs: Amitriptyline, nortriptyline, venlafaxine

Drug name	Mechanism of action	Indication[a]	Route of administration	Recommended dosage	Serious adverse effects or safety issues	Other
CCBs	Block L-type calcium channels	• Flunarizine: Migraine prophylaxis • Others: None for migraine • Various cardiovascular indications	Oral	Varies by drug	Heart block	Drugs: Flunarizine, verapamil
ACE inhibitors and ARBs	Inhibit effects of angiotensin II	• None for migraine • Hypertension • Heart failure	Oral	Varies by drug	Angioedema	Drugs: Lisinopril, candesartan
Pizotifen	Blocks serotonin-2 receptors, histamine H_1 receptors	Prevention of migraine: Recommended for those with ≥ 3 attacks monthly and who fail to respond to symptomatic treatment and have reduced QoL	Oral	1 mg per day to 6 mg per day, up to 3 mg in a single dose	Conditions that may be exacerbated by anticholinergic effects	NA

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; CGRP = calcitonin gene–related peptide; CM = chronic migraine; EM = episodic migraine; NA = not applicable; QoL = quality of life; SC = subcutaneous; SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant.

[a]Health Canada–approved indication.

Sources: Atogepant product monograph[20] and CADTH clinical review of galcanezumab.[21]

Stakeholder Perspectives

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups.

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, and both advocate for optimal care for patients experiencing migraines and support research to find cures to improve HRQoL. This joint submission was supported by the Women's Health Coalition of Alberta Society, a network that is committed to empowering individuals to learn, engage, and speak openly to address barriers, gaps, practices, and unconscious bias that impact women's menstrual, reproductive, and sexual health.

The information used to inform the submission was based on 2 online surveys conducted in the late fall of 2021 and mid-January 2022, as well as direct input from 8 patients (2 Canadians and 6 Americans) with experience with atogepant. A total of 1,165 patients and caregivers responded to the first survey conducted by Migraine Canada, the majority of whom were aged between 30 years and 59 years (68%). Among the respondents to the survey, 19% live with 1 migraine day per month to 6 migraine days per month, 28% live with 8 migraine days per month to 14 migraine days per month, and 52% live with 15 or more migraine days per month (i.e., CM). In a second survey conducted by Migraine Canada, a total of 300 patients living with migraine in Canada responded. Of these respondents, 15% live with 1 migraine day per month to 6 migraine days per month, 26% live with 8 migraine days per month to 14 migraine days per month, and 59% live with CM. The majority (74%) of respondents were aged between 30 years and 59 years.

Respondents to the surveys by Migraine Canada narrated how living with migraine has impacted their HRQoL and sleep, mental health, social relationships, and day-to-day functioning at work and school. The majority (73%) of respondents indicated 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. More than 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 required counselling and/or medications in 39% of patients, and 31% and 35% of respondents felt they were a burden to others for 16 days per month to 30 days per month and 6 days per month 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 preventive treatments and 5 or more preventive treatments, respectively. According to 66% of respondents, treatment discontinuation was a result of side effects associated with their preventive medication, while 25% of respondents reported they had experienced side effects but tolerated them. Most respondents to both surveys (85% for the first survey and 73% for the second survey) indicated there is a need for a new oral daily preventive medication. From the second

survey, 30% of respondents indicated they have found a preventive treatment that provides greater than 50% improvement in frequency and/or intensity of migraines with no significant side effects. Further, 25% of respondents indicated that the care they have received thus far has led to no improvement in HRQoL, while 49% of respondents reported mild improvement and 24% of respondents experienced marked improvement. Finally, 57% of respondents had not filled their prescription in the past 6 months due to cost and lack of coverage. Eight 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% of patients reported experiencing some side effects but these were either slight and/or improved or stopped over time.

According to all survey respondents, the most valuable outcomes for preventive medications are improvement in HRQoL, and decreases in headache intensity, headache frequency, and symptoms other than pain such as sensitivity to light and sound, nausea, and brain fog. Overall, Canadians 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.

A copy of the patient input is presented at the end of this report.

Clinician Input

Input From Clinical Experts Consulted by CADTH

All CADTH review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, providing guidance on the potential place in therapy). The following input was provided by 1 clinical specialist with expertise in the diagnosis and management of EM.

Unmet Needs

The clinical expert consulted by CADTH emphasized that currently available treatments for patients with migraine have several issues: notably, not all patients respond to current treatments and, in the case of mAbs for migraine prevention, patients become refractory to treatment, requiring a change of treatment. Additionally, the expert highlighted that some current migraine prevention therapies have a prolonged half-life, making them difficult to use with people of child-bearing potential who may wish to conceive.

Place in Therapy

The clinical expert consulted by CADTH noted that current migraine therapies provide significant relief and functional improvements compared to historical treatment methods, despite the fact that some patients do not benefit from available treatment options. Currently, the initiation of migraine treatment begins with the identification of triggers and subsequent lifestyle modifications. Early on, migraine attacks are treated with abortive drugs as well as preventive strategies, including the use of riboflavin, antidepressants, antihypertensives, and anticonvulsants. The goal of these preventive medications is to prevent the patient

from developing CM. mAbs (fremanezumab or galcanezumab) are used following the failure of prior prophylactic migraine prevention therapy. The clinical expert noted that atogepant would be used following the mAbs, as the mechanism of action of atogepant does not lead to a cure — rather, it reduces symptomatic events of EM.

Patient Population

The expert noted that at diagnosis, it is important for patients to understand their migraine (headache and interictal symptoms) and comorbid conditions (anxiety, depression, muscular pain syndromes); their physician should also reinforce the importance of a headache journal in assessment and follow-up. The expert also stated the importance of understanding medication overuse, though this may not be as much of an issue in patients with EM compared to patients with CM.

The clinical expert noted that identifying patients who would have better response to atogepant was unlikely. The expert noted that patients with higher migraine headache frequency and major functional disability are more likely to receive atogepant, though it likely would not be considered the first choice for most patients. It was highlighted that atogepant would likely be considered in patients who have not responded to or are intolerant of anti-CGRP mAbs or who are considering conceiving. The expert also noted that atogepant could be considered in patients who meet ICHD-3 criteria for CM but who have fewer than 15 MMDs. Conversely, the expert noted that patients with a history of poor compliance would not be suitable candidates for atogepant, mainly due to the daily dosing regimen.

Assessing Response to Treatment

In general, outcomes used in clinical practice reflect those typically used in clinical trials. The clinical expert noted that clinicians concentrate on what can be quickly quantified and understood from similar metrics used in studies, with a 50% reduction in MMDs, coupled with a change in consumption of abortive medications, used to demonstrate to third-party payers that a medication is working. The expert noted that HRQoL is important; however, it is not routinely quantified in clinical practice. The expert also noted that change in MMDs 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.

Discontinuing Treatment

The clinical expert stated that failure to reach a 50% reduction in MMDs, without any other improvements in HRQoL is the main reason to discontinue treatment with atogepant. Additionally, intolerable side effects or poor compliance with the medication are also considerable factors.

Prescribing Conditions

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

Additional Considerations

The clinical expert noted that the reimbursement request is not recognized by current international guidelines (ICHD-3), as only CM has a defined threshold, while EM represents patients who do not meet the

requirements for CM. The expert highlighted that the issues with this nomenclature may result in differing classifications of patients based on their migraine type.

Clinician Group Input

This section was prepared by CADTH staff based on the input provided by clinician groups.

One clinician group, CHS, consisting of 5 headache specialists, provided input to CADTH for the review of atogepant. CHS is a scientific society of health care professionals dedicated to research, the education of residents and physicians, and the promotion of better care for patients experiencing 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 unmet needs similar to those identified by the clinical expert consulted by CADTH — notably, that current treatments are not effective for all patients (a response rate of 40% to 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 and territory, particularly for triptans, onabotulinumtoxin A, 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 before other CGRP antibodies. Moreover, the clinician group 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 a last-line treatment or for use in specific circumstances such as nonresponse, intolerance, or a contraindication to, and where risks outweigh the benefits in people of child-bearing potential with other first-line treatment options (i.e., mAbs). The clinician group and clinical expert consulted by CADTH considered the potential for concurrent use of atogepant with mAbs or onabotulinumtoxin A.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's reimbursement review processes by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted by CADTH are summarized in Table 4.

Table 4: Summary of Drug Plan Input and Clinical Expert Response

Drug program implementation questions	Clinical expert response
Relevant comparators	
Atogepant was not compared to a relevant comparator drug but was compared to placebo in the pivotal clinical studies.	No response required. For CDEC consideration.
Considerations for initiation of therapy	
The following are per the CDEC recommended initiation criteria for fremanezumab: 1. The patient has a confirmed diagnosis of episodic	Given the similarities in the groups highlighted in the initiation criteria for fremanezumab, the clinical expert agreed that

Drug program implementation questions	Clinical expert response
migraine or chronic migraine according to the International Headache Society criteria, defined as: 1.1. episodic migraine — migraine headaches on at least 4 days per month and fewer than 15 headache days per month for more than 3 months 1.2. chronic migraine — headaches for at least 15 days per month for more than 3 months, of which at least 8 days per month are with migraine. 2. The patient has experienced an inadequate response, an intolerance, or a 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?	the initiation criteria for atogepant should be aligned with fremanezumab.
The ADVANCE study did not enrol patients younger than 18 years. Should patients aged < 18 years be treated with atogepant? The clinical studies for atogepant did not include a sufficient number of patients aged 65 years and older. Should patients aged ≥ 65 years be treated with atogepant?	The clinical expert was uncertain regarding whether prescribers would be comfortable using atogepant in patients younger than 18 years. It was noted that the upper age limit for mAbs in migraine is 70 years based on clinical trial inclusion criteria; thus, the expert expected that patients older than 65 years would be eligible to receive atogepant.
The sponsor's reimbursement request is for patients who have received at least 2 prophylactic migraine medications. Should patients be required to have had intolerance, inadequate response, or failure to at least 2 oral prophylactic migraine medications?	Patients should exhaust all options, including lifestyle management and prophylactic treatments, to ensure that patients are educated on the treatment options available to them before initiating atogepant.
If a patient has success on fremanezumab treatment, should they be transitioned to oral therapy with atogepant?	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 1 of the aforementioned reasons outlined was observed.
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 believed that atogepant could be used in patients with chronic migraine; however, they noted that other CGRP inhibitors should be used first. 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	
The 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	The clinical expert felt that renewal criteria 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

Drug program implementation questions	Clinical expert response
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?	stated that this aligns with general timelines for patient follow-up after initiation of treatment.
Considerations for discontinuation of therapy	
The 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?	The clinical expert stated that response to treatment would be observed early in migraine, and that discontinuation criteria for atogepant should be similar to fremanezumab. However, the clinical expert emphasized 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 or headache days; thus, this should be considered when discussing discontinuing treatment.
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.	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?	Given that atogepant represents a newer class of medications, with a novel mechanism of action, it should only be prescribed by physicians with experience in treating patients with migraine. 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 patients living with migraines find a treatment that works, it is difficult to get them to switch to other options. Thus, the clinical expert noted that the desire to switch is unlikely for these patients. The expert did note that nonresponders to CGRP mAbs would be candidates for switching to atogepant.
Care provision issues	
Compared to other CGRP inhibitors, atogepant is orally administered and can be initiated as outpatient therapy.	No response required. For CDEC consideration.

CDEC = CADTH Canadian Drug Expert Committee; CGRP = calcitonin gene–related peptide; ICHD = *International Classification of Headache Disorders;* mAb = monoclonal antibody.

Clinical Evidence

The clinical evidence included in the review of atogepant is presented in 3 sections. The first section, the systematic review, includes pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those studies that were selected according to an a priori protocol. The second section includes indirect evidence from the sponsor and indirect evidence selected from the literature that met the selection criteria specified in the review. The third section includes sponsor-submitted long-term extension studies and additional relevant studies that were considered to address important gaps in the evidence included in the systematic review.

Systematic Review (Pivotal and Protocol-Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of atogepant 10 mg, atogepant 30 mg, or atogepant 60 mg once daily for the prevention of migraine in adults with EM (< 15 migraine days per month).

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those meeting the selection criteria presented in Table 5. Outcomes included in the CADTH review protocol reflect outcomes considered to be important to patients, clinicians, and drug plans.

Table 5: Inclusion Criteria for the Systematic Review

Criteria	Description
Population	Adults with episodic migraine (< 15 migraine days per month) Subgroups: • Migraine days per month at baseline • Number of prior preventive migraine therapies received • Medication overuse headaches
Intervention	Atogepant (10 mg, 30 mg, or 60 mg once daily, oral tablet)
Comparator	• CGRP inhibitors (e.g., fremanezumab, galcanezumab) • Beta-blockers (e.g., propranolol, metoprolol) • Anticonvulsants (e.g., divalproex) or antiepileptics (e.g., topiramate) • Antidepressants (e.g., amitriptyline) • Calcium channel blockers (e.g., verapamil) • ACE inhibitors or angiotensin receptor blockers (e.g., candesartan) • Serotonin-norepinephrine reuptake inhibitors (e.g., venlafaxine) • Serotonin and tryptamine antagonists (e.g., pizotifen) • Placebo

Criteria	Description
Outcomes	**Efficacy outcomes** • Headache or migraine days (e.g., 50% reduction in migraine or headache days, change from baseline in migraine or headache days) • HRQoL (e.g., MSQ) • Headache symptoms (e.g., HIT-6 score) • Acute headache pain medication use • Other patient-reported outcomes (e.g., MIDAS, MPFID) • Loss of workdays **Harms outcomes** • AEs, SAEs, WDAEs, mortality • Notable harms or AEs of special interest (constipation, suicidal ideation, hepatic toxicity, renal toxicity)
Study designs	Published and unpublished phase III and phase IV RCTs

ACE = angiotensin-converting enzyme; AE = adverse event; CGRP = calcitonin gene–related peptide; HIT-6 = 6-item Headache Impact Test; HRQoL = health-related quality of life; MIDAS = Migraine Disability Assessment; MPFID = Migraine Physical Function Impact Diary; MSQ = Migraine-Specific Quality-of-Life Questionnaire; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the PRESS Peer Review of Electronic Search Strategies checklist.[22]

Published literature was identified by searching the following bibliographic databases: MEDLINE via Ovid and Embase via Ovid. All Ovid searches were run simultaneously as a multifile search. Duplicates were removed using Ovid deduplication for multifile searches, followed by manual deduplication in Endnote. The search strategy comprised both controlled vocabulary, such as the US National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was atogepant. Clinical trials registries were searched: the US National Institutes of Health's ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform search portal, Health Canada's Clinical Trials Database, and the European Union Clinical Trials Register.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. Refer to Appendix 1 for the detailed search strategies.

The initial search was completed on March 22, 2022. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee on April 26, 2023.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the Grey Matters: A Practical Tool For Searching Health-Related Grey Literature checklist. Included in this search were the websites of regulatory agencies (US FDA and European Medicines Agency). Google was used to search for additional internet-based materials. Refer to Appendix 1 for more information on the grey literature search strategy.

Two CADTH clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially

relevant by at least 1 reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Findings From the Literature

A total of 39 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 6.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

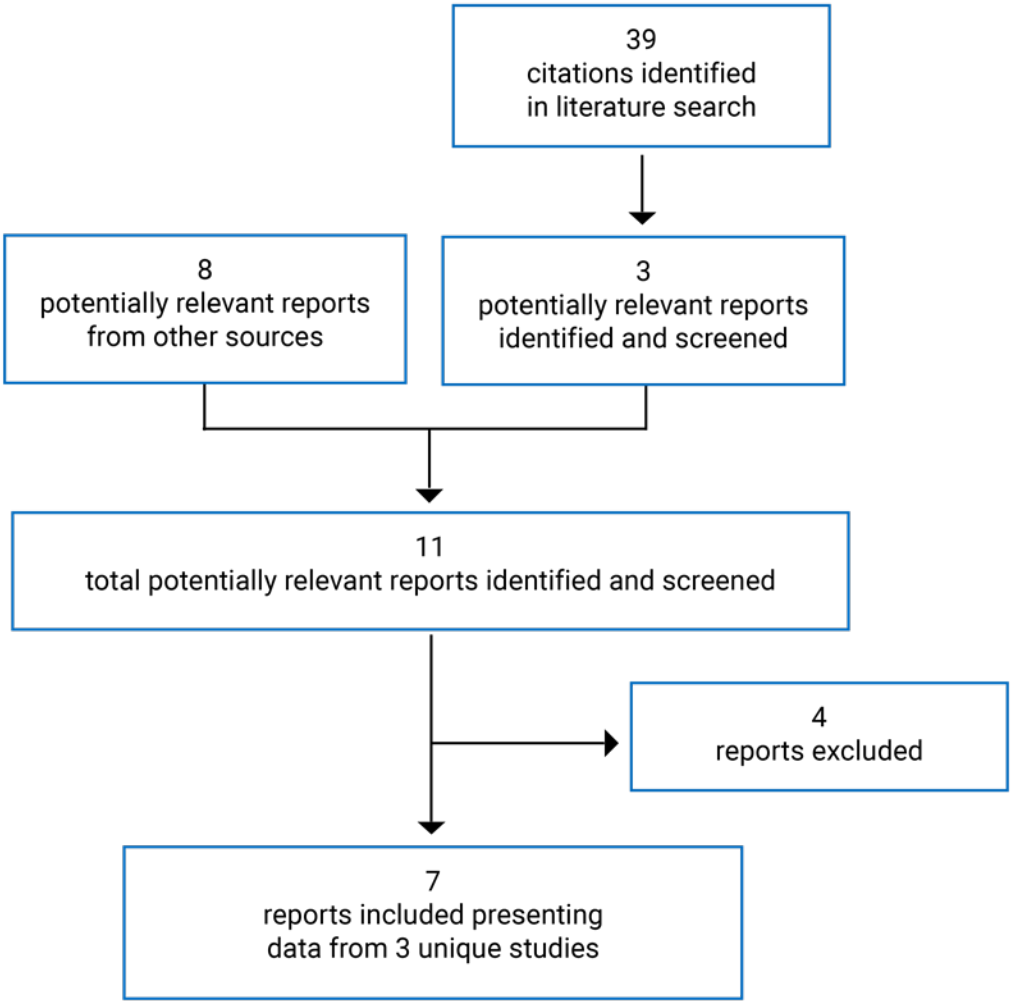


Table 6: Details of Included Studies

Detail	Study 301 (ADVANCE study)	Study CGP-MD-01	Study 304 (ELEVATE study)
Designs and populations			
Study design	Phase III, multicentre, DB, placebo-controlled, parallel-group RCT	Phase II/III multicentre, DB, placebo-controlled, parallel-group RCT	Phase III, multicentre, DB, placebo-controlled, parallel-group RCT
Locations	US	US	North America (Canada, US) and Europe
Patient enrolment dates	December 14, 2018, to June 19, 2020	September 6, 2016, to April 23, 2018	March 5, 2021, to August 4, 2022
Randomized (N)	N = 910 • Atogepant 10 mg q.d. (n = 222) • Atogepant 30 mg q.d. (n = 230) • Atogepant 60 mg q.d. (n = 235) • Placebo (n = 223)	N = 834 • Atogepant 10 mg q.d. (n = 94) • Atogepant 30 mg q.d. (n = 185) • Atogepant 30 mg b.i.d. (n = 89) • Atogepant 60 mg q.d. (n = 187) • Atogepant 60 mg b.i.d. (n = 93) • Placebo (n = 186)	N = 315 • Atogepant 60 mg q.d. (n = [redacted]) • Placebo (n = [redacted])
Inclusion criteria	• Male or female patients aged 18 to 80 years • 1 year history of migraine with or without aura consistent with a diagnosis according to ICHD-3, 2018	• Male or female patients aged 18 to 75 years • 1 year history of migraine with or without aura consistent with a diagnosis according to the ICHD-3 beta, 2013	• Male or female patients aged 18 to 80 years • 1 year history of migraine with or without aura consistent with a diagnosis according to ICHD-3, 2018 • Failed 2 to 4 of the following oral migraine prophylaxis medications: propranolol, metoprolol, atenolol, bisoprolol, timolol, or nadolol, topiramate, flunarizine, valproate or divalproex, amitriptyline or nortriptyline, venlafaxine or desvenlafaxine, lisinopril, candesartan, locally approved products (e.g., oxetorone, pizotifen); also failed at least 1 of the following treatments: propranolol or metoprolol, topiramate, flunarizine, amitriptyline

Detail	Study 301 (ADVANCE study)	Study CGP-MD-01	Study 304 (ELEVATE study)
	• Age at the time of migraine onset < 50 years • History of 4 migraine days per month to 14 migraine days per month on average in the 3 months before visit 1 • 4 migraine days per month to 14 migraine days in the 28-day baseline period • Completed at least 20 of 28 days in the eDiary during the baseline period and was able to read, understand, and complete the study questionnaires and eDiary		

Exclusion criteria	• History of migraine accompanied by diplopia or decreased level of consciousness or retinal migraine as defined by ICHD-3, 2018
	• Current diagnosis of CM, new persistent daily headache, trigeminal autonomic cephalgia (e.g., cluster headache), or painful cranial neuropathy as defined by ICHD-3, 2018
	• History of an inadequate response to > 4 medications (2 of which have different mechanisms of action) prescribed for the prevention of migraine
	• Clinically significant laboratory values **or** any of the following laboratory values at visit 1:
	  ◦ ALT or AST > 1 × ULN
	  ◦ total bilirubin > 1 × ULN (except for patients with a diagnosis of Gilbert syndrome)
	  ◦ serum albumin < 2.8 g/dL
	• Previous exposure to:
	  ◦ atogepant
	  ◦ injectable mAbs blocking the CGRP pathway within the last 6 months
	  ◦ ubrogepant and took more than 3 doses
	  ◦ rimegepant and took more than 3 doses
		• History of migraine accompanied by diplopia or decreased level of consciousness, or retinal migraine as defined by ICHD-3 beta, 2013
		• Current diagnosis of CM, new persistent daily headache, trigeminal autonomic cephalgia (e.g., cluster headache), or painful cranial neuropathy as defined by ICHD-3 beta, 2013
		• Inadequate response to 3 or more medications (2 of which have different mechanisms of action) prescribed for the prevention of migraine
		• Clinically significant abnormalities at screening (visit 1), including but not limited to:
		  ◦ ALT or AST > 1.5 × ULN
		  ◦ total bilirubin > 1.5 mg/dL (except for patients with a diagnosis of Gilbert syndrome)
		  ◦ serum albumin < 2.8 g/dL
		  ◦ estimated GFR < 30 mL per minute per 1.73 m^2
		• Was currently participating in or had participated in a study with an investigational compound within 30 days before screening (visit 1)
			• History of migraine accompanied by diplopia or decreased level of consciousness or retinal migraine as defined by ICHD-3, 2018
			• Current diagnosis of CM, new persistent daily headache, medication overuse headache, trigeminal autonomic cephalgia (e.g., cluster headache), or painful cranial neuropathy as defined by ICHD-3, 2018
			• Usage during 30 days before visit 1 (unless otherwise indicated) and throughout the study period of and requirement for any medication, diet item (i.e., grapefruit juice), or nonpharmacological treatment that is on the list of prohibited concomitant medications or treatments that cannot be discontinued or switched to an allowable alternative medication or treatment. This includes concomitant medications with demonstrated efficacy for the prevention of migraine (e.g., amitriptyline, topiramate, propranolol) regardless of indication.
			• Usage of therapeutic or cosmetic botulinum toxin injections (e.g., Dysport, Botox, Xeomin, Myobloc, Jeuveau) into areas of the head, face, or neck within 6

Detail	Study 301 (ADVANCE study)	Study CGP-MD-01	Study 304 (ELEVATE study)
		◦ If patient was currently participating in or had participated in a study with injectable mAbs blocking the CGRP pathway, the patient was not allowed to participate	months before visit 1 and throughout the study period • Clinically significant laboratory values **or** any of the following laboratory values at visit 1: ◦ ALT or AST > 1 × ULN ◦ total bilirubin > 1 × ULN (except for patients with a diagnosis of Gilbert syndrome) ◦ serum albumin < 2.8 g/dL • Previous exposure to: ◦ atogepant ◦ injectable mAbs blocking the CGRP pathway within the last 6 months ◦ any other investigational CGRP-RA
	• Difficulty distinguishing migraine headaches from tension-type or other headaches • ≥ 15 headache days per month on average across the 3 months before visit 1 • ≥ 15 headache days in the 28-day baseline period • Usage of opioids or barbiturates > 2 days per month, triptans or ergots ≥ 10 days per month, or simple analgesics (e.g., Aspirin, NSAIDs, acetaminophen) ≥ 15 days per month in the 3 months before visit 1, or during the baseline period. For all patients, barbiturates are excluded 30 days before screening and during the baseline period. • Clinically significant cardiovascular or cerebrovascular disease including, but not limited to: ◦ clinically significant ischemic heart disease (e.g., unstable angina pectoris) ◦ clinically significant cardiac rhythm or conduction abnormalities (e.g., atrial fibrillation, second-degree or third-degree heart block) or risk factors for torsades de pointes (e.g., heart failure, hypokalemia, bradycardia) ◦ myocardial infarction, transient ischemic attack, or stroke within 6 months before visit 1 ◦ heart failure defined as NYHA Class III or Class IV • Hypertension as defined by sitting SBP > 160 mm Hg or sitting DBP > 100 mm Hg at visit 1 or visit 2. Vital sign measurements that exceed these limits may be repeated only once. • ECG with clinically significant abnormalities at screening (visit 1)		

Detail	Study 301 (ADVANCE study)	Study CGP-MD-01	Study 304 (ELEVATE study)
	• QTcF > 450 milliseconds for males and QTcF > 470 milliseconds for females at visit 1 • History of acute hepatitis within 6 months of screening (visit 1); or chronic hepatitis (including nonalcoholic steatohepatitis); or a positive result on anti–hepatitis A IgM antibody, hepatitis B surface antigen, anti–hepatitis C antibody, or anti–hepatitis E IgM antibody testing • Any clinically significant hematologic, endocrine, pulmonary, renal, hepatic, GI, or neurologic disease • Confounding psychiatric conditions, dementia, epilepsy, or significant neurologic disorders other than migraine • Any other concurrent pain condition that may significantly impact the current headache disorder (e.g., fibromyalgia, facial pain) • Significant risk of self-harm based on a clinical interview and responses on the C-SSRS, or of harm to others; patients were excluded if they reported suicidal ideation with intent, with or without a plan (i.e., type 4 or type 5 on the C-SSRS) in the past 6 months, or reported suicidal behaviour in the 6 months before the visit 1 or visit 2 assessments • History of any GI prior procedures or GI conditions (e.g., diarrhea syndromes, inflammatory bowel disease) that may have affected the absorption or metabolism of the study intervention • History of malignancy in the 5 years before visit 1, except for adequately treated basal cell or squamous cell skin cancer, or in situ cervical cancer • Users of recreational or illicit drugs or with a history within the past year of drug or alcohol abuse or dependence • Positive result on the urine drug screen at visit 1 unless explained by concomitant medication use (e.g., opioids prescribed for migraine pain)		
Drugs			
Intervention	10 mg, 30 mg, or 60 mg atogepant orally once daily	• 10 mg, 30 mg, or 60 mg atogepant orally once daily • 30 mg, 60 mg atogepant orally twice daily	60 mg atogepant orally once daily
Comparator(s)	Placebo	Placebo	Placebo
Duration			
Phase			
Run-in	4 weeks		
Double-blind	12 weeks		
Follow-up	4 weeks		
Outcomes			
Primary end point	CFB in mean MMDs	CFB in mean MMDs	CFB in mean MMDs

Detail	Study 301 (ADVANCE study)	Study CGP-MD-01	Study 304 (ELEVATE study)
Secondary and exploratory end points	**Secondary end points** • CFB in mean MHDs across the 12-week treatment period • CFB in mean monthly acute MUDs across the 12-week treatment period • ≥ 50% reduction in 3-month average of MMDs • CFB in MSQ version 2.1 role function-restrictive domain score at week 12 • CFB in mean monthly performance of daily activities domain score of the AIM-D across the 12-week treatment period • CFB in mean monthly physical impairment domain score of the AIM-D across the 12-week treatment period **Other secondary end points** • ≥ 25%, ≥ 50%, ≥ 75%, 100% improvement (reduction) in MMDs at week 1 to week 4, week 5 to week 8, and week 9 to week 12 • ≥ 25%, ≥ 75%, 100% improvement (reduction) in 3-month average of MMDs • CFB in MMDs at week 1 to week 4, week 5 to week 8, and week 9 to week 12 • CFB in MHDs at week 1 to week 4, week 5 to week 8, and week 9 to week 12 • CFB in monthly cumulative headache hours at week 1 to week 4, week 5 to week 8, week 9 to week 12, and the average across the 12-week treatment period • CFB in monthly acute MUDs at week 1 to week 4, week 5 to week 8, and week 9 to week 12 • CFB in monthly triptan use days at week 1 to week 4, week 5 to week 8, week 9 to week 12,	**Secondary end points** • CFB in mean MHDs across the 12-week treatment period • Proportion of patients with at least a 50% reduction in mean MMDs across the 12-week treatment period • CFB in mean monthly acute MUDs across the 12-week treatment period **Additional efficacy variables** • Cumulative distribution graph of percentage of improvement (decrease) in mean MMDs across the 12-week treatment period • Proportion of patients who were responders, who had ≥ 25%, ≥ 50%, ≥ 75%, and 100% improvement (decrease) in mean MMDs at week 1 to week 4, week 5 to week 8, and week 9 to week 12 • CFB in migraine days at week 1 to week 4, week 5 to week 8, and week 9 to week 12 • CFB in headache days at week 1 to week 4, week 5 to week 8, and week 9 to week 12 • CFB in cumulative headache hours at week 1 to week 4, week 5 to week 8, and week 9 to week 12 • CFB in mean headache day pain intensity at week 1 to week 4, week 5 to week 8, and week 9 to week 12 • CFB in acute MUDs at week 1 to week 4, week 5 to week 8, and week 9 to week 12 • CFB in triptan use days at week 1 to week 4, week 5 to week 8, and week 9 to week 12	**Secondary end points** • CFB in mean MHDs across the 12-week treatment period • CFB in mean monthly acute MUDs across the 12-week treatment period • ≥ 50% reduction in 3-month average of MMDs • CFB in MSQ version 2.1 role function-restrictive domain score at week 12 • CFB in mean monthly performance of daily activities domain score of the AIM-D across the 12-week treatment period • CFB in mean monthly physical impairment domain score of the AIM-D across the 12-week treatment period **Exploratory efficacy variables** • ≥ 25%, ≥ 50%, ≥ 75%, 100% improvement (reduction) in MMDs at week 1 to week 4, week 5 to week 8, and week 9 to week 12 • ≥ 25%, ≥ 75%, 100% improvement (reduction) in 3-month average of MMDs • CFB in MMDs at week 1 to week 4, week 5 to week 8, and week 9 to week 12 • CFB in MHDs at week 1 to week 4, week 5 to week 8, and week 9 to week 12 • CFB in monthly cumulative headache hours at week 1 to week 4, week 5 to week 8, week 9 to week 12, and the average across the 12-week treatment period

Detail	Study 301 (ADVANCE study)	Study CGP-MD-01	Study 304 (ELEVATE study)
	and the average across the 12-week treatment period • CFB in monthly moderate to severe headache days at week 1 to week 4, week 5 to week 8, week 9 to week 12, and the average across the 12-week treatment period • CFB in monthly severe headache days at week 1 to week 4, week 5 to week 8, week 9 to week 12, and average across the 12-week treatment period • CFB in weekly migraine days at week 1 to week 4 • Patients having a migraine day on the day of initial dosage and on each day of the 6 days post the initial dosage • CFB in the HIT-6 total score at week 4, week 8, and week 12 • At least a 5-point improvement (decrease) from baseline in HIT-6 total score at week 4, week 8, and week 12 • Patient assessed by the PGIC as "much better" or "very much better" at week 12 • Patient reporting "satisfied" or "extremely satisfied" with study medication for the preventive treatment of migraine at week 4, week 8, and week 12 • CFB in percentage of work time missed, percentage of impairment while working, percentage of overall impairment, and percentage of activity impairment due to migraine at week 4, week 8, and week 12 as assessed by the WPAI:Migraine version 2.0 • CFB in MIDAS total score at week 12	• CFB in ACM-I total score and in each of the domain scores at week 2, week 4, week 6, week 8, and week 12 • CFB in the HIT-6 total score at week 4, week 8, and week 12 • Proportion of patients assessed by the PGIC as "much better" or "very much better" at week 12 • Proportion of patients "satisfied" or "extremely satisfied" with study medication for migraine prevention at week 6 and week 12 • CFB in percentage of work time missed, percentage of impairment while working, percentage of overall impairment, and percentage of activity impairment due to migraine at week 6 and week 12 as assessed by the WPAI:Migraine version 2.0 • CFB in EQ-5D-5L descriptive system index score at week 6 and week 12 • CFB in EQ VAS score at week 6 and week 12	• CFB in monthly acute MUDs at week 1 to week 4, week 5 to week 8, and week 9 to week 12 • CFB in monthly triptan use days at week 1 to week 4, week 5 to week 8, week 9 to week 12, and the average across the 12-week treatment period • CFB in monthly moderate to severe headache days at week 1 to week 4, week 5 to week 8, week 9 to week 12, and the average across the 12-week treatment period • CFB in monthly severe headache days at week 1 to week 4, week 5 to week 8, week 9 to week 12, and the average across the 12-week treatment period • CFB in the HIT-6 total score at week 4, week 8, and week 12 • At least a 5-point improvement (decrease) from baseline in HIT-6 total score at week 4, week 8, and week 12 • Patient assessed by the PGIC as "much better" or "very much better" at week 12 • Achievement of a rating of satisfied or extremely satisfied at week 4, week 8, and week 12 assessed by the PSSM • CFB in percentage of work time missed, percentage of impairment while working, percentage of overall impairment, and percentage of activity impairment due to migraine at week 4, week 8, and week 12 as assessed by the WPAI:Migraine version 2.0

Detail	Study 301 (ADVANCE study)	Study CGP-MD-01	Study 304 (ELEVATE study)
	• CFB in MIDAS absenteeism score (question 1, question 3, and question 5) and presenteeism score (question 2 and question 4) at week 12 • CFB in PGI-S score at week 4, week 8, and week 12 • CFB in the MSQ version 2.1 role function-preventive domain, role function-restrictive domain, and emotional function domain score at week 4, week 8, week 12, and week 16 • CFB in monthly performance of daily activities domain and physical impairment domain score of the AIM-D at week 1 to week 4, week 5 to week 8, and week 9 to week 12 • CFB in monthly AIM-D total score at week 1 to week 4, week 5 to week 8, week 9 to week 12, and average across the 12-week treatment period • CFB in monthly activity level at week 1 to week 4, week 5 to week 8, week 9 to week 12, and the average across the 12-week treatment period • CFB in monthly activity limitation at week 1 to week 4, week 5 to week 8, week 9 to week 12, and the average across the 12-week treatment period • CFB in EQ-5D-5L descriptive system index score at week 4, week 8, week 12, and week 16 • CFB in the EQ VAS score at week 4, week 8, week 12, and week 16 • CFB in PROMIS Pain Interference total score at week 4, week 8, and week 12		• CFB in EQ-5D-5L descriptive system index score at week 1 to week 2, and at specified windows around week 4, week 6, week 8, week 12, and week 16 • CFB in the EQ VAS score at week 1 to week 2, and at specified windows around week 4, week 6, week 8, week 12, and week 16 • CFB in MIDAS total score at week 12 • CFB in MIDAS absenteeism score (question 1, question 3, and question 5) and presenteeism score (question 2 and question 4) at week 12 • CFB in PGI-S score at week 4, week 8, and week 12 • CFB in the MSQ version 2.1 role function-preventive domain, role function-restrictive domain, and emotional function domain score at week 4, week 8, and week 12 • CFB in AIM-D total score, monthly performance of daily activities domain score, and monthly physical impairment domain score of the AIM-D at week 1 to week 4, week 5 to week 8, and week 9 to week 12 • CFB in monthly activity level at week 1 to week 4, week 5 to week 8, week 9 to week 12, and the average across the 12-week treatment period • CFB in monthly activity limitation at week 1 to week 4, week 5 to week 8, week 9 to week 12, and the average across the 12-week treatment period

Detail	Study 301 (ADVANCE study)	Study CGP-MD-01	Study 304 (ELEVATE study)
			• CFB in PROMIS Pain Interference total score at week 4, week 8, and week 12 • CFB in PHQ-9 score at week 12
Notes			
Publications	Ailani et al. (2021)[23] Schwedt et al. (2022)[24]	Goadsby et al. (2020)[25]	NR

ACM-I = Assessment of Chronic Migraine–Impact; AIM-D = Activity Impairment in Migraine–Diary; ALT = alanine aminotransferase; AST = aspartate aminotransferase; b.i.d. = twice a day; C-SSRS = Columbia-Suicide Severity Rating Scale; CFB = change from baseline; CGRP = calcitonin gene–related peptide; CGRP-RA = calcitonin gene–related peptide receptor antagonist; CM = chronic migraine; DB = double-blind; DBP = diastolic blood pressure; ECG = electrocardiogram; EQ VAS = EQ-5D Visual analogue scale; GFR = glomerular filtration rate; GI = gastrointestinal; HIT-6 = 6-item Headache Impact Test; ICHD-3 = *International Classification of Headache Disorders*; IgM = immunoglobulin M; mAb = monoclonal antibody; MHD = monthly headache day; MIDAS = Migraine Disability Assessment; MMD = monthly migraine day; MSQ = Migraine-Specific Quality-of-Life Questionnaire; MUD = medication use day; NSAID = nonsteroidal anti-inflammatory drug; NYHA = New York Heart Association; PGI-S = Patient Global Impression–Severity; PGIC = Patient Global Impression of Change; PHQ-9 = Patient Health Questionnaire-9; PROMIS = Patient-Reported Outcome Measurement Information System; PSSM = Patient Satisfaction with Study Medication; q.d. = once daily; QTcF = QT interval corrected for heart rate using the Fridericia formula; RCT = randomized controlled trial; SBP = systolic blood pressure; ULN = upper limit of normal; WPAI:Migraine = Work Productivity and Activity Impairment Questionnaire: Migraine.

Sources: ADVANCE Clinical Study Report,[13] CGP-MD-01 Clinical Study Report,[14] and ELEVATE Clinical Study Report.[15]

Description of Studies

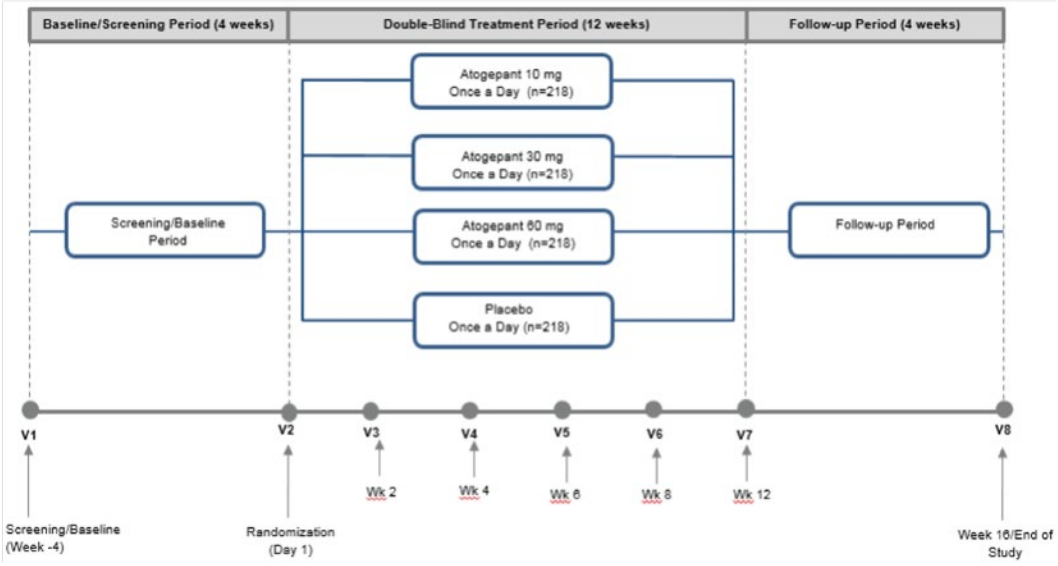
Initially, 2 studies were included in this review: Study 301 (the ADVANCE study) and the CGP-MD-01 study, which were a phase III RCT and a phase II/III RCT, respectively, comparing atogepant to placebo in adult patients with EM. Both studies were funded by the sponsor.

The Clinical Study Report for the ELEVATE study was provided to CADTH during the later stages of the review when the clinical review report was nearly complete. The ELEVATE study was conducted similarly to the ADVANCE study — as a phase III RCT comparing atogepant to placebo in adult patients with EM who have previously failed 2 classes to 4 classes of oral prophylactic treatments — and has been included within the body of the report. The ELEVATE study was also funded by the sponsor.

Study 301 (ADVANCE Study)

The ADVANCE study was conducted based on the results of the CGP-MD-01 study, and was a multicentre, randomized, double-blind, placebo-controlled, parallel-group study that enrolled patients with EM from 136 sites in the US. The objective of the ADVANCE study was to evaluate the safety and tolerability of atogepant for the preventive treatment of migraine in patients with EM, as well as to prospectively determine the superiority of atogepant versus placebo for the preventive treatment of migraine in patients with EM. A total of 910 patients were randomized in a 1:1:1:1 sequence to atogepant 10 mg once daily (n = 222), atogepant 30 mg once daily (n = 230), atogepant 60 mg once daily (n = 235), or placebo (n = 223). Randomization was stratified based on prior exposure (yes versus no) to a migraine prevention medication with proven efficacy.

Figure 2: Study Flow Diagram — ADVANCE Study



V = visit; wk = week.

Source: ADVANCE Clinical Study Report.[13]

No Canadian study sites or patients were included in the ADVANCE trial. The total study duration was 20

weeks, consisting of a 4-week screening and baseline period, a 12-week double-blind treatment period, and a 4-week safety follow-up period.[13] A schematic overview of the study design for the ADVANCE study is displayed in Figure 2. The last observation was June 19, 2020, and the study database was locked as of July 6, 2020.[13]

Study CGP-MD-01

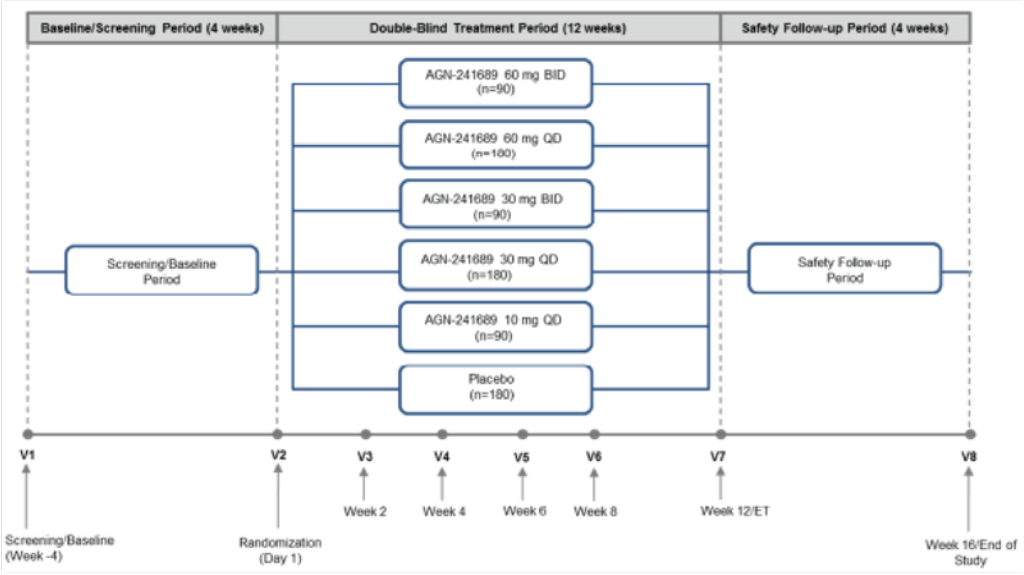
Study CGP-MD-01 was a phase II/III multicentre, randomized, double-blind, placebo-controlled, parallel-group study that enrolled adult patients with a history of EM (4 migraine days per month to 14 migraine days per month) from 78 sites in the US. The objective of the CGP-MD-01 study was to evaluate the safety and tolerability of 10 mg once daily, 30 mg once daily, 30 mg twice daily, 60 mg once daily, and 60 mg twice daily dosage regimens of atogepant for the prevention of EM. A total of 834 patients were randomized to 1 of 6 different groups in a 2:1:2:1:2:1 randomization sequence of placebo (n = 186), atogepant 10 mg once daily (n = 94), atogepant 30 mg once daily (n = 185), atogepant 30 mg twice daily (n = 89), atogepant 60 mg once daily (n = 187), or atogepant 60 mg twice daily (n = 93), respectively. No stratification was performed. No Canadian study sites or patients were included in the CGP-MD-01 study. The total study duration was 20 weeks, consisting of a 4-week screening and baseline period, a 12-week double-blind treatment period, and a 4-week safety follow-up period, for a total of 8 scheduled clinic visits.[14] A schematic overview of the study design for the CGP-MD-01 study is displayed in Figure 3. The last observation was April 23, 2018, and the study database was locked as of May 23, 2018.[14]

Only Health Canada–approved dosages are summarized in this report; thus, results for the atogepant 30 mg twice daily and atogepant 60 mg twice daily dosages are not discussed.

Study 304 (ELEVATE Study)

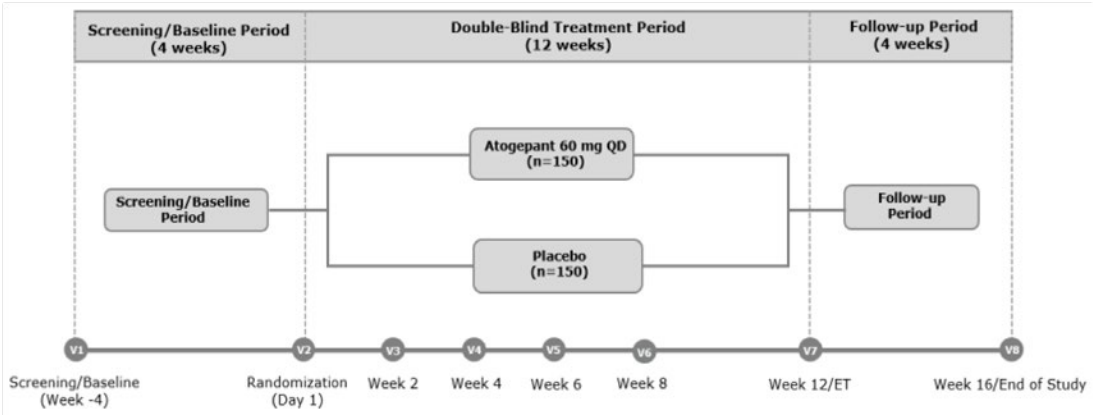
ELEVATE was a phase III, randomized, double-blind, placebo-controlled study. The objective of the ELEVATE study was to evaluate the efficacy and safety of atogepant 60 mg once daily for the prevention of migraine in adult patients with EM who have previously failed 2 classes to 4 classes of oral medications for the prophylaxis of migraine. A total of 315 patients were randomized 1:1 to atogepant 60 mg once daily ([redacted]) or placebo ([redacted]). Randomization was stratified via IWRS based on region (North America and Europe), number of migraine days during the screening or baseline period (4 to < 8 and ≥ 8), and number of classes of failed prior prophylactic treatments (2 and > 2). A total of 73 sites in North America (Canada and the US) and Europe (Czech Republic, Denmark, France, Germany, Hungary, Italy, the Netherlands, Poland, Russia, Spain, and the UK) screened patients for eligibility. The total study duration was 20 weeks, consisting of a 4-week screening and baseline period, a 12-week double-blind treatment period, and a 4-week safety follow-up period.[15] A schematic overview of the study design for the ELEVATE study is displayed in Figure 4.

Figure 3: Study Flow Diagram— CGP-MD-01 Study



BID = twice daily; QD = once daily; V = visit.
Source: CGP-MD-01 Clinical Study Report.[14]

Figure 4: Study Flow Diagram — ELEVATE Study



ET = end of treatment; QD = once daily; V = visit.
Source: ELEVATE Clinical Study Report.[15]

Populations

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for the ADVANCE study, the CGP-MD-01 study, and the ELEVATE study are summarized in Table 6. Overall, the 3 included trials had similar inclusion criteria. In general, adult patients (18 years to 80 years) with a 1-year history of migraine consisting of 4 migraine days per month to 14 migraine days per month, with or without aura, and migraine onset before aged 50 years were included.[13,14] In study CGP-MD-01, diagnosis was confirmed according to ICHD-3 beta, 2013,[14] while

ICHD-3, 2018, was used in the ADVANCE and ELEVATE studies.[13,15] One additional inclusion criterion for the ELEVATE trial was the failure of 2 to 4 oral migraine prophylaxis medications,[15] which was in line with the reimbursement request for patients who have experienced an inadequate response, an intolerance, or a contraindication to at least 2 oral prophylactic migraine medications. In the ADVANCE study, patients were excluded if they had had inadequate response to more than 4 medications (2 of which had different mechanisms of action) prescribed for the prevention of migraine,[13] and patients in the CGP-MD-01 trial were excluded who had inadequate response to 3 or more medications (2 of which had different mechanisms of action) prescribed for the prevention of migraine.[14]

All trials also had similar exclusion criteria. Patients were ineligible if they had a history of migraine accompanied by diplopia or decreased level of consciousness, or retinal migraine, or a diagnosis of CM according to ICHD-3, 2018 (the ADVANCE and ELEVATE studies) or ICHD-3 beta, 2013 (study CGP-MD-01). Patients with 15 or more MHDs in the 3 months before visit 1 or in the baseline period were also excluded. In all trials, patients were also ineligible based on the prior use of acute migraine medications, including opioids or barbiturates, more than 2 days per month, triptans or ergots 10 or more days per month, or simple analgesics (e.g., Aspirin, nonsteroidal anti-inflammatory drugs [NSAIDs], acetaminophen) 15 or more days per month in the 3 months before visit 1, or during the baseline period. Patients in the ADVANCE study and study CGP-MD-01 were also excluded based on prior exposure to the investigational product and other CGRP inhibitors.[13-15]

Baseline Characteristics

Baseline characteristics for the ADVANCE, CGP-MD-01, and ELEVATE studies are summarized in Table 7. Baseline characteristics were well balanced across groups in each trial. In all studies, most patients were female (ADVANCE study = 86.1% to 90.5%, CGP-MD-01 study = 82.8% to 90.7%, ELEVATE study = [redacted]) and white (ADVANCE study = 81.1% to 89.2%, CGP-MD-01 study = 71.5% to 79.2%, ELEVATE study = [redacted]), and the median age ranged from 38.5 years to 42.0 years in the ADVANCE study, from 38.0 years to 40.5 years in study CGP-MD-01, and [redacted] years in the ELEVATE study.[13-15]

In the ADVANCE study, the mean duration of migraine disorder was [redacted], and [redacted] of patients had received prior migraine prevention medicine, with the most frequently used acute migraine treatments consisting of NSAIDs ([redacted]), triptans ([redacted]), and others ([redacted]). The mean number of migraine days per month 3 months before the study ranged from 7.2 (SD = 2.47) days to 7.7 (SD = 2.57) days, with the mean number of MHDs ranging from 9.1 (SD = 2.71) days to 9.5 (SD = 2.76) days.[13]

In study CGP-MD-01, the mean duration of migraine was 18.65 (SD = 10.9) years to 20.58 (SD = 11.7) years, and contrary to the ADVANCE trial, the majority of patients did not have prior migraine prevention therapy (range = [redacted]). The most frequently used acute migraine treatments were NSAIDs ([redacted]), triptans ([redacted]), and others ([redacted]). Similar to the ADVANCE trial, the mean number of migraine days per month ranged from [redacted], with the mean number of MHDs ranging from [redacted].[14]

In the ELEVATE study, all patients had prior prophylactic migraine therapy. The mean duration of migraine disorder was similar across the atogepant and placebo groups ([redacted]), with the most

frequently used acute migraine treatments consisting of triptans ([redacted]), NSAIDs ([redacted]), and others ([redacted]). The mean number of migraine days per month 3 months before the study was higher in the ELEVATE study than in the ADVANCE study and was [redacted]).[15]

Interventions

Treatments Administered

The ADVANCE study, the CGP-MD-01 study, and the ELEVATE study were double-blind, placebo-controlled RCTs comparing atogepant to placebo.

In the ADVANCE study, eligible patients were randomized (at visit 2) in a 1:1:1:1 ratio via IWRS to 1 of 4 treatment groups, as follows:[13]

- placebo once daily (placebo 10 mg, placebo 30 mg, and placebo 60 mg)
- atogepant 10 mg once daily (atogepant 10 mg, placebo 30 mg, and placebo 60 mg)
- atogepant 30 mg once daily (atogepant 30 mg, placebo 10 mg, and placebo 60 mg)
- atogepant 60 mg once daily (atogepant 60 mg, placebo 10 mg, and placebo 30 mg).

Patients were instructed to take the study intervention (3 tablets) once a day at approximately the same time each day. Patients took their first dose of study intervention at the clinic at visit 2 (i.e., at randomization). Randomization was stratified based on prior exposure (yes versus no) to a migraine prevention medication with proven efficacy. Each site was dynamically allocated entire blocks based on strata, and treatment was assigned sequentially within a block. A double-dummy design was used to maintain blinding.[13]

In study CGP-MD-01, eligible patients were randomly assigned by blocks in a 2:1:2:1:2:1 ratio via IWRS into the following groups:[14]

- placebo (placebo in the morning and placebo in the evening)
- atogepant 10 mg once daily (atogepant 10 mg in the morning and placebo in the evening)
- atogepant 30 mg once daily (atogepant 30 mg in the morning and placebo in the evening)
- atogepant 60 mg once daily (atogepant 60 mg in the morning and placebo in the evening).

The last 2 groups of the CGP-MD-01 trial were for atogepant 30 mg and 60 mg twice daily; however, given that these dosages are not approved by Health Canada, they were omitted from this report.

Table 7: Summary of Baseline Characteristics of Included Studies

Characteristic	ADVANCE study				CGP-MD-01 study				ELEVATE study	
	ATO 10 mg q.d.	ATO 30 mg q.d.	ATO 60 mg q.d.	PBO	ATO 10 mg q.d.	ATO 30 mg q.d.	ATO 60 mg q.d.	PBO	ATO 60 mg q.d.	PBO
Demographic and disease characteristics (safety population)										
N	**221**	**228**	**231**	**222**	**93**	**183**	**186**	**186**	[redacted]	[redacted]
Age, n (%)										
Mean (SD)	41.4 (12.05)	42.1 (11.68)	42.5 (12.41)	40.3 (12.81)	39.4 (12.4)	41.0 (13.6)	40.4 (11.7)	40.5 (11.7)	[redacted]	[redacted]
Median (range)	41.0 (18 to 73)	42.0 (19 to 70)	42.0 (18 to 72)	38.5 (18 to 69)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex, n (%)										
Male	21 (9.5)	24 (10.5)	32 (13.9)	24 (10.8)	11 (11.8)	17 (9.3)	30 (16.1)	32 (17.2)	[redacted]	[redacted]
Female	200 (90.5)	204 (89.5)	199 (86.1)	198 (89.2)	82 (88.2)	166 (90.7)	156 (83.9)	154 (82.8)	[redacted]	[redacted]
Race or ethnicity, n (%)										
White	181 (81.9)	185 (81.1)	192 (83.1)	194 (87.4)	69 (74.2)	145 (79.2)	133 (71.5)	137 (73.7)	[redacted]	[redacted]
Black or African American	34 (15.4)	38 (16.7)	28 (12.1)	24 (10.8)	20 (21.5)	29 (15.8)	44 (23.7)	45 (24.2)	[redacted]	[redacted]
Asian	2 (0.9)	1 (0.4)	7 (3.0)	2 (0.9)	1 (1.1)	2 (1.1)	3 (1.6)	1 (0.5)	[redacted]	[redacted]
American Indian or Alaska Native	1 (0.5)	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.5)	2 (1.1)	3 (1.6)	[redacted]	[redacted]
Multiple[a, b]	3 (1.4)	3 (1.3)	2 (0.9)	2 (0.9)	0 (0.0)	2 (1.1)	0 (0.0)	0 (0.0)	[redacted]	[redacted]
Missing	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	3 (3.2)	4 (2.2)	4 (2.2)	0 (0.0)	[redacted]	[redacted]
BMI, kg/m^2										
Mean (SD)	30.35 (7.597)	31.15 (7.631)	29.91 (7.318)	30.83 (8.713)	29.92 (7.3)	30.04 (7.1)	30.02 (7.8)	30.42 (7.6)	[redacted]	[redacted]

Characteristic	ADVANCE study				CGP-MD-01 study				ELEVATE study	
	ATO 10 mg q.d.	ATO 30 mg q.d.	ATO 60 mg q.d.	PBO	ATO 10 mg q.d.	ATO 30 mg q.d.	ATO 60 mg q.d.	PBO	ATO 60 mg q.d.	PBO
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Migraine diagnosis, n (%)										
With aura	[redacted]	[redacted]	[redacted]	[redacted]	21 (22.6)	37 (20.2)	36 (19.4)	45 (24.2)	[redacted]	[redacted]
Without aura	[redacted]	[redacted]	[redacted]	[redacted]	48 (51.6)	93 (50.8)	96 (51.6)	94 (50.5)	[redacted]	[redacted]
Both	[redacted]	[redacted]	[redacted]	[redacted]	24 (25.8)	53 (29.0)	54 (29.0)	47 (25.3)	[redacted]	[redacted]
Migraine disorder duration in years										
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	18.65 (10.9)	19.85 (13.7)	18.84 (12.1)	20.58 (11.7)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	17.0 ([redacted])	17.0 ([redacted])	17.21 ([redacted])	19.50 ([redacted])	[redacted]	[redacted]
Migraine prevention medication, n (%)										
Yes	[redacted]	[redacted]	[redacted]	[redacted]	29 (31.2)	46 (25.1)	51 (27.4)	53 (28.5)	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	64 (68.8)	137 (74.9)	135 (72.6)	133 (71.5)	[redacted]	[redacted]
Number of migraine days per month in last 3 months										
Mean (SD)	7.2 (2.47)	7.3 (2.40)	7.3 (2.43)	7.7 (2.57)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of headache days per month in last 3 months										
Mean (SD)	9.3 (2.69)	9.2 (2.69)	9.1 (2.71)	9.5 (2.76)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute migraine treatment, n (%)										

Characteristic	ADVANCE study				CGP-MD-01 study				ELEVATE study	
	ATO 10 mg q.d.	ATO 30 mg q.d.	ATO 60 mg q.d.	PBO	ATO 10 mg q.d.	ATO 30 mg q.d.	ATO 60 mg q.d.	PBO	ATO 60 mg q.d.	PBO
Triptans	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ergots	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NSAIDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Opiates	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antiemetic drugs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Barbiturates	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline efficacy parameters (mITT population)										
N (% of ITT)	**214 (96.40)**	**223 (96.96)**	**222 (96.10)**	**214 (95.96)**	**92 (97.87)**	**182 (98.38)**	**177 (94.65)**	**178 (95.70)**	**151 (96.8)**	[redacted]
Number of monthly migraine days										
Mean (SD)	7.5 (2.46)	7.9 (2.32)	7.8 (2.31)	7.5 (2.39)	7.63 (2.51)	7.64 (2.37)	7.74 (2.59)	7.81 (2.51)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of monthly headache days										
Mean (SD)	8.4 ([redacted])	8.8 ([redacted])	9.0 ([redacted])	8.4 ([redacted])	8.89 ([redacted])	8.74 ([redacted])	8.86 ([redacted])	9.07 ([redacted])	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of monthly acute medication use days										
Mean (SD)	6.6 ([redacted])	6.7 ([redacted])	6.9 ([redacted])	6.5 ([redacted])	6.16 ([redacted])	6.62 ([redacted])	6.79 ([redacted])	6.57 ([redacted])	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MSQ version 2.1 role function-restrictive domain score										

Characteristic	ADVANCE study				CGP-MD-01 study				ELEVATE study	
	ATO 10 mg q.d.	ATO 30 mg q.d.	ATO 60 mg q.d.	PBO	ATO 10 mg q.d.	ATO 30 mg q.d.	ATO 60 mg q.d.	PBO	ATO 60 mg q.d.	PBO
Mean (SD)	44.9 (21.37)	44.0 (19.61)	46.8 (20.36)	46.8 (19.67)	NA	NA	NA	NA	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monthly performance of daily activities domain score of the AIM-D										
Mean (SD)	15.5 (8.85)	16.9 (8.02)	15.9 (8.34)	15.2 (8.25)	NA	NA	NA	NA	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	[redacted]	[redacted]
Monthly physical impairment domain score of the AIM-D										
Mean (SD)	11.7 (8.46)	13.0 (8.00)	11.6 (7.85)	11.2 (8.11)	NA	NA	NA	NA	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	[redacted]	[redacted]

AIM-D = Activity Impairment in Migraine–Diary; ATO = atogepant; BMI = body mass index; ITT = intention to treat; mITT = modified intention to treat; MSQ = Migraine-Specific Quality-of-Life Questionnaire; NA = not applicable; NSAID = nonsteroidal anti-inflammatory drug; PBO = placebo; q.d. = once daily; SD = standard deviation.

[a]In the ADVANCE study, patients who reported multiple races or ethnicities are only included in the "multiple" category.

[b]In the CGP-MD-01 study, patients who reported 2 or more races or ethnicities, including patients who reported white and 1 or more other races or ethnicities were included in the "multiple" category.

Sources: ADVANCE Clinical Study Report,[13] CGP-MD-01 Clinical Study Report,[14] and ELEVATE Clinical Study Report.[15]

All investigational products were provided in identical blister cards to maintain blinding. Over-encapsulation was implemented to maintain study masking. Given the twice daily dosing regimen in 2 groups, all patients took their first dose of study intervention at the clinic at visit 2 (i.e., at randomization) and were to take the second dose of study intervention (or placebo) approximately 12 hours later. No stratification was performed.[14]

In the ELEVATE trial, eligible patients were randomized 1:1 via IWRS to atogepant 60 mg once daily or placebo. Randomization was stratified based on region (North America and Europe), number of migraine days during the screening or baseline period (4 to < 8 and ≥ 8), and number of classes of failed prior prophylactic treatments (2 and > 2). Patients were instructed to take the study intervention once a day at approximately the same time each day. A randomization cap of 20% was instituted to ensure that the planned randomized patients included no more than 20% of patients with 4 migraine days to fewer than 8 migraine days at baseline. Approximately 50% of randomized patients were also to have failed more than 2 classes of prior prophylactic treatments.[15]

In all studies, atogepant and placebo were provided as oral tablets containing placebo, atogepant 10 mg (or matching placebo), atogepant 30 mg (or matching placebo), or atogepant 60 mg (or matching placebo) on an outpatient basis. Patients were required to take the assigned intervention for 12 weeks and were followed for 4 weeks after discontinuation of the study intervention. Study sites dispensed the study intervention to patients at visit 3, visit 4, visit 5, and visit 6. Compliance was closely monitored by counting the number of tablets dispensed and returned.[13-15]

Withdrawal criteria for all studies included patients who became pregnant, patients who had postbaseline clinical laboratory values that met any of the laboratory criteria related to abnormal liver function (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] ≥ 3 × ULN and the patient was symptomatic with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia [> 5%], ALT or AST ≥ 3 × ULN and total bilirubin > 2 × ULN, ALT or AST ≥ 3 × ULN and international normalized ratio > 1.5, ALT or AST ≥ 5 × ULN for more than 2 weeks, or ALT or AST ≥ 8 × ULN), and who were advised not to be rechallenged, and patients who replied with “yes” to question 4 or question 5 in the suicidal ideation section or “yes” to any question in the suicidal behaviour section of the C-SSRS at visit 3 through visit 6. A patient with a condition and/or a situation that, in the investigator's opinion, may have put them at significant risk, may have confounded the study results, or may have interfered significantly with their participation in the study were withdrawn from treatment. All randomized patients who prematurely discontinued from the study, regardless of cause, were to return to the clinic for final study assessments.[13-15]

Prior and Concomitant Therapy

The following medications for acute migraine treatment were allowed during all studies: any triptan, any ergot derivative, any opioid (although opioids were not permitted in the ELEVATE study),[15] any other form of analgesic (including acetaminophen), any NSAID, and any antiemetic drug.[13,14] In all studies, Aspirin up to 325 mg per day was allowed for cardiac prophylaxis and selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors were permitted if treatment had been stable for at least 60 days before

screening and continued without change in dose throughout the studies.[13-15] Study CGP-MD-01 noted that the daily use of pregabalin was permitted.[14]

The following medications were prohibited 30 days before visit 1 and throughout the study period for the ADVANCE, CGP-MD-01, and ELEVATE studies: strong and moderate cytochrome P450 3A4 inhibitors (e.g., itraconazole, ketoconazole, fluconazole) and inducers (e.g., phenobarbital and primidone), strong organic anion-transporting polypeptide 1B1 inhibitors (e.g., gemfibrozil), drugs with narrow therapeutic margins with theoretical potential for cytochrome P450 drug interactions (e.g., warfarin), medications with demonstrated efficacy for the prevention of migraine (e.g., amitriptyline, topiramate, propranolol), botulinum toxin injections into areas of the head, face, or neck within 6 months before visit 1, and acupuncture, transcutaneous electrical nerve stimulation, cranial traction, nociceptive trigeminal inhibition or occipital nerve block treatments, or dental splints for headache, within 4 weeks before entry into the baseline phase.[13-15] Additional prohibited medications in the ADVANCE and ELEVATE studies included cannabidiol oil, and injectable mAbs blocking the CGRP pathway (e.g., Aimovig, Emgality, Ajovy) within 6 months before visit 1 and through the study period.[13,15]

In addition, patients in all studies were asked to refrain from making significant changes to their diet or caffeine intake during the study and were to refrain from consuming grapefruit or grapefruit juice. Alcohol intake was to be limited to no more than 1 drink per day in the ADVANCE and ELEVATE studies,[13,15] and 3 drinks per day in study CGP-MD-01.[14]

Table 8: Summary of Outcomes of Interest Identified in the CADTH Review Protocol

Outcome measure	ADVANCE study	CGP-MD-01 study	ELEVATE study
Migraine days	Primary	Primary	Primary
Headache days	Secondary	Secondary	Secondary
MSQ version 2.1	Secondary	Not assessed	Secondary
HIT-6	Secondary	Secondary	Secondary
AIM-D	Secondary	Not assessed	Secondary
Acute MUDs	Secondary	Secondary	Secondary
Triptan use day	Secondary	Secondary	Secondary
MIDAS	Secondary	Not assessed	Secondary
PGIC	Secondary	Secondary	Secondary
PGI-S	Secondary	Not assessed	Secondary
WPAI:Migraine	Secondary	Secondary	Secondary

AIM-D = Activity Impairment in Migraine–Diary; HIT-6 = 6-item Headache Impact Test; MIDAS = Migraine Disability Assessment; MSQ = Migraine-Specific Quality-of-Life Questionnaire; MUD = medication use day; PGI-S = Patient Global Impression–Severity; PGIC = Patient Global Impression of Change; WPAI:Migraine = Work Productivity and Activity Impairment Questionnaire: Migraine.

Outcomes

A list of efficacy end points identified in the CADTH review protocol that were assessed in the clinical trials included in this review is summarized in Table 8. A detailed discussion and critical appraisal of the outcome measures is provided in Appendix 4.

Efficacy Outcomes

In all studies, efficacy measurements including headache duration, headache characteristics, symptoms, and acute medication use were based on information recorded by the patient in an eDiary.[13-15]

A complete list of the primary and secondary end points in the included trials is summarized in Table 6. The primary efficacy end point of the ADVANCE, CGP-MD-01, and ELEVATE studies was the change from baseline in mean MMDs across the 12-week treatment period.[13,14] Baseline was defined as the number of migraine days during the last 28 days of the baseline phase. A migraine day (a migraine headache day in study CGP-MD-01) was defined as any calendar day on which a headache occurred that met criteria 1, 2, and 3, or met criteria 4 and 5 (a probable migraine headache day in study CGP-MD-01), per the eDiary:[13-15]

1. Headache with at least 2 of the following characteristics — unilateral location, pulsating quality, or moderate or severe pain intensity, or had been aggravated by or causing avoidance of routine physical activity (e.g., walking, climbing stairs)
2. Headache with at least 1 of the following — nausea and/or vomiting, photophobia and phonophobia, or typical aura (i.e., visual, sensory, or speech and/or language) accompanying or within 60 minutes before headache begins
3. Headache whose duration lasts 2 hours or longer on a calendar day unless an acute, migraine-specific medication (i.e., triptan or ergot derivative) was used after the start of the headache, in which case no minimum duration was specified
4. Any headache that fulfilled 1 criterion from (1) and at least 1 criterion from (2) **or** fulfilled at least 2 criteria from (1) and no criteria from (2)
5. Headache whose duration lasts 2 hours or longer on a calendar day unless an acute, migraine-specific medication (i.e., triptan or ergot derivative) was used after the start of the headache, in which case no minimum duration was specified.

Additional headache-related outcomes and definitions in the included trials were:[13-15]

- headache days, which were defined as any calendar day on which headache pain lasting 2 hours or longer occurred unless an acute headache medication (e.g., ibuprofen, triptan) was used after the start of the headache, in which case no minimum duration was specified
- monthly acute MUDs, which were defined as any day on which a patient reported, per their eDiary, the intake of allowed medication(s) for the acute treatment of migraine
- monthly triptan use days, which were defined as any day on which a patient reported the intake of a triptan to treat a migraine per patient eDiary.

Health outcome measures included in the ADVANCE study and the CGP-MD-01 study included MSQ version 2.1, HIT-6, AIM-D, MIDAS, Patient Global Impression of Change (PGIC), Patient Global Impression–Severity

(PGI-S), and the Work Productivity and Activity Impairment questionnaire.[13,14] A detailed discussion of these outcomes is provided in Appendix 4.

The MSQ version 2.1 is a 14-item questionnaire designed to measure HRQoL impairments attributed to migraine in the past 4 weeks. It is divided into 3 domains: role function-restrictive, which assesses how migraines limit one's daily social and work-related activities; role function-preventive, which assesses how migraines prevent these activities; and the emotional function (EF) domain, which assesses the emotions associated with migraines. Patients respond to items using a 6-point scale ranging from "none of the time" to "all of the time." Raw dimension scores are computed as a sum of item responses and rescaled to a 0 to 100 scale, where higher scores indicate better quality of life.[13,26] The minimal important difference (MID) at the group level has been estimated at a change of 3.2 points for the role function-restrictive domain, 4.6 points for the role function-preventive domain, and 7.5 points for the EF domain.[27]

AIM-D is an 11-item daily diary measure that assesses the impact of migraine; it comprises 2 domains that evaluate performance of daily activities (7 items) and physical impairment (4 items). Patients are asked to rate the level of difficulty experienced in the past 24 hours with performance of daily activities (i.e., difficulty with household chores, errands, leisure activities at home, leisure or social activities outside the home, strenuous physical activities, concentrating, and thinking clearly) and physical impairment (i.e., difficulty walking, moving body, bending forward, and moving head) using a 6-point rating scale ranging from "not difficult at all," "a little difficult," "somewhat difficult," "very difficult," "extremely difficult," and "I could not do it at all." In addition to the 2 domain scores, a total score using all 11 items can also be calculated. Each raw daily domain score, as well as the raw daily total score, is transformed to a 0 to 100 scale, with higher scores indicating greater impact of migraine.[13,15,26] Two items based on a 24-hour recall were administered daily using headache and non-headache versions as additional health outcome measures and for the evaluation of AIM-D. The first item was used to assess activity level within the past 24 hours with a 5-level response scale ranging from "no activity – spent all day lying down" to "exercised – brisk walk, running, jogging, biking or other activity for 30 or more minutes." The second item was used to evaluate activity limitation with a 5-level response scale ranging from "not at all limited – I could do everything" to "extremely limited."[13,15,26] No MID was identified for patients with EM.

HIT-6 is a 6-question assessment used to measure the impact headaches have on a participant's ability to function on the job, at school, at home, and in social situations. It assesses the effect that headaches have on normal daily life and the participants' ability to function. Responses are based on frequency using a 5-point scale ranging from "never" to "always." The HIT-6 total score, which ranges from 36 to 78, is the sum of the responses — each of which is assigned a score ranging from 6 points (never) to 13 points (always).[13-15,26] The estimated within-group MID for the HIT-6 was 2.5 points, while the estimated between-group MID was 1.5 points in patients with EM.[28]

MIDAS is a 7-item questionnaire designed to quantify headache-related disability over a 3-month period. The MIDAS score is the sum of missed work or school days, days at work or school plus days of household work where productivity was reduced by half or more, missed household workdays, and missed nonwork activity

days due to headaches in the last 3 months.[13,15,26] The estimated MID for MIDAS was a change of 3.7 points to 4.5 points for patients with EM and CM.[29,30]

PGIC is a single item used to measure the participant's impression of overall change in migraine since the first dose of study intervention. The measure uses a 7-point rating scale with responses ranging from "very much better" to "very much worse."[13,14,26] No MID was identified for patients with EM.

The Work Productivity and Activity Impairment Questionnaire: Migraine (WPAI:Migraine) is used to assess work productivity specific to migraine. The measure uses a 1-week recall and contains 6 questions related to work productivity. The WPAI:Migraine measures both presenteeism and absenteeism. The measure yields 4 scores expressed as impairment percentages ranging from 0 to 100%: the percentage of work time missed, the percentage of impairment while working, the percentage of overall work impairment, and the percentage of activity impairment due to migraine.[13,14,26] No MID was identified for patients with EM.

PGI-S is a single item used to measure the participant's impression of severity in relation to migraine symptoms overall at the time of administration of the measure. The measure uses a 5-point rating scale with responses ranging from "none" to "very severe."[13,26] No MID was identified for patients with EM.

In the ADVANCE and ELEVATE studies, the AIM-D data were collected daily via the eDiary. Additional health outcome measures such as HIT-6, MIDAS, PGIC, WPAI:Migraine, and MSQ version 2.1 were administered in an eTablet at specified clinic visits.[13]

In study CGP-MD-01, health outcome measures (HIT-6, PGIC, WPAI:Migraine) were completed via the eDiary — at predose (baseline) and at week 4, week 8, and week 12 (for HIT-6), at week 12 (for PGIC), and at predose (baseline) and at week 6 and week 12 (for WPAI:Migraine).[14]

Harms Outcomes

The safety and tolerability of atogepant in the ADVANCE, CGP-MD-01, and ELEVATE studies was measured by AEs, SAEs, clinical laboratory evaluations, vital sign measurements, electrocardiogram (ECG) parameters, and the C-SSRS. Subjective AEs were collected throughout the study and at each 4-week follow-up visit. For all AEs, the investigator provided an assessment of the severity, causal relationship to the investigational product, start and stop dates, and seriousness of the event. The following criteria defined AEs of special interest for this study: treatment-emergent suicidal ideations with intent, with or without a plan (i.e., type 4 or type 5 on C-SSRS) or any suicidal behaviours; treatment-emergent elevated ALT or AST laboratory value 3 or more times the ULN; and potential Hy's law cases (defined as concurrent ALT or AST elevation ≥ 3 × ULN and total bilirubin elevation ≥ 2 × ULN and alkaline phosphatase value < 2 × ULN).[13-15,26]

AEs were defined as any untoward medical occurrence in a patient or clinical study patient associated with the use of study intervention, whether or not considered related to the study intervention. SAEs were defined as those AEs that resulted in death, were considered to be life-threatening, resulted in the hospitalization or prolongation of existing hospitalization, resulted in persistent disability or incapacity, or were congenital anomalies or birth defects.[13-15,26]

Statistical Analysis

Sample Size and Power Calculation

Study 301 (ADVANCE Study)

The sample size of the ADVANCE study was selected to provide sufficient power for the primary efficacy end point (change from baseline in mean MMDs over 12 weeks) and the first 3 secondary end points (change from baseline in mean MHDs, mean monthly acute MUDs, and the proportion of participants with at least a 50% reduction in mean MMDs over 12 weeks).[13,26]

A total sample size of 218 participants per treatment group provided at least 98% power to detect the treatment difference between each of the 3 atogepant doses (assumed equally effective) and placebo for the primary efficacy end point. A treatment difference of −1.5 days and a SD of 3.5 days from placebo in change from baseline in mean MMDs across the 12-week treatment period was assumed for the primary end point, based on the phase II/III CGP-MD-01 study, and studies of telcagepant and the CGRP mAbs, as well as an internal study that randomized approximately 800 participants. The statistical testing plan controlled the overall type I error at 5%.[13,26]

The power calculations of the primary and secondary end points have taken the multiple comparisons into consideration by testing each dose versus placebo at a 2-sided 0.0167 significance level. Once the primary end point for each dose was significant at 0.0167 (2-sided), the secondary end points were tested sequentially. The treatment differences from placebo for the secondary end points were −1.5 (SD = 3.8) for change from baseline in mean MHDs over 12 weeks, −1.2 (SD = 3.2) for mean monthly acute MUDs over 12 weeks, and 33% placebo rate (SD = 50% atogepant rate) for the proportion of participants with at least a 50% reduction in mean MMDs over 12 weeks, resulting in statistical power of 95%, 93%, and 89%, respectively.[13,26]

Study CGP-MD-01

Statistical comparisons for study CGP-MD-01 were conducted for 30 mg atogepant or 60 mg atogepant once daily versus placebo, and 30 mg atogepant or 60 mg atogepant twice daily versus placebo. The statistical power calculations focused on dosages of 30 mg atogepant once daily, 60 mg atogepant once daily, 30 mg atogepant twice daily, and 60 mg atogepant twice daily, because the 10 mg atogepant once daily was considered to be a suboptimal dose and was only tested if at least 1 of the 4 dose comparisons was significant.

The assumed effect size and estimated power for the primary end point of study CGP-MD-01 are summarized in Table 9. For critical alpha level 0.0125, the powers are displayed based on an SD estimate of 4.0 in the study's Statistical Analysis Plan. In the protocol and Clinical Study Report, however, the powers were based on an SD estimate of 3.0. Power was calculated via 10,000 simulations based on multiplicity adjustment for the 5 doses and primary and secondary end points. With the allocated one-quarter weight, each of the hypotheses will be tested at an alpha level of 0.0125 using the Bonferroni approach.[14,26]

Differences between treatment groups in the change from baseline in the mean number of migraine or probable migraine headache days at the primary time point (week 9 to week 12) was assumed to be 1.5 for the comparison of 30 mg atogepant or 60 mg atogepant once daily (assumed equally effective) versus

placebo and 1.75 for the comparison of 30 mg atogepant or 60 mg atogepant twice daily (assumed equally effective) versus placebo. Treatment differences were assumed based on results from other EM prevention studies. The placebo-adjusted reduction in MMDs observed from other EM prevention studies ranged from 1.1 days to 2 days (topiramate, telcagepant, and CGRP mAbs).[14,26]

Table 9: Assumed Effect Size and Estimated Power for Primary Efficacy End Point

Factor	60 mg q.d. (n = 180)	30 mg q.d. (n = 180)	10 mg q.d. (n = 90)
Assumed treatment difference vs. placebo (placebo n = 180)	−1.5	−1.4	−1.2
Effect size (common SD[a] = 3.0)	0.5	0.47	0.4
Power	99.3%	98.1%	80.3%

q.d. = once daily; SD = standard deviation; vs. = versus.

[a]The common SD was estimated based on blinded interim data assessments.

Source: Sponsor's submission.[26]

Study 304 (ELEVATE Study)

The sample size for the ELEVATE study was selected to provide sufficient power for the primary efficacy end point (change from baseline in mean MMDs) and the secondary end points in both the US and European Union (EU) applications (a 50% reduction in MMDs, change from baseline in mean MHDs, acute MUDs, MSQ version 2.1 role function-restrictive domain score, mean monthly AIM-D performance of daily activities domain score, and physical impairment domain score).[15] Statistical power for the primary and secondary end points of the ELEVATE study are summarized in Table 10.

Assuming a 15% dropout rate, the sample size of 150 patients per treatment group was selected to provide a 97% power to detect the treatment difference of −1.7 MMDs (SD = 3.5 days) between atogepant and placebo for the primary efficacy end point. Treatment differences were assumed based on the results of the comparison between atogepant 60 mg once daily and placebo from the ADVANCE study. Assumptions for SD were based on the variance in the LIBERTY study[31] and monthly variance observed in the ADVANCE study for the primary end point.[15]

A dropout rate of 21% was assumed for the AIM-D end points based on the higher missingness of AIM-D end points observed in the ADVANCE study.[15]

Table 10: Statistical Power for Primary and Secondary End Points for the US Filing — mITT Population, ELEVATE Study

Hypothesis testing	End point	Treatment difference vs. PBO	SD	Statistical power
Primary	CFB in mean MMDs at week 12	−1.7	3.5	97%
Secondary 1	50% reduction in mean MMD	PBO: 29% ATO: 60%	NA	99%
Secondary 2	CFB in mean MHDs at week 12	−1.7	3.7	95%
Secondary 3	CFB in mean monthly acute MUDs at week 12	−1.5	3.1	97%
Secondary 4	CFB in MSQ version 2.1 role function-restrictive domain score at week 12	10.8	22.6	96%
Secondary 5	CFB in mean monthly performance of daily activities domain score of the AIM-D	−3.3	7.3	93%
Secondary 6	CFB in mean monthly physical impairment domain score of the AIM-D	−2.4	6.4	81%

AIM-D = Activity Impairment in Migraine–Diary; ATO = atogepant; CFB = change from baseline; MHD = monthly headache day; mITT = modified intention to treat; MMD = monthly migraine day; MSQ = Migraine-Specific Quality-of-Life Questionnaire; MUD = medication use day; NA = not applicable; PBO = placebo; SD = standard deviation; vs. = versus.

Source: ELEVATE Clinical Study Report.[15]

Statistical and Analytical Plans

Efficacy Analysis

ADVANCE and ELEVATE Studies

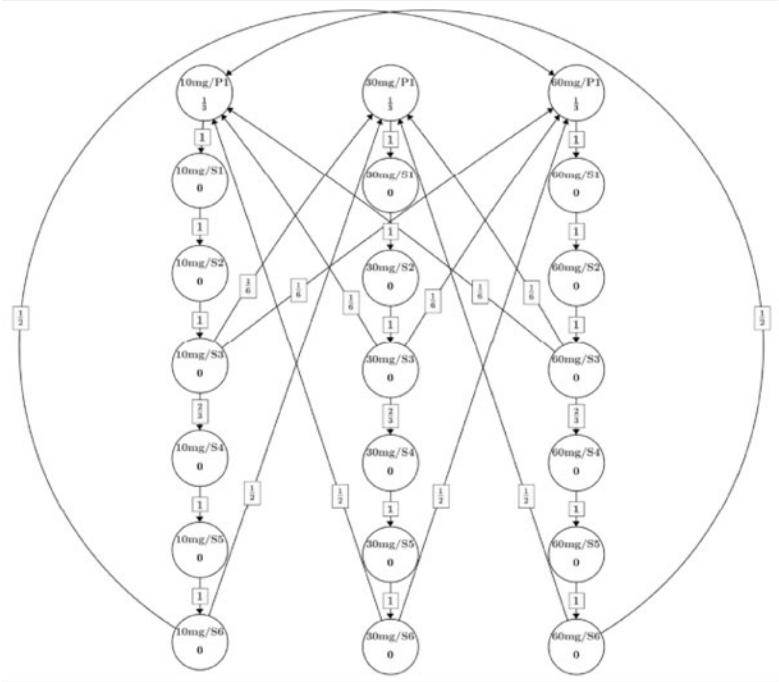
Primary and secondary end point analyses: In the ADVANCE and ELEVATE studies, all efficacy analyses were performed using the modified intention-to-treat (mITT) population. The primary comparison between treatment groups in the ADVANCE and ELEVATE trials was analyzed using a mixed model of repeated measures (MMRM) of the change from baseline. In the ADVANCE study, the statistical model included treatment group, visit, prior exposure to a migraine prevention medication with proven efficacy (yes or no), and treatment-group-by-visit interaction as categorical fixed effects. It also included the baseline score and baseline-by-visit interaction as covariates. An unstructured covariance matrix was used to model the covariance of within-participant repeated measurements. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom. The analysis was performed based on all postbaseline values using only the observed cases without imputation of missing values. Pairwise contrasts in the MMRM model were used to make the pairwise comparisons of each atogepant dose to placebo. A reduction of at least 50% in the 3-month average of MMDs was analyzed using a logistic regression model. The other secondary efficacy end points were analyzed in the same manner as that used to analyze the primary end point.[13]

In the ELEVATE study, the statistical model included treatment group, visit (derived as week 1 to week 4, week 5 to week 8, and week 9 to week 12), region, number of classes of failed prior prophylactic treatments (2 and > 2), and treatment-group-by-visit interaction as categorical fixed effects, as well as baseline MMDs and baseline-by-visit interaction as covariates. A restricted maximum likelihood method was used, including

an unstructured covariance matrix to model the covariance of within-participant repeated measurements. If there was no convergence in the model, then the Toeplitz covariance structure was used, and if the Toeplitz model did not converge, the compound symmetry covariance structure was used. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom. Treatment effect and treatment comparison were estimated by the LSMs and their difference in LSMs, along with their SE and 95% CI, and the P value corresponding to the between–treatment group difference. The secondary end points for MHDs, acute MUDs, the performance of daily activities domain score of the AIM-D, and the physical impairment domain score of the AIM-D were analyzed in the same manner as that used to analyze the primary end point. For the MSQ version 2.1 role function-restrictive domain score and the HIT-6 total score, the analyses were performed similarly to the primary MMRM, with a focus on the pairwise contrasts of the atogepant dose group to placebo at week 12. A logistic regression model was used to analyze the 50% responders across the 12-week treatment period. The model assumed a binary distribution for the response and used a logit link. The analysis model included treatment group, region, the stratification of number of classes of failed prior prophylactic treatments (2 and > 2), and baseline MMDs. The treatment difference in terms of the odds ratio (OR) between each atogepant dose group and placebo was estimated and tested from this model.[15]

In the ADVANCE study, the overall familywise error rate was controlled at an alpha of 0.05 for the set of primary and secondary end point comparisons between each dose level of atogepant versus placebo. Specifically, the overall type I error rate for multiple comparisons across 3 atogepant doses and the primary and secondary efficacy end points was controlled at the 0.05 level using a graphical approach with a weighted Bonferroni test procedure. The graphical approach to multiplicity adjustment is summarized in Figure 5. The 3 doses were treated equally. The initial allocation of the overall significance level to the 3 primary hypotheses was one-third of the overall significance level for each dose, and no initial alpha level was allocated to the hypotheses for secondary end points. Within each individual dose, testing started from the primary end point (change from baseline in mean MMDs), and the secondary end points were then tested in a prespecified order (change from baseline in MHDs, change from baseline in acute MUDs, a 50% or greater reduction in a 3-month average of MMDs, change from baseline in the MSQ version 2.1 role function-restrictive domain score, change from baseline in the performance of daily activities domain score of AIM-D, and change from baseline in the mean monthly physical impairment domain score of AIM-D). If the null hypotheses for both the primary and the first 3 secondary end points were rejected for 1 of the doses, one-third of the associated alpha was passed to the other doses (a one-sixth fraction for each dose) to increase the chances of success for the other doses in testing end points in the primary positions of the hierarchy, and the remaining two-thirds of the associated alpha was reserved for testing health outcome end points (MSQ version 2.1, AIM-D) within the same dose. If hypotheses for 3 health outcome end points were rejected within a dose based on the remaining alpha, the alpha for this dose was propagated to the other 2 doses to make full use of the alpha.

Figure 5: Multiple Comparisons Procedure — ADVANCE Study



P = primary; S = secondary.

Source: ADVANCE Statistical Analysis Plan.[26]

In the ELEVATE study, the overall familywise type I error rate was controlled at the 0.05 level using a fixed sequence procedure for primary and secondary efficacy variables, where once the primary end point for atogepant versus placebo was significant at the 2-sided 0.05 level, the secondary end points were tested sequentially (following the hierarchy outlined in Table 10). Statistical powers for secondary end points were conditional on the success of prior end points in the sequence. All additional secondary and exploratory efficacy end point analyses were performed at the nominal significance level, without adjusting for multiplicity.[15]

Sensitivity analyses: In the ADVANCE study, a total of 4 sensitivity analyses for missing data handling were conducted.[13,26]

- **Analysis of covariance (ANCOVA) model based on a 3-month average of MMDs:** The response variable for the ANCOVA model was the change from baseline in a 3-month average of MMDs for each patient. The ANCOVA model included terms for treatment, prior exposure (yes or no) to a migraine prevention medication with proven efficacy, and baseline score. The treatment difference for atogepant doses versus placebo was estimated and reported along with the corresponding 95% CI and nominal P value for superiority testing. This analysis was also termed as supportive analysis.
- **Within-group imputation based on observed data:** A sensitivity analysis was performed based on imputation using patients from the same treatment group with observed data under the missing at

random (MAR) assumption. Missing data for patients who prematurely discontinued were assumed to copy the profile of patients in the same treatment group with observed data.

- **Copy-reference approach:** The copy-reference approach was performed on the primary end point to assess the robustness of the MMRM analysis to possible violation of the MAR assumption. This sensitivity analysis is 1 type of pattern-mixture models (PMMs), under which data could be missing not at random, with repeated analyses combined via the reference-based multiple imputation procedure. Patients who discontinued in the atogepant groups were assumed to have no treatment effect after the discontinuation. Patients were assumed to copy the profile of the placebo group and missing values were imputed based on the distribution estimated from the placebo group under the MAR using the copy-reference approach.
- **MMRM based on primary measures collected during the double-blind and follow-up periods:** The off-treatment hypothetical estimand in support of the EU filing served as 1 sensitivity analysis in support of the US filing.

One additional sensitivity analysis for possible violations of the normality assumption was conducted in the ADVANCE trial. The normality test was performed on the residuals that were generated by the same MMRM that was used for the primary efficacy analysis. The residuals are scaled by the inverse Cholesky root of its estimated variance-covariance matrix. The Kolmogorov-Smirnov test for normality was applied to the decorrelated and scaled residuals and the normality test was rejected if the P value from the Kolmogorov-Smirnov test was less than 0.01. If the normality test was rejected, the sensitivity analysis used multiple imputation in conjunction with robust regression to assess the robustness of the primary MMRM analysis to the possible violation of normality assumption.[13,26]

In the ELEVATE study, sensitivity analyses on the primary end point for handling missing data were identical to those of the ADVANCE study and included an ANCOVA model based on a 3-month average of the MMDs, a within-group imputation based on observed data, and a copy-reference approach, using the off-treatment hypothetical estimand in support of the EU filing as a sensitivity analysis for the US filing. An additional sensitivity analysis for possible violations of the normality assumption was conducted. As noted, all sensitivity analyses were conducted in the same manner as those of the ADVANCE study described earlier; however, model factors varied with the ELEVATE study, including terms for treatment, region, and number of classes of failed prior prophylactic treatments (2 and > 2) as fixed factors, and baseline MMD as a covariate.[15]

Subgroup analysis: Prespecified subgroups in the ADVANCE study were conducted in the mITT population for 2 subgroups of patients based on prior exposure to migraine prevention medication with proven efficacy. One subgroup had prior exposure to migraine prevention medication with proven efficacy (N = 608) and the other subgroup, also referred to as the naive subgroup, did not (N = 265).[13]

Prespecified subgroup analyses for the primary efficacy end point in the ELEVATE study included region (North America and Europe), patients who had baseline migraine days (4 to < 8 and ≥ 8), patients who had failed 2 classes of prior oral prophylactic treatments, patients who had failed 3 or more classes of prior oral prophylactic treatments, and patients who had failed 3 classes of prior oral prophylactic treatments. For

each subgroup analysis, treatment effect and treatment comparison were estimated by the LSMs and their difference in LSMs, along with SEs and 95% CIs.[15]

Other efficacy analyses: Other efficacy and health outcomes research analyses in the ADVANCE and ELEVATE trials, including the HIT-6, MIDAS, PGIC, PGI-S, WPAI:Migraine, and time point analyses of primary and key secondary end point analyses, were performed at the nominal significance level, without adjusting for multiplicity.[13,15]

Safety analyses: Safety parameters in the ADVANCE and ELEVATE trials included AEs, clinical laboratory evaluations, vital sign measurements, ECG parameters, and the C-SSRS tool. All safety analyses were performed using the safety population, which consisted of all participants who took at least 1 dosage of study intervention.[13,15]

In both the ADVANCE and ELEVATE studies, an independent data safety monitoring board was established to review unblinded safety data and summary reports, identify any safety issues and trends, and make recommendations to the sponsor, including modification or early termination of the trial if emerging data showed unexpected and clinically significant AEs.[13,15]

Study CGP-MD-01

Primary and secondary end point analyses: The primary efficacy end point of change from baseline in mean MMDs across the 12-week treatment period was analyzed using a MMRM. The response variable was the change from baseline to each postbaseline month in MMDs. The model included baseline MMDs as a covariate, treatment group and visit (month) as fixed factors, and treatment-group-by-visit and baseline-by-visit as interaction terms. The analysis was performed based on evaluable postbaseline data using only the observed cases without imputation of missing values. The restricted maximum likelihood method was used. The within-patient correlation was modelled using the unstructured covariance matrix. If the model did not converge, then the compound symmetry covariance structure would be used. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. Contrasts were constructed to obtain the average treatment effects across the 12-week treatment period to compare each atogepant treatment group with the placebo group. All treatment effects and treatment comparisons were estimated by the LSMs and their differences in LSMs, along with their SEs and 95% CIs, and the P value corresponding to the between–treatment group difference.[14]

The overall type I error rate for multiple comparisons across active treatment doses and the primary and secondary efficacy parameters was controlled at the 0.05 level. The weighting strategy of the multiple comparisons was designed to allocate initial alpha equally to the once daily and twice daily dose regimens. Within each dosing regimen, individual atogepant doses were tested in a hierarchical order from high to low dose (i.e., for primary efficacy end point, the low dose was tested only if the high dose comparison showed statistical significance). In addition, for a given dose comparison versus placebo, the strategy had the primary end point (change from baseline in mean MMDs) as gatekeeper to the secondary end points (change from baseline in mean MHDs, proportion of patients with at least a 50% reduction in mean MMDs, and change from baseline in mean monthly acute MUDs) so that secondary end points could be tested only

if the primary hypothesis of the corresponding dose comparison reached statistical significance. Weighted Bonferroni tests were used for testing the hypotheses.[14]

For continuous variables, pairwise comparisons were analyzed using MMRM, with baseline covariates. For variables where data were binary, comparisons between treatment groups were done by pairwise contrasts using logistic regressions for variables with only 1 postbaseline assessment or using a generalized linear mixed model for variables with multiple postbaseline assessments.[14]

Sensitivity analyses: In study CGP-MD-01, 2 sensitivity analyses were performed on the primary end point. The first used a PMM approach based on the copy-reference method for missing value imputation using a missing-not-at-random mechanism for missing data to assess the impact of potential deviation from a MAR assumption in the primary analysis. The PMM analysis used the placebo group as the reference. The missing pattern was defined by the patient's last visit with an observed value. Any intermediate missing values were imputed using the last observation carried forward approach. The missing values in the reference group were imputed using the observed data in that group under the MAR assumption. The missing values in any other treatment group were then imputed using the observed data from that treatment group and the distribution estimated from the reference group. The dataset with missing values imputed were analyzed using an ANCOVA model with treatment group as a factor and baseline value as a covariate for treatment comparison at week 9 to week 12. The imputation of missing values and the analysis were performed multiple times, and the inference was based on the combined estimates using the standard multiple imputation technique.[14,26]

The second sensitivity analysis used multiple imputations in conjunction with robust regression to assess the robustness of the primary MMRM analysis with respect to the possibility of a violation of the normality assumption.[26]

Other efficacy analyses: In general, other efficacy analyses were performed at the nominal significance level, without adjusting for multiplicity. Descriptive statistics were provided by visit for each efficacy variable by treatment group. An analysis of change from baseline in the EQ-5D visual analogue scale score at week 6 and week 12 were limited to descriptive summary statistics.[14]

Safety analyses: The safety analyses were performed using the safety population. The safety parameters were AEs and clinical laboratory, vital sign, and ECG parameters, and the C-SSRS tool. For each of the clinical laboratory, vital sign, and ECG parameters, the last nonmissing safety assessment before the initial dose of treatment was used as the baseline for all analyses of that safety parameter. Continuous variables were summarized by the number of patients and mean, SD, median, minimum, and maximum values. Categorical variables were summarized by the number and percentage of patients.[14]

An independent data safety monitoring board was established to review unblinded safety data and summary reports, identify any safety issues and trends, and make recommendations to the sponsor, including modification or early termination of the trial if emerging data showed unexpected and clinically significant AEs.[14]

Analysis Populations

The following analysis populations were defined in the ADVANCE, CGP-MD-01, and ELEVATE studies:

- the intention-to-treat (ITT) population included all randomized patients
- the safety population included all patients who received at least 1 dosage of study intervention
- the mITT population included all randomized patients who received at least 1 dosage of study intervention, had an evaluable baseline period of eDiary data, and had at least 1 evaluable postbaseline 4-week period of eDiary data during the double-blind treatment period. In study CGP-MD-01, "evaluable" was defined as having at least 20 days of diary data during the 4-week baseline period and as having at least 12 days of diary data for each postbaseline 4-week treatment period.

In the ADVANCE and ELEVATE studies, an additional analysis population was included. The analysis population for an off-treatment hypothetical estimand, which was used as the primary population in support of the EU filing and was defined as all randomized participants who received at least 1 dosage of study treatment, had an evaluable baseline period of eDiary data, and had at least 1 evaluable postbaseline 4-week period (week 1 to week 4, week 5 to week 8, week 9 to week 12) of eDiary data, regardless of whether on study treatment or off study treatment. Analyses from this population were not included in this report.

Protocol Amendments and Deviations

Protocol deviations in the ADVANCE, CGP-MD-01, and ELEVATE studies are summarized in Table 11.

In the ADVANCE trial, the proportion of patients with protocol deviations was similar across groups, ranging from 14.0% of patients to 17.4% of patients. The most frequently reported protocol deviations were prohibited concomitant medications (7.5% overall). There were 3 amendments to the original protocol for the ADVANCE study (dated September 25, 2018): Protocol Amendment 1 (dated November 30, 2018), Protocol Amendment 2 (dated February 25, 2019), and Protocol Amendment 3 (dated May 14, 2020). Protocol Amendment 1 occurred before the enrolment of any patients. The main revisions in Protocol Amendment 2 were to clarify the definition for subgroups. Protocol Amendment 3 included new methods for handling the COVID-19 pandemic to ensure patient safety, and maintaining data integrity and allowing for remote visits for visit 3 to visit 8. Investigators were allowed to conduct an in-person follow-up visit at their discretion if there were safety concerns. Aside from the potential logistical and missing data concerns due to the COVID-19 pandemic, protocol amendments generally had no major impact on the conduct of studies.[13]

In study CGP-MD-01, there was a greater range of protocol deviations across groups, ranging from 7.0% to 17.0%. The most common protocol deviation was the use of prohibited concomitant medication (placebo = 6.5%; atogepant = 7.0%). There were 2 amendments to the original protocol (dated May 9, 2016). Protocol Amendment 1 (dated November 11, 2016) specified the following significant changes: the exclusion of patients who had used injectable mAbs for CGRP and patients who had used benzodiazepines. Significant changes specified in Protocol Amendment 2 (dated September 11, 2017) included the following: allowing the participation of patients with a history of hemiplegic migraine, the revision of the primary and secondary efficacy end points to evaluate treatment effects across the entire 12 weeks of treatment instead of the last 28 days of treatment as well as the addition of sensitivity analyses of the primary end point, and the revision

of the multiple comparisons procedure and sample size calculation to reflect a revised primary end point and multiplicity strategy.[14]

In the ELEVATE trial, the proportion of patients with any major protocol deviations was similar across groups ([redacted]). The most common protocol deviation was patients entering the study despite not satisfying the entry criteria ([redacted]). The original study protocol for the ELEVATE trial (dated December 17, 2019) was amended 2 times. Protocol Amendment 1 (dated April 3, 2020) included changes to the exclusion criteria, where patients with medication overuse headache were not enrolled; randomization methods, where block randomization was applied with a block size of 6 (3 treatment groups × 2); and the primary and secondary analysis methods, where "region" was added as a factor. Protocol Amendment 2 (dated December 1, 2020) included changes to the study design, where the atogepant 30 mg once daily dose was removed based on the results of the ADVANCE study. In turn, the randomization block size and the sample size determination were also changed. Additional changes included the specification of the first 3 secondary end points, sensitivity analyses of the primary efficacy data, and the addition of various exploratory end points. Both protocol amendments occurred before the first patients' first visit.[15]

Results

Patient Disposition

Table 12 summarizes the disposition of patients enrolled in the ADVANCE and CGP-MD-01 studies. The ADVANCE study was a randomized, double-blind phase III RCT. A total of 2,270 patients were screened for eligibility, and 910 patients were randomized 1:1:1:1 to receive atogepant 10 mg (N = 222), atogepant 30 mg (N = 230), atogepant 60 mg (N = 235), or placebo (N = 223), comprising the ITT population. In total, 86.8% to 90.1% of patients completed the double-blind period of the ADVANCE study. Discontinuations were balanced between groups, with the main reasons for discontinuation in the double-blind treatment period consisting of withdrawal by patient (3.5% to 4.3%), AEs (1.7% to 4.1%), and protocol deviations (1.8% to 3.4%). Only 16.5% to 24.3% of patients entered the follow-up period, with 13.9% to 22.1% of patients completing the follow-up period.[13]

Study CGP-MD-01 was a randomized, double-blind phase II/III RCT. A total of 1,772 patients were screened for eligibility, and 834 patients were randomized 2:1:2:1:2:1 to receive placebo (N = 186), atogepant 10 mg once daily (N = 94), atogepant 30 mg once daily (N = 185), atogepant 60 mg once daily (N = 187), atogepant 30 mg twice daily (N = 89), atogepant 60 mg twice daily (N = 93), comprising the ITT population. Completion rates for the double-blind treatment period were similar across groups (79.6% to 87.7%). The most common reasons for discontinuation were withdrawal of consent, which was numerically higher in the placebo group (10.8%) compared to the atogepant groups (3.2% to 6.4%), and the occurrence of AEs, which was numerically higher in the atogepant groups (3.2% to 5.9%) compared to placebo (2.7%).[14]

Table 11: Summary of Protocol Deviations — ADVANCE Study (All Randomized Patients) and CGP-MD-01 and ELEVATE Studies (Intention-to-Treat Population)

	ADVANCE study				CGP-MD-01 study				ELEVATE study	
Protocol deviation category	Atogepant 10 mg q.d. (N = 222)	Atogepant 30 mg q.d. (N = 230)	Atogepant 60 mg q.d. (N = 235)	Placebo (N = 223)	Atogepant 10 mg q.d. (N = 94)	Atogepant 30 mg q.d. (N = 185)	Atogepant 60 mg q.d. (N = 187)	Placebo (N = 186)	Atogepant 60 mg q.d. (N = 157)	Placebo (N = 158)
Any major deviation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exclusion criteria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclusion criteria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Informed consent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pregnancy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prohibited concomitant medications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAE reporting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Safety assessment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal criteria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wrong IP treatment or incorrect dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protocol compliance: IRT — incorrect entry of patient data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Entered despite not satisfying entry criteria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

IP = investigational product; IRT = interactive response technology; q.d. = once daily; SAE = serious adverse event.

Sources: ADVANCE Clinical Study Report,[13] CGP-MD-01 Clinical Study Report,[14] and ELEVATE Clinical Study Report.[15]

The ELEVATE study was a randomized, double-blind phase III RCT. A total of [redacted] patients were screened for eligibility. Of these, [redacted] had failed the screening process, and 315 patients were randomized 1:1 to atogepant 60 mg once daily (N = [redacted]) or placebo (N = [redacted]), comprising the ITT population. In total, [redacted] of patients completed the double-blind period of the ELEVATE study. The main reasons for discontinuation ([redacted]) in the double-blind treatment period consisted of AEs ([redacted]), and protocol deviations ([redacted] Only [redacted] patients entered the follow-up period, with only [redacted] from the placebo group not completing the follow-up period due to a withdrawal by the patient.

Exposure to Study Treatments

Exposure to study treatments and the duration of treatment for the ADVANCE, CGP-MD-01, and ELEVATE studies are summarized in Table 13. The mean treatment duration with atogepant and placebo was similar across studies.

The mean duration of treatment in the ADVANCE trial was similar across treatment groups, ranging from [redacted] days in the atogepant groups compared with [redacted] in the placebo group.[13]

In study CGP-MD-01, the mean duration of treatment ranged from [redacted] in the atogepant groups compared with [redacted] in the placebo group.[14]

In the ELEVATE study, the mean duration of treatment in the atogepant 60 mg once daily group was [redacted] compared to [redacted] in the placebo group.

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported as follows. Refer to Appendix 3 for detailed efficacy data.

Migraine or Headache Days

Monthly Migraine Days

The primary end point of all included studies was the reduction in mean MMDs across the 12-week treatment period. The mean change from baseline in MMDs for all studies is summarized in Table 14.

For LSM change from baseline in MMDs in the ADVANCE study, a dose-response relationship was observed for the 3 atogepant doses, with each increasing atogepant dose: −3.69 days (95% CI, −4.11 to −3.28 days) for atogepant 10 mg, −3.86 days (95% CI, −4.27 to −3.46 days) for atogepant 30 mg, and −4.20 days (95% CI, −4.60 to −3.80 days) for atogepant 60 mg, compared with −2.48 days (95% CI, −2.90 to −2.07 days) for placebo. Results for the observed change from baseline in mean MMDs were consistent with the imputed values. Each of the 3 atogepant doses demonstrated statistically significant differences compared with placebo in the reduction of mean MMDs across the 12-week treatment period (atogepant 10 mg = −1.21 days [95% CI, −1.78 to −0.64 days; P < 0.0001]; atogepant 30 mg = −1.38 days [95% CI, −1.94 to −0.82 days; P < 0.0001]; atogepant 60 mg = −1.72 days [95% CI, −2.28 to −1.15 days; P < 0.0001]).[13]

For study CGP-MD-01, the mean change in MMDs was generally similar across the atogepant treatment groups (range = −4.00 days with atogepant 10 mg once daily to −3.55 days for atogepant 60 mg once daily) compared to −2.85 days (95% CI, −3.30 to −2.39 days) for placebo. No dose-response relationship was

evident. In all cases, decreases in mean MMDs during the treatment period were statistically significantly larger in all atogepant groups compared with placebo (atogepant 10 mg once daily = −1.15 days [95% CI, −1.93 to −0.37 days; P = 0.0039]; atogepant 30 mg once daily = −0.91 days [95% CI, −1.55 to −0.27 days; P = 0.0056]; and atogepant 60 mg once daily = −0.70 days [95% CI, −1.35 to −0.06 days; P = 0.0325]).[14]

In the ELEVATE study, the LSM change from baseline at 12 weeks of [redacted] for atogepant 60 mg once daily compared to [redacted] for placebo and the LSM difference in mean change from baseline in MMDs between atogepant 60 mg once daily and placebo was [redacted] in favour of atogepant.[15]

Sensitivity analysis: Results for the sensitivity analyses conducted in the ADVANCE, CGP-MD-01, and ELEVATE studies are summarized in Table 32, Table 34, and Table 35, respectively. In all cases, sensitivity analyses were consistent with the primary analyses, demonstrating statistically significant reductions in mean MMD with atogepant doses across the 12-week treatment periods.[13]

Results for the additional supportive analysis conducted in the ADVANCE and ELEVATE studies of the MMRM based on primary measures collected during the double-blind and follow-up periods (Table 33 and Table 36) were consistent with the primary analysis.[13]

Subgroup analysis: Results for the subgroup analyses in patients with or without prior exposure to migraine prevention therapy in the ADVANCE study are summarized in Table 37 of Appendix 3. In the subgroup of patients who had prior exposure to migraine prevention medication with proven efficacy, results were consistent with the primary analysis — with a dose-response relationship with each increasing atogepant dose with mean change from baseline in MMDs of −3.63 days (95% CI, −4.13 to −3.13 days) for atogepant 10 mg, −3.77 days (95% CI, −4.24 to −3.29 days) for atogepant 30 mg, and −4.42 days (95% CI, −4.91 to −3.94 days) for atogepant 60 mg compared to −2.26 days (95% CI, −2.74 to −1.77 days) for placebo.[13]

A post hoc subgroup analysis by number of prior preventive treatment failures was provided by the sponsor. Results for change from baseline in MMDs in this subgroup are summarized in Table 44. Among patients with 1 or more prior preventive treatment failures (N = 436), and 2 or more prior preventive treatment failures (N = 119), atogepant was associated with a greater change from baseline in MMDs compared with placebo, with the greatest LSM difference versus placebo in the atogepant 60 mg once daily group (≥ 1 = −2.24 [SE = 0.44]; ≥ 2 = −3.12 [SE = 0.88]).[13]

Table 12: Patient Disposition

Characteristic	ADVANCE study				CGP-MD-01 study				ELEVATE study	
	Atogepant 10 mg q.d.	Atogepant 30 mg q.d.	Atogepant 60 mg q.d.	Placebo	Atogepant 10 mg q.d.	Atogepant 30 mg q.d.	Atogepant 60 mg q.d.	Placebo	Atogepant 60 mg q.d.	Placebo
Screened, N	2,270				1,772				[redacted]	
Screening failure, N	1,360				938				[redacted]	
Randomized, N	222	230	235	223	94	185	187	186	[redacted]	[redacted]
DB treatment period										
Completed DB treatment period, N (%)	193 (86.9)	207 (90.0)	204 (86.8)	201 (90.1)	80 (85.1)	149 (80.5)	164 (87.7)	148 (79.6)	[redacted]	[redacted]
Discontinued from DB treatment period, N (%)	29 (13.1)	23 (10.0)	31 (13.2)	22 (9.9)	14 (14.9)	36 (19.5)	23 (12.3)	38 (20.4)	[redacted]	[redacted]
Reason for discontinuation, N (%)										
AE	9 (4.1)	4 (1.7)	6 (2.6)	6 (2.7)	4 (4.3)	11 (5.9)	6 (3.2)	5 (2.7)	[redacted]	[redacted]
Lack of efficacy	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	[redacted]	[redacted]
Withdrawal by patient or of consent	9 (4.1)	8 (3.5)	10 (4.3)	8 (3.6)	6 (6.4)	9 (4.9)	6 (3.2)	20 (10.8)	[redacted]	[redacted]
Lost to follow-up	3 (1.4)	4 (1.7)	5 (2.1)	3 (1.3)	1 (1.1)	11 (5.9)	7 (3.7)	5 (2.7)	[redacted]	[redacted]
Pregnancy	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	[redacted]	[redacted]
Protocol deviation or violation	5 (2.3)	7 (3.0)	8 (3.4)	4 (1.8)	3 (3.2)	4 (2.2)	2 (1.1)	4 (2.2)	[redacted]	[redacted]
Noncompliance	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	4 (2.2)	[redacted]	[redacted]
Other	2 (0.9)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	[redacted]	[redacted]
Follow-up period										
Number of patients entered, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Characteristic	ADVANCE study				CGP-MD-01 study				ELEVATE study	
	Atogepant 10 mg q.d.	Atogepant 30 mg q.d.	Atogepant 60 mg q.d.	Placebo	Atogepant 10 mg q.d.	Atogepant 30 mg q.d.	Atogepant 60 mg q.d.	Placebo	Atogepant 60 mg q.d.	Placebo
Number of patients completed, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients discontinued, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal by patient or of consent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ITT, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
mITT, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Safety, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Off-treatment hypothetical estimand,[a] N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; DB = double-blind; ITT = intention to treat; mITT = modified intention to treat; q.d. = once daily.

[a]The off-treatment hypothetical estimand population includes all randomized patients who received at least 1 dosage of study treatment, had evaluable baseline period data, and had at least 1 evaluable postbaseline 4-week period data during the DB treatment period and follow-up period, regardless of whether the patient was on or off study treatment. This population was used for the primary estimand in support of European Union filing.

Sources: ADVANCE Clinical Study Report,[13] CGP-MD-01 Clinical Study Report,[14] and ELEVATE Clinical Study Report.[15]

Table 13: Summary of Treatment Duration — Safety Population

Treatment duration[a] (days), n1[b] (%)	ADVANCE study				CGP-MD-01 study				ELEVATE study	
	Atogepant 10 mg q.d. (N = 221)	Atogepant 30 mg q.d. (N = 228)	Atogepant 60 mg q.d. (N = 231)	Placebo (N = 222)	Atogepant 10 mg q.d. (N = 93)	Atogepant 30 mg q.d. (N = 183)	Atogepant 60 mg q.d. (N = 186)	Placebo (N = 186)	Atogepant 60 mg q.d. (N = 156)	Placebo (N = 157)
≥ 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 35	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 56	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 63	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 70	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 77	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient-years[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

q.d. = once daily; SD = standard deviation.

[a]Treatment duration = (last study treatment date – first study treatment date) + 1.

[b]n1 = Number of participants within a specific category.

[c]Participant-years = (total treatment duration in days) / 365.25.

Sources: ADVANCE Clinical Study Report,[13] CGP-MD-01 Clinical Study Report,[14] and ELEVATE Clinical Study Report.[15]

Subgroup analysis of the ELEVATE study is summarized by the number of prior oral prophylactic treatment failures in Table 38, and by migraine days at baseline in Table 39. Results by the number of oral prophylactic treatment failures were consistent with the primary analysis, with the LSM difference in mean change from baseline in MMDs between atogepant 60 mg once daily and placebo balanced across the number of prior prophylactic treatment failures (≥ 2 = [redacted] ≥ 3 = [redacted]) in favour of atogepant, representing an LSM change from baseline at 12 weeks of [redacted]) for atogepant 60 mg once daily compared to [redacted] for placebo.[15]

For the subgroup analysis by migraine days at baseline, results were also consistent with the primary analysis, with LSM difference in mean change from baseline in MMDs between atogepant 60 mg once daily and placebo of ([redacted]) for patients with 4 migraine days to fewer than 8 migraine days at baseline, and ([redacted]) for patients with 8 or more migraine days at baseline.[15]

50% Reduction in MMDs

The proportion of patients who achieved a greater than or equal to 50% reduction in the 3-month average of MMDs was a secondary outcome in all studies. Results for a 50% reduction in mean MMDs are summarized in Table 15.

In the ADVANCE study, the OR for the proportion of patients who achieved a greater than or equal to 50% reduction in mean MMDs with atogepant versus placebo was 3.06 (95% CI, 2.05 to 4.56; P < 0.0001) for atogepant 10 mg, 3.53 (95% CI, 2.37 to 5.26; P < 0.0001) for atogepant 30 mg, and 3.82 (95% CI, 2.56 to 5.71; P < 0.0001) for atogepant 60 mg. A greater proportion of patients achieved a greater than or equal to 50% reduction in mean MMDs with atogepant (55.6%, 58.7%, and 60.8% for atogepant 10 mg, 30 mg, and 60 mg, respectively) compared to placebo (29.0%).[13]

In study CGP-MD-01, the OR for the proportion of patients who achieved a 50% or greater reduction in mean MMDs with atogepant versus placebo ranged from 1.42 (95% CI, 1.00 to 2.03) to 1.50 (95% CI, 0.98 to 2.31). The proportion of patients achieving a 50% reduction in mean MMDs in the atogepant groups was 57.6%, 53.3%, and 52.0% in the atogepant 10 mg, atogepant 30 mg, and atogepant 60 mg groups compared with 40.4% in the placebo group.[14]

In the ELEVATE study, the proportion of patients in the atogepant 60 mg once daily group versus the placebo group with a 50% or greater reduction in mean MMDs was [redacted] The OR for the proportion of patients who achieved a 50% or greater reduction in mean MMDs with atogepant 60 mg once daily over placebo was [redacted] in favour of atogepant. [15]

Table 14: Change From Baseline in Mean Monthly Migraine Days — mITT Population

Factor	ADVANCE study[a]				CGP-MD-01 study[b]				ELEVATE study[c]	
	Atogepant 10 mg q.d. (N = 214)	Atogepant 30 mg q.d. (N = 223)	Atogepant 60 mg q.d. (N = 222)	Placebo (N = 214)	Atogepant 10 mg q.d. (N = 92)	Atogepant 30 mg q.d. (N = 182)	Atogepant 60 mg q.d. (N = 177)	Placebo (N = 178)	Atogepant 60 mg q.d. (N = [redacted])	Placebo (N = [redacted])
Baseline										
Mean (SD)	7.45 (2.463)	7.86 (2.316)	7.75 (2.307)	7.51 (2.388)	7.63 (2.51)	7.64 (2.37)	7.74 (2.59)	7.81 (2.51)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Postbaseline (month 1 to month 3)[c]										
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline										
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMRM										
LSM (SE)	−3.69 (0.210)	−3.86 (0.206)	−4.20 (0.206)	−2.48 (0.210)	−4.00 (0.32)	−3.76 (0.23)	−3.55 (0.23)	−2.85 (0.23)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant vs. placebo										
LSM difference (SE)	−1.21 (0.291)	−1.38 (0.287)	−1.72 (0.288)	Reference	−1.15 (0.40)	−0.91 (0.33)	−0.70 (0.33)	Reference	[redacted]	Reference
95% CI	−1.78 to −0.64	−1.94 to −0.82	−2.28 to −1.15	Reference	−1.93 to −0.37	−1.55 to −0.27	−1.35 to −0.06	Reference	[redacted]	Reference
P value	< 0.0001	< 0.0001	< 0.0001	Reference	0.0039	0.0056	0.0325	Reference	[redacted]	Reference

CI = confidence interval; LSM = least squares mean; mITT = modified intention to treat; MMD = monthly migraine day; MMRM = mixed model of repeated measures; q.d. = once daily; SD = standard deviation; SE = standard error; vs. = versus.

[a]The MMRM for change from baseline included baseline MMDs as a covariate; prior exposure to migraine prevention medications (yes or no), treatment group, and visit (month) as fixed factors; and treatment-group-by-visit and baseline-by-visit as interaction terms, with an unstructured covariance matrix. P values were from the test between the atogepant dose group and the placebo group.

[b]The model includes treatment group and visit as fixed effects, the baseline value as a covariate, and treatment-group-by-visit and baseline-by-visit as interaction terms, with an unstructured covariance matrix. P values are from the test between the atogepant dose group and the placebo group.

[c]The MMRM for change from baseline included baseline MMDs as a covariate; treatment group, visit (month), region, and number of classes of failed prior prophylactic treatments (2 and > 2) as fixed factors; and treatment-group-by-visit and baseline-by-visit as interaction terms, with an unstructured covariance matrix.

Sources: ADVANCE Clinical Study Report,[13] CGP-MD-01 Clinical Study Report,[14] and ELEVATE Clinical Study Report.[15]

Additional responder analysis: The proportions of participants who had a 25% or more, 75% or more, and 100% reduction (improvement) in the 3-month average of MMDs was an additional efficacy outcome in the ADVANCE and ELEVATE studies and is summarized in Table 40. In the ADVANCE trial, the proportion of patients with a 25% or more reduction in 3-month mean MMDs ranged from [redacted] in the atogepant groups compared with 58.9% in the placebo group. For a 75% or more reduction in MMDs, the proportion of patients ranged from [redacted] in the atogepant groups compared with 10.7% in the placebo group. The proportion of patients with 100% reductions in 3-month mean MMDs ranged from [redacted] in the atogepant groups compared with 0.9% in the placebo group.[13]

In study CGP-MD-01, a 25% or more reduction in MMDs were observed in [redacted] of patients in the atogepant groups compared to 50.8% of patients in the placebo group at week 1 to week 4, 73.4% to 79.1% for atogepant compared to 67.3% for placebo at week 5 to week 8, and [redacted] for atogepant compared to [redacted] for placebo at week 9 to week 12. Reductions of 75% or more in MMDs were observed in [redacted] of patients in the atogepant groups compared to [redacted] for placebo at week 1 to week 4, [redacted] for atogepant groups compared to 24.8% for placebo at week 5 to week 8, and [redacted] for atogepant groups compared to [redacted] for placebo at week 9 to week 12. A 100% reduction in MMDs was observed in [redacted] of patients in the atogepant groups compared to [redacted] for placebo at week 1 to week 4; [redacted] for atogepant groups compared to [redacted] for placebo at week 5 to week 8; and [redacted] for atogepant groups compared to [redacted] for placebo at week 9 to week 12.[14]

In the ELEVATE study, the OR for the difference between atogepant 60 mg once daily and placebo in the proportion of patients achieving 25% or more, 75% or more, and 100% reductions in the 3-month mean MMDs was [redacted], [redacted], and [redacted], respectively, with [redacted], [redacted], and [redacted] patients in the atogepant 60 mg once daily group compared to [redacted], [redacted], and [redacted] patients in the placebo group achieving 25%, 75%, and 100% reductions, respectively.[15]

Subgroup analysis: Subgroup analysis results for the ADVANCE study for the subgroup of patients with or without prior exposure to migraine prevention therapy are summarized in Table 43. Results for subgroup analyses for each of the response categories (≥ 50%, ≥ 75%, and 100%) were consistent with the primary analysis regardless of prior exposure to a migraine prevention medication with proven efficacy.[13]

Results for the unplanned subgroup analysis by the number of prior preventive treatment failures provided by the sponsor for 50% reduction in MMDs are summarized in Table 44. Among patients with 1 or more prior preventive treatment failures (N = [redacted]), and 2 or more prior preventive treatment failures (N = [redacted]), results were consistent with the primary analysis that atogepant was associated with a greater proportion of patients with a 50% reduction in mean MMDs [redacted].[26]

Monthly Headache Days

The first secondary end point of the ADVANCE, CGP-MD-01, and ELEVATE studies was the change from baseline in mean MHDs across the 12-week treatment period, which is summarized in Table 16.

In the ADVANCE study, a dose-response relationship with each increasing atogepant dose was observed for the LSM change from baseline in MHDs across the 12-week treatment period: atogepant 10 mg was −3.94

days ([redacted]), atogepant 30 mg was −4.04 days ([redacted]), atogepant 60 mg was −4.23 days ([redacted]), and placebo was −2.52 days ([redacted]). Results for the observed mean change were consistent with the MMRM. All 3 doses of atogepant demonstrated statistically significant reductions in LSM difference in MHDs from baseline to 12 weeks, with the LSM difference versus placebo of −1.42 days (95% CI, −2.03 to −0.81 days; P < 0.0001) for atogepant 10 mg, −1.53 days (95% CI, −2.13 to −0.92 days; P < 0.0001) for atogepant 30 mg, and −1.71 days (95% CI, −2.32 to −1.10 days; P < 0.0001) for atogepant 60 mg.[13]

In study CGP-MD-01, the observed mean change from baseline in MHD ranged from [redacted] days across the atogepant groups and [redacted] days for placebo; however, no dose-related trend was evident in the responses. In all cases, decreases in LSM difference in MHDs during the treatment period were statistically significantly larger in all atogepant groups compared with placebo (atogepant 10 mg once daily = −1.38 days [95% CI, −2.23 to −0.54 days; P = 0.0014]; atogepant 30 mg once daily = −1.24 days [95% CI, −1.94 to −0.55 days; P = 0.0005]; and atogepant 60 mg once daily = −0.94 days [95% CI, −1.64 to −0.24 days; P = 0.0087]).[14]

In the ELEVATE trial, the LSM difference between atogepant 60 mg once daily and placebo was [redacted] in favour of atogepant. The LSM change from baseline was [redacted] for atogepant 60 mg once daily compared to [redacted] for placebo.[15]

Subgroup analysis: In the ADVANCE study, subgroup analyses based on prior exposure to migraine therapy are summarized in Table 41. Results were consistent with the primary analysis for all 3 atogepant groups compared to placebo in both the subgroup of patients who had prior exposure to migraine prevention medication with proven efficacy and the naive subgroup.[13]

Results for the unplanned subgroup analysis by number of prior preventive treatment failures provided by the sponsor for change from baseline in MHDs are summarized in Table 44. Among patients with 1 or more prior preventive treatment failures (N = [redacted]), and 2 or more prior preventive treatment failures (N = [redacted]), atogepant was associated with a greater change from baseline in MHDs compared with placebo [redacted]).[13]

Monthly Cumulative Headache Hours

Change from baseline in the mean monthly cumulative headache hours was an additional efficacy outcome of the ADVANCE, CGP-MD-01, and ELEVATE studies.

In the ADVANCE study, the LSM reduction from baseline in mean monthly cumulative headache hours across the 12-week treatment period was [redacted] for atogepant 10 mg, [redacted] for atogepant 30 mg, and [redacted] for atogepant 60 mg, compared to [redacted] for placebo. The LSM difference versus placebo was [redacted] in favour of atogepant 10 mg, atogepant 30 mg, and atogepant 60 mg, respectively.[13]

Table 15: Reduction of 50% or More in 3-Month Average of Monthly Migraine Days — mITT Population

Factor	ADVANCE study				CGP-MD-01 study				ELEVATE study	
	Atogepant 10 mg q.d. (N = 214)	Atogepant 30 mg q.d. (N = 223)	Atogepant 60 mg q.d. (N = 222)	Placebo (N = 214)	Atogepant 10 mg q.d. (N = 92)	Atogepant 30 mg q.d. (N = 182)	Atogepant 60 mg q.d. (N = 177)	Placebo (N = 178)	Atogepant 60 mg q.d. (N = [redacted])	Placebo (N = [redacted])
Responders, n (%)	119 (55.6)	131 (58.7)	135 (60.8)	62 (29.0)	53 (57.6)	97 (53.3)	92 (52.0)	72 (40.4)	[redacted]	[redacted]
Nonresponders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OR[a] vs. placebo (95% CI)[b,c]	3.06 (2.05 to 4.56)	3.53 (2.37 to 5.26)	3.82 (2.56 to 5.71)	Reference	1.50 (0.98 to 2.31)	1.46 (1.02 to 2.08)	1.42 (1.00 to 2.03)	Reference	[redacted]	Reference
P value	< 0.0001	< 0.0001	< 0.0001	Reference	0.0617	0.0369	0.0512	Reference	[redacted]	Reference

CI = confidence interval; mITT = modified intention to treat; OR = odds ratio; q.d. = once daily; vs. = versus.

[a]The OR (95% CI) and P value are based on logistic regression with treatment group, baseline value, and prior exposure (yes or no) to a migraine prevention medication with proven efficacy as explanatory variables.

[b]Analyses were based on a generalized linear mixed model of repeated measures. The model included treatment group and visit as fixed effects, the baseline value as a covariate, and treatment-group-by-visit and baseline-by-visit as interaction terms, with an unstructured covariance matrix. P values were from the test between the atogepant dose group and the placebo group.

[c]For the ELEVATE study, the OR (95% CI) and P value are based on logistic regression with treatment group, region, baseline monthly migraine days, and number of classes of failed prior prophylactic treatments (2 and > 2) as explanatory variables.

Sources: ADVANCE Clinical Study Report,[13] CGP-MD-01 Clinical Study Report,[14] and ELEVATE Clinical Study Report.[15]

In study CGP-MD-01, the change from baseline in the number of cumulative headache hours was measured in a time course manner from week 1 to week 4, week 5 to week 8, and week 9 to week 12. The LSM difference versus placebo in the number of cumulative headache hours ranged from [redacted] for week 1 to week 4, [redacted] in favour of atogepant for week 5 to week 8, and [redacted] for week 9 to week 12.[14]

In the ELEVATE study, the LSM change from baseline in the number of cumulative headache hours across the 12-week treatment period was [redacted] hours ([redacted]) for atogepant 60 mg once daily compared to [redacted]. The LSM difference between atogepant and placebo was [redacted] in favour of atogepant.[15]

Monthly Moderate to Severe Headache Days

The mean reduction from baseline in mean monthly severe headache days was an additional efficacy outcome of the ADVANCE and CGP-MD-01 studies. In the ADVANCE study, the LSM difference versus placebo in change from baseline in mean monthly severe headache days was [redacted] for atogepant 10 mg, [redacted] for atogepant 30 mg, and [redacted] for atogepant 60 mg. The LSM difference versus placebo for change from baseline in moderate to severe headache days was [redacted] for atogepant 10 mg, atogepant 30 mg, and atogepant 60 mg, respectively.[13]

In study CGP-MD-01, the change from baseline in the average headache day pain intensity, defined as the worst pain intensity participants reported on any headache day with a scale from 0 (no pain), 1 (mild), and 2 (moderate) to 3 (severe), was measured in a time course manner from week 1 to week 4, week 5 to week 8, and week 9 to week 12. The LSM difference for atogepant versus placebo in change from baseline in the average headache day pain intensity ranged from [redacted] for week 1 to week 4, [redacted] for week 5 to week 8, and [redacted] for week 9 to week 12.[14]

In the ELEVATE study, the LSM change from baseline in mean monthly severe headache days across the 12-week treatment period was [redacted] for atogepant 60 mg once daily compared to [redacted] for placebo. The LSM difference between atogepant and placebo was [redacted] in favour of atogepant.[15]

Health-Related Quality of Life

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

Change from baseline at week 12 for the MSQ version 2.1 role function-restrictive domain score was a secondary end point for the ADVANCE and ELEVATE studies and is summarized in Table 17. In the ADVANCE trial, at week 12, the LSM difference change from baseline versus placebo for the 3 atogepant treatment groups was 9.90 points (95% CI, 5.45 points to 14.36 points) for atogepant 10 mg, 10.08 points (95% CI, 5.71 points to 14.46 points) for atogepant 30 mg, and 10.80 points (95% CI, 6.42 points to 15.18 points) for atogepant 60 mg.[13]

Table 16: Change From Baseline in Mean Monthly Headache Days — mITT Population

Factor	ADVANCE study[a]				CGP-MD-01 study[b]				ELEVATE study[c]	
	Atogepant 10 mg q.d. (N = 214)	Atogepant 30 mg q.d. (N = 223)	Atogepant 60 mg q.d. (N = 222)	Placebo (N = 214)	Atogepant 10 mg q.d. (N = 92)	Atogepant 30 mg q.d. (N = 182)	Atogepant 60 mg q.d. (N = 177)	Placebo (N = 178)	Atogepant 60 mg q.d. (N = [redacted])	Placebo (N = [redacted])
Baseline										
Mean (SD)	8.41 (2.754)	8.78 (2.621)	9.00 (2.556)	8.43 (2.552)	8.89 (2.70)	8.74 (2.51)	8.86 (2.76)	9.07 (2.70)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Postbaseline (month 1 to month 3)[c]										
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline										
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMRM										
LSM (SE)	−3.94 (0.225)	−4.04 (0.221)	−4.23 (0.221)	−2.52 (0.225)	−4.31 (0.35)	−4.17 (0.25)	−3.86 (0.25)	−2.93 (0.25)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant vs. placebo										
LSM difference (SE)	−1.42 ([redacted])	−1.53 ([redacted])	−1.71 ([redacted])	Reference	−1.38 ([redacted])	−1.24 ([redacted])	−0.94 ([redacted])	Reference	[redacted]	Reference
95% CI	−2.03 to −0.81	−2.13 to −0.92	−2.32 to −1.10	Reference	−2.23 to −0.54	−1.94 to −0.55	−1.64 to −0.24	Reference	[redacted]	Reference

Factor	ADVANCE study[a]				CGP-MD-01 study[b]				ELEVATE study[c]	
	Atogepant 10 mg q.d. (N = 214)	Atogepant 30 mg q.d. (N = 223)	Atogepant 60 mg q.d. (N = 222)	Placebo (N = 214)	Atogepant 10 mg q.d. (N = 92)	Atogepant 30 mg q.d. (N = 182)	Atogepant 60 mg q.d. (N = 177)	Placebo (N = 178)	Atogepant 60 mg q.d. (N = [redacted])	Placebo (N = [redacted])
P value	< 0.0001	< 0.0001	< 0.0001	Reference	0.0014	0.0005	0.0087	Reference	[redacted]	Reference

CI = confidence interval; LSM = least squares mean; MHD = monthly headache day; mITT = modified intention to treat; MMRM = mixed model of repeated measures; NR = not reported; q.d. = once daily; SD = standard deviation; SE = standard error; vs. = versus.

[a]The MMRM for change from baseline included baseline as a covariate; prior exposure to migraine prevention medications (yes or no), treatment group, and visit (month) as fixed factors; and treatment-group-by-visit and baseline-by-visit as interaction terms, with an unstructured covariance matrix. P values were from the test between the atogepant dose group and the placebo group.

[b]The MMRM included treatment group and visit as fixed effects, the baseline value as a covariate, and treatment-group-by-visit and baseline-by-visit as interaction terms, with an unstructured covariance matrix. P values were from the test between the atogepant dose group and the placebo group.

[c]The MMRM for change from baseline included baseline MHDs as a covariate; treatment group, visit (month), region, number of classes of failed prior prophylactic treatments (2 and > 2), and number of migraine days during the screening or baseline period (4 to ≥ 8) as fixed factors; and treatment-group-by-visit and baseline-by-visit as interaction terms, with an unstructured covariance matrix.

Sources: ADVANCE Clinical Study Report,[13] CGP-MD-01 Clinical Study Report,[14] and ELEVATE Clinical Study Report.[15]

Table 17: Change From Baseline in Mean Monthly MSQ Version 2.1 Role Function-Restrictive Domain Score at Week 12 — mITT Population, ADVANCE and ELEVATE Studies

Factor	ADVANCE study[a]				ELEVATE study[b]	
	Atogepant 10 mg q.d. (N = 214)	Atogepant 30 mg q.d. (N = 223)	Atogepant 60 mg q.d. (N = 222)	Placebo (N = 214)	Atogepant 60 mg q.d. (N =)	Placebo (N =)
Baseline						
n (%)						
Mean (SD)						
Median (range)						
Postbaseline (month 1 to month 3)						
n (%)						
Mean (SD)						
Median (range)						
Change from baseline						
n (%)						
Mean (SD)						
Median (range)						
MMRM						
LSM (SE)	30.35 (1.639)	30.53 (1.593)	31.25 (1.591)	20.45 (1.617)		
95% CI						
Atogepant vs. placebo						
LSM difference (SE)	9.90 ( )	10.08 ( )	10.80 ( )	Reference		Reference
95% CI	5.45 to 14.36	5.71 to 14.46	6.42 to 15.18	Reference		Reference
P value	< 0.0001	< 0.0001	< 0.0001	Reference		Reference

CI = confidence interval; LSM = least squares mean; mITT = modified intention to treat; MMRM = mixed model of repeated measures; MSQ = Migraine-Specific Quality-of-Life Questionnaire; q.d. = once daily; SD = standard deviation; SE = standard error; vs. = versus.

Note: N = number of participants available for analysis at week 12 in the mITT population.

[a]The MMRM for change from baseline included baseline as a covariate; prior exposure to migraine prevention medications (yes or no), treatment group, and visit (month) as fixed factors; and treatment-group-by-visit and baseline-by-visit as interaction terms, with an unstructured covariance matrix. P values were from the test between the atogepant dose group and the placebo group.

[b]The MMRM for change from baseline included baseline Role Function domain score as a covariate, treatment group, visit (month), region, number of classes of failed prior prophylactic treatments (2 and > 2) and number of migraine days during the screening/baseline period (4 to ≥ 8) as fixed factors, and treatment group-by-visit and baseline-by-visit as interaction terms, with an unstructured covariance matrix. P values were from the test between the atogepant dose group and the placebo group.

Sources: ADVANCE Clinical Study Report[13] and ELEVATE Clinical Study Report.[15]

In the ELEVATE study at week 12, the LSM change from baseline of for atogepant 60 mg once daily compared to for placebo, and the LSM difference change from baseline versus placebo was in favour of atogepant 60 mg once daily.[15]

An additional efficacy outcome of the ADVANCE and ELEVATE studies was the change from baseline in the MSQ version 2.1 role function-restrictive, role function-preventive, and EF domain scores at each 4-week interval of the double-blind treatment period. These outcomes are summarized in Table 45 and Table 46 of Appendix 3.[13,15]

Subgroup analysis: Results for the unplanned subgroup analysis of the ADVANCE study by number of prior preventive treatment failures provided by the sponsor for change from baseline in the MSQ version 2.1 role function-restrictive domain are summarized in Table 44. Among patients with 1 or more prior preventive treatment failures (N = [redacted]), and 2 or more prior preventive treatment failures (N = [redacted]), the impact of atogepant was consistently greater than placebo; however, the results compared to placebo were generally greater for the subgroup of patients with 1 or more prior treatment failures. The overall LSM change from baseline was lower in the subgroups of patients with 1 or more, or 2 or more prior treatment failures compared to the primary analysis in the atogepant 10 mg and atogepant 30 mg groups.[13]

Six-Item Headache Impact Test

Change from baseline in the HIT-6 total score at all time points was an additional efficacy outcome end point of the ADVANCE, CGP-MD-01, and ELEVATE studies, and is summarized in Table 18.

In the ADVANCE study, each of the 3 atogepant groups demonstrated a greater change from baseline in HIT-6 total score compared to placebo at all times of assessment, with LSM difference at week 4 of [redacted] for atogepant 10 mg, [redacted] for atogepant 30 mg, and [redacted] for atogepant 60 mg. At week 8, the LSM difference was [redacted] for atogepant 10 mg, [redacted] for atogepant 30 mg, and [redacted] for atogepant 60 mg. At week 12, the LSM difference 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, atogepant 30 mg, and atogepant 60 mg groups compared to the placebo group, at each time point ([redacted]).[13]

In study CGP-MD-01, the change from baseline in HIT-6 scores for atogepant compared to placebo over 12 weeks was [redacted] for atogepant 10 mg, [redacted] for atogepant 30 mg, and [redacted] for atogepant 60 mg.[14]

In the ELEVATE study, the LSM change from baseline at week 4, week 8, and week 12 were [redacted], [redacted], and [redacted] for atogepant 60 mg once daily compared to [redacted], [redacted], and [redacted] for placebo. The LSM difference change from baseline in the HIT-6 total score between atogepant 60 mg once daily and placebo at week 4, week, 8, and week 12 was [redacted], [redacted], and [redacted] in favour of atogepant, respectively.[15]

Acute Headache Medication Use

Monthly Acute Medication Use Days

Acute MUDs was a secondary outcome of the ADVANCE, CGP-MD-01, and ELEVATE studies. Results for the mean change from baseline in acute MUDs for all studies are summarized in Table 19.

In the ADVANCE study, all 3 atogepant doses showed similar results for the change from baseline in mean monthly acute MUDs in the ADVANCE study. The LSM change from baseline in monthly acute MUDs was −3.66 days [redacted] for atogepant 10 mg, −3.68 days [redacted] for atogepant 30 mg, and −3.85 days ([redacted]) for atogepant 60 mg, compared with −2.35 days ([redacted] for placebo. Results for the observed change from baseline in mean monthly acute MUDs were consistent with the imputed values. Each of the 3 atogepant doses demonstrated statistically significant differences compared with placebo in the reduction of mean monthly acute MUDs across the 12-week treatment period (atogepant 10 mg = −1.31 days [95% CI, −1.81 to −0.82 days; P < 0.0001]; atogepant 30 mg = −1.33 days [95% CI, −1.82 to −0.83 days; P < 0.0001]; atogepant 60 mg = −1.50 [95% CI, −2.00 to −1.01 days; P < 0.0001]).[13]

For study CGP-MD-01, the mean change in monthly acute MUDs was generally similar across the atogepant treatment groups (range = −3.53 days for atogepant 60 mg once daily to −3.86 days for atogepant 30 mg once daily) compared to −2.42 days ([redacted]) for placebo. In all cases, decreases in mean monthly acute MUDs during the treatment period were statistically significantly larger in all atogepant groups compared with placebo (atogepant 10 mg once daily = −1.30 days [95% CI, −1.99 to −0.60 days; P = 0.0002]; atogepant 30 mg once daily = −1.44 days [95% CI, −2.01 to −0.87 days; P < 0.0001]; atogepant 60 mg once daily = −1.11 days [95% CI, −1.68 to −0.54 days; P = 0.0001]). Following adjustment for multiplicity, the treatment differences in the once daily groups for this end point did not achieve statistical significance as the results for the 50% responder end point, which were placed higher in the testing hierarchy, did not achieve significance.[14]

In the ELEVATE study, the LSM changes from baseline of [redacted] for atogepant 60 mg once daily compared to [redacted] for placebo and the LSM difference change from baseline in mean monthly acute MUDs between atogepant 60 mg once daily and placebo at week 12 was [redacted] in favour of atogepant.[15]

Subgroup analysis: In the ADVANCE study, subgroup analyses for monthly acute MUDs based on prior exposure to migraine therapy are summarized in Table 42. Results were consistent with the primary analysis for all 3 atogepant groups compared to placebo in both the subgroup of patients who had prior exposure to migraine prevention medication with proven efficacy and the naive subgroup.[13]

Results for the unplanned subgroup analysis by number of prior preventive treatment failures provided by the sponsor for change from baseline in monthly acute MUDs are summarized in Table 44. Among patients with 1 or more ([redacted]) or 2 or more prior preventive treatment failures ([redacted]), results were consistent with the primary analysis.[26]

Table 18: Change From Baseline (MMRM) in the HIT-6 Total Score at Week 4, Week 8, and Week 12 — mITT Population

Factor	ADVANCE study[a]				CGP-MD-01 study[b]				ELEVATE study	
	Atogepant 10 mg q.d. (N = 214)	Atogepant 30 mg q.d. (N = 223)	Atogepant 60 mg q.d. (N = 222)	Placebo (N = 214)	Atogepant 10 mg q.d. (N = 92)	Atogepant 30 mg q.d. (N = 182)	Atogepant 60 mg q.d. (N = 177)	Placebo (N = 178)	Atogepant 60 mg q.d. (N = [redacted])	Placebo (N = [redacted])
Week 4										
Baseline										
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMRM										
LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant vs. placebo										
LSM difference (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8										
Baseline										
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMRM										
LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant vs. placebo										

Factor	ADVANCE study[a]				CGP-MD-01 study[b]				ELEVATE study	
	Atogepant 10 mg q.d. (N = 214)	Atogepant 30 mg q.d. (N = 223)	Atogepant 60 mg q.d. (N = 222)	Placebo (N = 214)	Atogepant 10 mg q.d. (N = 92)	Atogepant 30 mg q.d. (N = 182)	Atogepant 60 mg q.d. (N = 177)	Placebo (N = 178)	Atogepant 60 mg q.d. (N =)	Placebo (N =)
LSM difference (SE)										
95% CI										
P value[c]										
Week 12										
Baseline										
n (%)										
Mean (SD)										
MMRM										
LSM (SE)										
95% CI										
Atogepant vs. placebo										
LSM difference (SE)										
95% CI										
P value[c]										

CI = confidence interval; HIT-6 = 6-item Headache Impact Test; LSM = least squares mean; mITT = modified intention to treat; MMRM = mixed model of repeated measures; NR = not reported; q.d. = once daily; SD = standard deviation; SE = standard error; vs. = versus.

[a]The MMRM for change from baseline included baseline as a covariate; prior exposure to migraine prevention medications (yes or no), treatment group, and visit (month) as fixed factors; and treatment-group-by-visit and baseline-by-visit as interaction terms, with an unstructured covariance matrix. P values were from the test between the atogepant dose group and the placebo group.

[b]The MMRM included treatment group and analysis visit as fixed factors, the baseline value as a covariate, and interactions of treatment group by analysis visit and baseline value by analysis visit. An unstructured covariance matrix was used to model the covariance of within-patient scores. P values were from the test between the atogepant dose group and the placebo group.

[c]Not adjusted for multiplicity.

Sources: ADVANCE Clinical Study Report,[13] CGP-MD-01 Clinical Study Report,[14] and ELEVATE Clinical Study Report.[15]

Table 19: Change From Baseline in Mean Monthly Acute Medication Use Days — mITT Population

Factor	ADVANCE study[a]				CGP-MD-01 study[b]				ELEVATE study[c]	
	Atogepant 10 mg q.d. (N = 214)	Atogepant 30 mg q.d. (N = 223)	Atogepant 60 mg q.d. (N = 222)	Placebo (N = 214)	Atogepant 10 mg q.d. (N = 92)	Atogepant 30 mg q.d. (N = 182)	Atogepant 60 mg q.d. (N = 177)	Placebo (N = 178)	Atogepant 60 mg q.d. (N = [redacted])	Placebo (N = [redacted])
Baseline										
Mean (SD)	6.57 (2.992)	6.69 (3.024)	6.89 (3.171)	6.48 (3.149)	6.16 (3.31)	6.62 (3.04)	6.79 (3.27)	6.57 (3.21)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Postbaseline (month 1 to month 3)										
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline										
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMRM										
LSM (SE)	−3.66 (0.183)	−3.68 (0.180)	−3.85 (0.180)	−2.35 (0.184)	−3.71 (0.29)	−3.86 (0.20)	−3.53 (0.21)	−2.42 (0.21)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant vs. placebo										
LSM difference (SE)	−1.31 ([redacted])	−1.33 ([redacted])	−1.50 ([redacted])	Reference	−1.30 ([redacted])	−1.44 ([redacted])	−1.11 ([redacted])	Reference	[redacted]	Reference
95% CI	−1.81 to −0.82	−1.82 to −0.83	−2.00 to −1.01	Reference	−1.99 to −0.60	−2.01 to −0.87	−1.68 to −0.54	Reference	[redacted]	Reference
P value	< 0.0001	< 0.0001	< 0.0001	Reference	0.0002	< 0.0001	0.0001	Reference	[redacted]	Reference

CI = confidence interval; LSM = least squares mean; mITT = modified intention to treat; MMRM = mixed model of repeated measures; NR = not reported; q.d. = once daily; SD = standard deviation; SE = standard error; vs. = versus.

[a]The MMRM for change from baseline included baseline as a covariate; prior exposure to migraine prevention medications (yes or no), treatment group, and visit (month) as fixed factors; and treatment-group-by-visit and baseline-by-visit as interaction terms, with an unstructured covariance matrix. P values were from the test between the atogepant dose group and the placebo group.

[b]The MMRM included treatment group and visit as fixed effects, the baseline value as a covariate, and treatment-group-by-visit and baseline-by-visit as interaction terms, with an unstructured covariance matrix. P values were from the test between the atogepant dose group and the placebo group.

[c]The MMRM for change from baseline included baseline monthly acute medication use days as a covariate; treatment group, visit (month), region, number of classes of failed prior prophylactic treatments (2 and > 2), and number of migraine days during the screening or baseline period (4 to ≥ 8) as fixed factors; and treatment-group-by-visit and baseline-by-visit as interaction terms, with an unstructured covariance matrix. The P value was from the test between the atogepant dose group and the placebo group.

Sources: ADVANCE Clinical Study Report,[13] CGP-MD-01 Clinical Study Report,[14] and ELEVATE Clinical Study Report.[15]

Monthly Triptan Use

Change from baseline in triptan use days was an additional efficacy outcome in the ADVANCE, CGP-MD-01, and ELEVATE studies, and was assessed in 4-week intervals and across the 12-week treatment period in the ADVANCE and ELEVATE trials, and was only assessed in 4-week intervals in study CGP-MD-01. In the ADVANCE study, the LSM change from baseline in mean monthly triptan use days over 12 weeks was [redacted] for atogepant 10 mg, [redacted] for atogepant 30 mg, [redacted] for atogepant 60 mg, and [redacted] for placebo. The LSM difference versus placebo was [redacted], [redacted], and [redacted] for atogepant 10 mg, atogepant 30 mg, and atogepant 60 mg, respectively.[13]

In study CGP-MD-01, the LSM change from baseline in monthly triptan use was greater for atogepant 10 mg, atogepant 30 mg, and atogepant 60 mg compared to placebo through week 1 to week 4 [redacted]), week 5 to week 8 [redacted], and week 9 to week 12 [redacted]). Results for observed change from baseline were similar to imputed change from baseline.[14]

In the ELEVATE study, the LSM change from baseline was [redacted] for atogepant compared to [redacted] for placebo. The LSM difference between atogepant 60 mg once daily and placebo for mean monthly triptan use days over 12 weeks was [redacted].[15]

Other Patient-Reported Outcomes

Migraine Disability Assessment

Reductions from baseline to week 12 in the MIDAS total score, MIDAS absenteeism score, and MIDAS presenteeism score were an additional efficacy outcome of the ADVANCE and ELEVATE studies. Results for MIDAS are summarized in Table 20. In the ADVANCE study, the LSM change from baseline to week 12 in the MIDAS total score was [redacted] for atogepant 10 mg, [redacted] for atogepant 30 mg, [redacted] for atogepant 60 mg, and [redacted] for placebo. There was no difference in reduction in the MIDAS total score from baseline to week 12 for any of 3 atogepant treatment groups compared with placebo (atogepant 10 mg LSM difference = [redacted] atogepant 30 mg LSM difference = [redacted], and atogepant 60 mg LSM difference [redacted]). Change from baseline in the absenteeism and presenteeism score at 12 weeks was consistent with the MIDAS total score, with LSM difference from placebo ranging from [redacted] for MIDAS absenteeism score and [redacted] for MIDAS presenteeism score.[13]

In the ELEVATE study, the LSM difference between atogepant 60 mg once daily and placebo for change from baseline in the MIDAS total score at week 12 was [redacted] The observed mean change from baseline was [redacted] for atogepant compared to [redacted] for placebo. The LSM difference between atogepant 60 mg once daily and placebo in the absenteeism score was [redacted], with an observed change from baseline of [redacted] for atogepant compared to [redacted]

[redacted]), with an observed change from baseline of [redacted] for atogepant compared to [redacted] for placebo.[15]

Table 20: Change From Baseline in MIDAS Total, Absenteeism, and Presenteeism Scores at Week 12 — mITT Population, ADVANCE and ELEVATE Studies

Factor	ADVANCE study[a]				ELEVATE study[b]	
	Atogepant 10 mg q.d. (N = 214)	Atogepant 30 mg q.d. (N = 223)	Atogepant 60 mg q.d. (N = 222)	Placebo (N = 214)	Atogepant 60 mg q.d. (N = [redacted])	Placebo (N = [redacted])
MIDAS total score						
Baseline						
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Postbaseline (week 12)						
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ANCOVA						
LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant vs. placebo						
LSM difference (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MIDAS absenteeism score						
Baseline						
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Postbaseline (week 12)						

Factor	ADVANCE study[a]				ELEVATE study[b]	
	Atogepant 10 mg q.d. (N = 214)	Atogepant 30 mg q.d. (N = 223)	Atogepant 60 mg q.d. (N = 222)	Placebo (N = 214)	Atogepant 60 mg q.d. (N =)	Placebo (N =)
n (%)						
Mean (SD)						
Median (range)						
Change from baseline						
Mean (SD)						
Median (range)						
ANCOVA						
LSM (SE)						
95% CI						
Atogepant vs. placebo						
LSM difference (SE)						
95% CI						
P value[c]						
MIDAS presenteeism score						
Baseline						
n (%)						
Mean (SD)						
Median (range)						
Postbaseline (week 12)						
n (%)						
Mean (SD)						
Median (range)						
Change from baseline						
Mean (SD)						
Median (range)						
ANCOVA						
LSM (SE)						
95% CI						
Atogepant vs. placebo						

Factor	ADVANCE study[a]				ELEVATE study[b]	
	Atogepant 10 mg q.d. (N = 214)	Atogepant 30 mg q.d. (N = 223)	Atogepant 60 mg q.d. (N = 222)	Placebo (N = 214)	Atogepant 60 mg q.d. (N =)	Placebo (N =)
LSM difference (SE)						
95% CI						
P value						

ANCOVA = analysis of covariance; CI = confidence interval; LSM = least squares mean; MIDAS = Migraine Disability Assessment; mITT = modified intention to treat; NR = not reported; q.d. = once daily; SD = standard deviation; SE = standard error; vs. = versus.

[a]The LSM difference was estimated from an ANCOVA model on change from baseline in total score, absenteeism score (question 1, question 3, and question 5), and presenteeism score (question 2 and question 4) at week 12 with terms for treatment, prior exposure (yes or no) to a migraine prevention medication with proven efficacy, and baseline score.

[b]The LSM difference was estimated from an ANCOVA model on change from baseline in presenteeism score (question 2 and question 4) at week 12 with treatment group, region, number of classes of failed prior prophylactic treatments (2 and > 2), and number of migraine days during the screening or baseline period (4 to ≥ 8) as fixed factors, and baseline score as a covariate.

[c]Not adjusted for multiplicity.

Sources: ADVANCE Clinical Study Report[13] and ELEVATE Clinical Study Report.[15]

Activity Impairment in Migraine–Diary

The mean monthly AIM-D performance of daily activities domain score and physical impairment domain score across the 12-week treatment period was a secondary end point in the ADVANCE and ELEVATE studies and is summarized in Table 21. At week 12, the change from baseline LSM difference versus placebo for the impact of migraine on performance of daily activities as measured by AIM-D was −1.19 points (95% CI, −2.56 points to 0.17 points), −2.54 points (95% CI, −3.91 points to −1.18 points), −3.32 points (95% CI, −4.68 points to −1.96 points) for the atogepant 10 mg, atogepant 30 mg, and atogepant 60 mg once daily treatment groups, respectively. For the physical impairment domain of AIM-D, the LSM difference change from baseline for atogepant versus placebo was −1.08 points (95% CI, −2.27 points to 0.11 points) for atogepant 10 mg, −1.99 points (95% CI, −3.18 points to −0.80 points) for atogepant 30 mg, and −2.46 points (95% CI, −3.65 points to −1.28 points) for atogepant 60 mg.[13]

In the ELEVATE study, the LSM change from baseline of for atogepant compared to for placebo for the impact of migraine on performance of daily activities as measured by AIM-D and the LSM difference in change from baseline for atogepant 60 mg once daily compared to placebo was . For the physical impairment domain, the LSM changes from baseline of for atogepant compared to for placebo, and the LSM difference change from baseline for atogepant 60 mg once daily compared to placebo was .[15]

Table 21: Change From Baseline in Mean Monthly AIM-D Domain Scores at Week 12 — mITT Population, ADVANCE and ELEVATE Studies

Factor	ADVANCE study[a]				ELEVATE study[b]	
	Atogepant 10 mg q.d. (N = 214)	Atogepant 30 mg q.d. (N = 223)	Atogepant 60 mg q.d. (N = 222)	Placebo (N = 214)	Atogepant 60 mg q.d. (N = [redacted])	Placebo (N = [redacted])
Performance of daily activities domain						
Baseline						
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	15.59 (8.886)	16.89 (8.089)	15.74 (8.336)	15.06 (8.319)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Postbaseline (month 1 to month 3)						
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMRM						
LSM (SE)	−7.28 (0.500)	−8.63 (0.502)	−9.41 (0.504)	−6.09 (0.504)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant vs. placebo						
LSM difference (SE)	−1.19 [redacted])	−2.54 ([redacted])	−3.32 ([redacted])	Reference	[redacted]	Reference
95% CI	−2.56 to 0.17	−3.91 to −1.18	−4.68 to −1.96	Reference	[redacted]	Reference
P value	0.0856	0.0003	< 0.0001	Reference	[redacted]	Reference
Physical impairment domain						
Baseline						
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	11.78 (8.602)	12.96 (8.065)	11.48 (7.773)	10.99 (8.032)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Postbaseline (month 1 to month 3)						
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Factor	ADVANCE study[a]				ELEVATE study[b]	
	Atogepant 10 mg q.d. (N = 214)	Atogepant 30 mg q.d. (N = 223)	Atogepant 60 mg q.d. (N = 222)	Placebo (N = 214)	Atogepant 60 mg q.d. (N =)	Placebo (N =)
Median (range)						
Change from baseline						
Mean (SD)						
Median (range)						
MMRM						
LSM (SE)	−5.11 (0.436)	−6.02 (0.438)	−6.49 (0.439)	−4.03 (0.439)		
95% CI						
Atogepant vs. placebo						
LSM difference (SE)	−1.08 (	−1.99 (	−2.46 (	Reference		Reference
95% CI	−2.27 to 0.11	−3.18 to −0.80	−3.65 to −1.28	Reference		Reference
P value	0.0743	0.0011	< 0.0001	Reference		Reference

CI = confidence interval; LSM = least squares mean; mITT = modified intention to treat; MMRM = mixed model of repeated measures; q.d. = once daily; SD = standard deviation; SE = standard error; vs. = versus.

Note: Postbaseline (month 1 to month 3) = average of the monthly performance of daily activities domain score and the physical impairment domain score of AIM-D across the 12-week treatment period.

[a]The MMRM for change from baseline included baseline as a covariate; prior exposure to migraine prevention medications (yes or no), treatment group, and visit (month) as fixed factors; and treatment-group-by-visit and baseline-by-visit as interaction terms, with an unstructured covariance matrix. P values were from the test between the atogepant dose group and the placebo group.

[b]The MMRM for change from baseline included baseline monthly Performance of Daily Activities domain score or baseline monthly Physical Impairment domain score as a covariate, treatment group, visit (month), region, number of classes of failed prior prophylactic treatments (2 and > 2) and number of migraine days during the screening/baseline period (4 to ≥ 8) as fixed factors, and treatment group-by-visit and baseline-by-visit as interaction terms, with an unstructured covariance matrix. P value is from the test between the atogepant dose group and the placebo group.

Sources: ADVANCE Clinical Study Report[13] and ELEVATE Clinical Study Report.[15]

A summary of change from baseline in the monthly AIM-D performance of daily activities domain score and physical impairment domain score at week 1 to week 4, week 5 to week 8, and week 9 to week 12, which was an additional efficacy outcome of the ADVANCE and ELEVATE studies, is summarized in Table 47 and Table 48 of Appendix 3. [13,15]

Subgroup analysis: Results for the unplanned subgroup analysis by number of prior preventive treatment failures in the ADVANCE study provided by the sponsor for change from baseline in the AIM-D performance of daily activities and physical impairment domains are summarized in Table 44. In general, [13]

Patient Global Impression of Change

PGIC was an additional efficacy outcome end point of the ADVANCE study. A higher proportion of patients in the atogepant groups assessed PGIC as much better or very much better at week 12 compared to placebo

([redacted]). The OR was [redacted]) for atogepant 30 mg, and [redacted] for atogepant 60 mg.[13]

PGIC was also an additional efficacy outcome end point of the CGP-MD-01 study. A higher proportion of patients in the atogepant groups assessed PGIC as much better or very much better at week 12 compared to placebo ([redacted] for atogepant 10 mg, [redacted] for atogepant 30 mg, and [redacted] for atogepant 60 mg versus [redacted] for placebo) in the mITT population after Protocol Amendment 1, as the wording of the PGIC was changed. Results for responders who were assessing PGIC as much better or very much better were consistent with the primary analysis for any dates during the study period.[14]

In the ELEVATE study, PGIC was an additional secondary outcome. At week 12, a greater proportion of patients in the atogepant 60 mg once daily group reported a response of much better or very much better compared to placebo (OR = [redacted]), with response occurring in [redacted] patients, in the atogepant 60 mg once daily and placebo groups, respectively.[15]

Patient Global Impression–Severity

PGI-S was an additional efficacy outcome of the ADVANCE and ELEVATE studies. In the ADVANCE study, each of the 3 atogepant groups was associated with improvement in patients' global impression of severity of their disease as assessed by PGI-S at week 4, week 8, and week 12. At week 4, the LSM difference change from baseline in PGI-S was [redacted]) for atogepant 10 mg, [redacted]) for atogepant 30 mg, and [redacted]) for atogepant 60 mg. At week 8, the LSM difference change from baseline in PGI-S was [redacted]) for atogepant 10 mg, [redacted]) for atogepant 30 mg, and [redacted]) for atogepant 60 mg. At week 12, the LSM difference change from baseline in PGI-S was [redacted]) for atogepant 10 mg, [redacted]) for atogepant 30 mg, and [redacted] for atogepant 60 mg.[13]

At week 4, week 8, and week 12 in the ELEVATE study, the LSM difference between atogepant 60 mg once daily compared to placebo was [redacted] respectively. The LSM change from baseline at week 4 was [redacted]) for atogepant compared to [redacted] for placebo. The LSM change from baseline at week 8 was [redacted]) for atogepant compared to [redacted] for placebo. The LSM change from baseline at week 12 was [redacted] for atogepant compared to [redacted] for placebo.[15]

Work Productivity and Activity Impairment Questionnaire: Migraine, Version 2.0

Change from baseline in WPAI:Migraine scale scores was an additional efficacy outcome of the ADVANCE, CGP-MD-01, and ELEVATE studies. Changes in WPAI:Migraine scores at week 12 are summarized in Table 22.

In the ADVANCE study, the LSM difference versus placebo ranged from [redacted] for the absenteeism domain, [redacted] for the presenteeism domain, [redacted] for the overall productivity loss domain, and [redacted] for the activity impairment domain in favour of atogepant.[13]

In study CGP-MD-01, the LSM change from baseline was greater in the atogepant groups compared to the placebo groups in all domains. The LSM difference versus placebo ranged from [redacted] for the absenteeism domain, [redacted] for the presenteeism domain, [redacted] for the overall work productivity loss domain, and [redacted] for the activity impairment domain in favour of atogepant.[14]

In the ELEVATE study, the LSM difference of atogepant 60 mg once daily versus placebo in change from baseline of the performance of daily activities domain score was [redacted] at week 1 to week 4, [redacted] at week 5 to week 8, and [redacted] at week 9 to week 12. The LSM difference of atogepant 60 mg once daily versus placebo in change from baseline of the physical impairment domain score was [redacted] at week 1 to week 4, [redacted] at week 5 to week 8, and [redacted] for week 9 to week 12.[15]

Harms

Only those harms identified in the review protocol are reported as follows. Refer to Table 23 for detailed harms data.

Adverse Events

TEAEs in the ADVANCE, CGP-MD-01, and ELEVATE studies are summarized in Table 23. In the ADVANCE study, more than half of all patients in each group experienced at least 1 TEAE (52.9% of patients with atogepant 10 mg, 52.2% of patients with atogepant 30 mg, 53.7% of patients with atogepant 60 mg, and 56.8% of patients with placebo). The most frequently reported TEAEs in the ADVANCE study 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, atogepant 30 mg, atogepant 60 mg, and placebo groups, respectively. In the ADVANCE study, most TEAEs in the atogepant and placebo groups were mild (26.8% to 29.4% versus 29.7%) or moderate (22.4% to 26.0% versus 23.0%) in severity. Severe TEAEs were reported for 0.4% to 1.8% of participants across the 3 atogepant treatment groups (constipation, contusion, ligament sprain, back pain, optic neuritis, and asthma in the atogepant 10 mg treatment group; dizziness in the atogepant 30 mg treatment group; and blood creatine phosphokinase [increased] and insomnia in the atogepant 60 mg treatment group), and 4.1% of participants in the placebo treatment group (kidney infection, tendon rupture, migraine, brain injury, depression, renal colic, nephrolithiasis, and negative pressure pulmonary edema).[13]

Table 22: Change From Baseline of WPAI:Migraine Subscales at Week 12 — mITT Population

Factor	ADVANCE study[a]			CGP-MD-01 study[b]				ELEVATE study[c]		
	Atogepant 10 mg q.d. (N = 214)	Atogepant 30 mg q.d. (N = 223)	Atogepant 60 mg q.d. (N = 222)	PBO (N = 214)	Atogepant 10 mg q.d. (N = 87)	Atogepant 30 mg q.d. (N = 159)	Atogepant 60 mg q.d. (N = 177)	PBO (N = 159)	Atogepant 60 mg q.d. (N = 151)	PBO (N = 154)
Percentage of work time missed due to migraine (absenteeism)										
Baseline										
n (%)	[redacted]									
Mean (SD)	[redacted]									
MMRM										
LSM (SE)	[redacted]									
LSM difference (SE) vs. PBO	[redacted]									
95% CI	[redacted]									
Percentage of impairment while working due to migraine (presenteeism)										
Baseline										
n (%)	[redacted]									
Mean (SD)	[redacted]									
MMRM										
LSM (SE)	[redacted]									
LSM difference (SE) vs. PBO	[redacted]									
95% CI	[redacted]									
Percentage of overall impairment due to migraine (overall work productivity loss)										
Baseline										

Factor	ADVANCE study[a]			CGP-MD-01 study[b]				ELEVATE study[c]		
	Atogepant 10 mg q.d. (N = 214)	Atogepant 30 mg q.d. (N = 223)	Atogepant 60 mg q.d. (N = 222)	PBO (N = 214)	Atogepant 10 mg q.d. (N = 87)	Atogepant 30 mg q.d. (N = 159)	Atogepant 60 mg q.d. (N = 177)	PBO (N = 159)	Atogepant 60 mg q.d. (N = 151)	PBO (N = 154)
n (%)	[redacted]									
Mean (SD)	[redacted]									
MMRM										
LSM (SE)	[redacted]									
LSM difference (SE) vs. PBO	[redacted]									
95% CI	[redacted]									
Percentage of activity impairment due to migraine (activity impairment)										
Baseline										
n (%)	[redacted]									
Mean (SD)	[redacted]									
MMRM										
LSM (SE)	[redacted]									
LSM difference (SE) vs. PBO	[redacted]									
95% CI	[redacted]									

CI = confidence interval; LSM = least squares mean; MMRM = mixed model of repeated measures; PBO = placebo; q.d. = once daily; SD = standard deviation; SE = standard error; vs. = versus; WPAI:Migraine = Work Productivity and Activity Impairment Questionnaire: Migraine.

[a]The MMRM for change from baseline included baseline as a covariate; prior exposure to migraine prevention medications (yes or no), treatment group, and visit (month) as fixed factors; and treatment-group-by-visit and baseline-by-visit as interaction terms, with an unstructured covariance matrix. P values were from the test between the atogepant dose group and the placebo group.

[b]The MMRM included treatment group and analysis visit as fixed factors, the baseline value as covariate, and interactions of treatment group by analysis visit and baseline value by analysis visit. An unstructured covariance matrix was used to model the covariance of within-patient scores. P values were from the test between the atogepant dose group and the placebo group.

[c]The MMRM for change from baseline. The model includes baseline value as a covariate, treatment group, visit (month), region, number of classes of failed prior prophylactic treatments (2 and > 2) and number of migraine days during the screening/baseline period (4 to = 8) as fixed factors, and treatment group-by-visit and baseline-by-visit as interaction terms, with an unstructured covariance matrix. P value is from the test between the atogepant dose group and the placebo group.

Sources: ADVANCE Clinical Study Report,[13] CGP-MD-01 Clinical Study Report,[14] and ELEVATE Clinical Study Report.[15]

In study CGP-MD-01, TEAEs were reported more frequently in the atogepant groups compared to placebo (65.6%, 62.8%, and 57.5% in atogepant 10 mg, atogepant 30 mg, and atogepant 60 mg, respectively, versus 49.5% for placebo). The most frequently reported TEAEs in the atogepant groups were nausea (5.5%, 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 once daily, atogepant 30 mg once daily, and atogepant 60 mg once daily, compared to placebo, respectively. TEAEs in the atogepant groups and placebo group were mostly mild (26.9% to 39.8% versus 21.0%) to moderate (23.7% to 26.9% versus 25.8%) in severity, with severe AEs reported infrequently (2.2% to 5.5% versus 2.7%).[14]

In the ELEVATE study, TEAEs were balanced between the atogepant and placebo groups [redacted] The most frequently reported TEAEs between atogepant and placebo consisted of constipation ([redacted], nausea ([redacted]), COVID-19 ([redacted]), and nasopharyngitis ([redacted]). Most TEAEs were considered mild ([redacted]) in severity in the atogepant and placebo groups, respectively.[15]

Serious Adverse Events

SAEs in the ADVANCE study and study CGP-MD-01 are summarized in Table 23. In the ADVANCE study, SAEs were infrequently reported, occurring in only 2 (0.9%) patients in the atogepant 10 mg and placebo groups, each. The SAE of optic neuritis was considered by the investigator to be related to study intervention. The SAE was experienced on day 23 of the study and was resolved on day 108. Study intervention (atogepant 10 mg) was stopped.[13]

In study CGP-MD-01, SAEs were also infrequently reported, with 8 SAEs occurring in 7 patients: 1 (1.1%) patient in the atogepant 10 mg once daily group, 2 (1.1%) patients in the atogepant 30 mg once daily group, 2 (1.1%) patients in the atogepant 60 mg once daily group, and 2 (1.1%) in the placebo group. The only SAE reported in the atogepant 10 mg once daily group was cholecystitis (1 [1.1%] patient). In the atogepant 30 mg once daily group, SAEs included migraine (1 [0.5%] patient) and ureteritis (1 [0.5%] patient). SAEs in the 60 mg once daily group consisted of abortion (1 [0.6%] patient), major depression (1 [0.5%] patient), and overdose (1 [0.5%] patient). In the placebo group, SAEs consisted of Hodgkin disease (1 [0.5%] patient) and ureterolithiasis (1 [0.5%] patient). All SAEs in the atogepant group resolved, and only 1 SAE (worsening migraine) resulted in the discontinuation of atogepant.[14]

The reporting of SAEs in the ELEVATE study was infrequent, occurring in [redacted] and [redacted] patients in the atogepant and placebo groups, respectively, with | of abortion, ventricular tachycardia, stage II breast cancer, and invasive breast carcinoma occurring in the atogepant group.[15]

Withdrawals Due to Adverse Events

WDAEs in the ADVANCE study and study CGP-MD-01 are summarized in Table 23. In the ADVANCE study, the incidence of WDAEs was similar across treatment groups, occurring in 4 (1.8%) atogepant-treated patients to 9 (4.1%) atogepant-treated patients and 6 (2.7%) patients in the placebo group. The most common TEAE that led to discontinuation in the atogepant treatment groups was constipation (1 [0.5%] patient in the atogepant 10 mg group, 2 [0.9%] patients in the atogepant 30 mg group, and 1 [0.4%] patient in the atogepant 60 mg group).[13]

In study CGP-MD-01, WDAEs were more common in the atogepant groups (4.3%, 6.0%, and 3.2% in the atogepant 10 mg once daily, atogepant 30 mg once daily, and atogepant 60 mg once daily groups, respectively) than in the placebo group (2.7%). The most common AEs causing withdrawals in the atogepant patients were nausea (3 [1.6%] patients with atogepant 30 mg once daily), constipation (1 patient each in atogepant 30 mg once daily and 60 mg once daily), and dizziness (1 [0.5%] patients with atogepant 30 mg once daily).[14]

In the ELEVATE study, [redacted] patients in the atogepant group discontinued treatment due to AEs consisting of constipation, nausea, and somnolence ([redacted]) compared to [redacted]) patients in the placebo group due to migraine, general pruritus, and skin exfoliation ([redacted]).[15]

Mortality

There were no deaths reported during the ADVANCE, CGP-MD-01, or ELEVATE studies.[13-15]

Notable Harms

AEs of special interest were identical in the ADVANCE, CGP-MD-01, and ELEVATE studies and are summarized in Table 23. In the ADVANCE study, 1 patient in the placebo group reported suicidal behaviour during the double-blind treatment period. No patients reported suicidal ideation with intent to act via their C-SSRS assessments. Treatment-emergent ALT or AST of 3 or more times the ULN was reported by 9 patients: 2 (0.9%) patients each in the atogepant 10 mg and atogepant 30 mg treatment groups, 1 (0.4%) patient in the atogepant 60 mg group, and 4 (1.8%) patients in the placebo group. No patients met the criteria for potential Hy's law.[13]

In study CGP-MD-01, 1 patient-reported suicidal ideation during the 6 months before screening. No patients reported suicidal behaviour during the study; however, 1 patient in the placebo group reported suicidal ideation limited to a "wish to be dead" during the double-blind treatment period. Treatment-emergent ALT or AST of 3 or more times the ULN was reported by 9 patients: 6 patients in the atogepant groups and 3 patients in the placebo group. No patients met the criteria for potential Hy's law.[14]

In the ELEVATE study, [redacted] and [redacted] patients experienced the TEAE of constipation, and [redacted] and [redacted] patients in the atogepant and placebo groups reported suicidal behaviours during the study, respectively. No patients reported treatment-emergent ALT or AST of 3 or more times the ULN or met the criteria for potential Hy's law during the study.[15]

Critical Appraisal

Internal Validity

Given the similarities in the design and conduct of the included studies, particularly the phase III ADVANCE and ELEVATE studies, internal and external validity points were similar across studies. The ADVANCE, CGP-MD-01, and ELEVATE studies were all double-blind RCTs. In each trial, appropriate methods for randomization (via IWRS), treatment allocation (stratified by prior exposure to migraine prevention medication in sequential blocks in the ADVANCE and CGP-MD-01 trials, and stratified by number of migraine days during the screening period [4 to < 8 and ≥ 8] and the number of classes of failed prior prophylactic

treatment [2 and > 2] in ELEVATE), and the maintenance of blinding to treatment assignment (double-dummy identical blister cards) were used, reducing the possibility for selection, performance, and detection biases. Overall, there were few discontinuations across groups, with [redacted] in the ELEVATE study ([redacted]) compared to the ADVANCE study (ranging from 9.9% to 13.2%), and to the CGP-MD-01 study (ranging from 12.3% to 20.4%). It is unclear how such discontinuations would have affected blinding or the study results, particularly for the CGP-MD-01 trial, where more patients discontinued based on the withdrawal of consent or withdrawal by the patient in the placebo group. The rate of constipation was more frequent in the atogepant groups across trials, which may have led to unblinding. Despite being double-blind RCTs, this result could have revealed treatment assignment; however, given that the overall rates were generally low, it is unclear what effect this would have on the results.

There were no notable differences in most baseline characteristics within the studies, though there were differences across studies. Given the minimal differences in baseline characteristics and discontinuations, the potential for attrition bias was limited. The primary and secondary analyses for the ADVANCE and CGP-MD-01 trials were conducted on the mITT population, which had a reduced number of patients compared to the true ITT population. It is uncertain whether this had any effect on the results; however, it is unlikely.

The primary and secondary end points of all trials were evaluated using an MMRM to analyze comparisons between treatment groups and included treatment group, visit, prior exposure to a migraine prevention medication with proven efficacy, and treatment-group-by-visit interaction as categorical fixed effects. It also included the baseline score and baseline-by-visit interaction as covariates. The primary analysis of MMRM assumes the data were MAR, which is unlikely to hold true. The analysis was performed based on all postbaseline values using only observed cases without imputation of missing values. There was a low to moderate rate of overall dropout seen across trials. However, the total number of cases of missing data was not reported for each outcome; thus, the extent of missing data for each outcome remains unknown and it is unclear how the discontinuations may have affected the overall study results. Sensitivity analyses to account for missing data were conducted on the primary end point, and results were in line with the primary analysis, suggesting that missing data had little impact. The other secondary efficacy end points were analyzed in the same manner as the primary end point, and therefore did not account for missing data. Additionally, no sensitivity analyses were conducted for the secondary end points and therefore it is unclear if missing data may have biased the study results. The numerous study visits that occurred may potentially have reduced the amount of missing data; however, there was a moderately high number of dropouts in the CGP-MD-01 study, and the sensitivity analyses accounting for missing data were only conducted for the primary end point. As a result, it is uncertain whether missing data impacted the other study outcomes. For example, outcomes related to HRQoL were limited by the smaller numbers of patients at 12-week times of assessment, the potential for missing data, and the lack of imputation or sensitivity analyses. Thus, outcomes related to HRQoL may have been at a risk of bias in the observed treatment effect.

Table 23: Summary of Harms

Preferred term	ADVANCE study (safety population)				CGP-MD-01 study (safety population)				ELEVATE study (safety population)	
	Atogepant 10 mg q.d. (N = 221)	Atogepant 30 mg q.d. (N = 228)	Atogepant 60 mg q.d. (N = 231)	Placebo (N = 222)	Atogepant 10 mg q.d. (N = 93)	Atogepant 30 mg q.d. (N = 183)	Atogepant 60 mg q.d. (N = 186)	Placebo (N = 186)	Atogepant 60 mg q.d. (N = [redacted])	Placebo (N = [redacted])
TEAEs (≥ 2%), n (%)										
Overall	**117 (52.9)**	**119 (52.2)**	**124 (53.7)**	**126 (56.8)**	**61 (65.6)**	**115 (62.8)**	**107 (57.5)**	**92 (49.5)**	[redacted]	[redacted]
Constipation	17 (7.7)	16 (7.0)	16 (6.9)	1 (0.5)	2 (2.2)	10 (5.5)	9 (4.8)	4 (2.2)	[redacted]	[redacted]
Nausea	11 (5.0)	10 (4.4)	14 (6.1)	4 (1.8)	5 (5.4)	13 (7.1)	22 (11.8)	9 (4.8)	[redacted]	[redacted]
Fatigue	3 (1.4)	7 (3.1)	9 (3.9)	4 (1.8)	1 (1.1)	3 (1.6)	5 (2.7)	6 (3.2)	[redacted]	[redacted]
Upper respiratory tract infection	9 (4.1)	13 (5.7)	9 (3.9)	10 (4.5)	6 (6.5)	14 (7.7)	10 (5.4)	15 (8.1)	[redacted]	[redacted]
Urinary tract infection	3 (1.4)	9 (3.9)	9 (3.9)	8 (3.6)	2 (2.2)	11 (6.0)	5 (2.7)	4 (2.2)	[redacted]	[redacted]
Nasopharyngitis	4 (1.8)	8 (3.5)	8 (3.5)	8 (3.6)	3 (3.2)	11 (6.0)	14 (7.5)	4 (2.2)	[redacted]	[redacted]
Blood CPK, increased	5 (2.3)	2 (0.9)	7 (3.0)	2 (0.9)	4 (4.3)	3 (1.6)	2 (1.1)	3 (1.6)	[redacted]	[redacted]
Anxiety	2 (0.9)	1 (0.4)	5 (2.2)	2 (0.9)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Influenza	3 (1.4)	2 (0.9)	5 (2.2)	2 (0.9)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sinusitis	4 (1.8)	3 (1.3)	5 (2.2)	3 (1.4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sinus congestion	1 (0.5)	2 (0.9)	4 (1.7)	5 (2.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Somnolence	7 (3.2)	4 (1.8)	4 (1.7)	2 (0.9)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastroenteritis	2 (0.9)	5 (2.2)	3 (1.3)	4 (1.8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AST, increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALT, increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Preferred term	ADVANCE study (safety population)				CGP-MD-01 study (safety population)				ELEVATE study (safety population)	
	Atogepant 10 mg q.d. (N = 221)	Atogepant 30 mg q.d. (N = 228)	Atogepant 60 mg q.d. (N = 231)	Placebo (N = 222)	Atogepant 10 mg q.d. (N = 93)	Atogepant 30 mg q.d. (N = 183)	Atogepant 60 mg q.d. (N = 186)	Placebo (N = 186)	Atogepant 60 mg q.d. (N =)	Placebo (N =)
COVID-19										
Decreased appetite										
Insomnia										
Migraine										
Diarrhea										
Dyspepsia										
SAEs, n (%)										
Overall	**2 (0.9)**	**0 (0.0)**	**0 (0.0)**	**2 (0.9)**	**1 (1.1)**	**2 (1.1)**	**2 (1.1)**	**2 (1.1)**		
Gastric ulcer hemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Brain injury	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Optic neuritis	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Asthma	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
NPPE	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Abortion[a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)		
Cholecystitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)		
Hodgkin disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)		
Major depression	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)		
Migraine	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)		
Overdose	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)		

Preferred term	ADVANCE study (safety population)				CGP-MD-01 study (safety population)				ELEVATE study (safety population)	
	Atogepant 10 mg q.d. (N = 221)	Atogepant 30 mg q.d. (N = 228)	Atogepant 60 mg q.d. (N = 231)	Placebo (N = 222)	Atogepant 10 mg q.d. (N = 93)	Atogepant 30 mg q.d. (N = 183)	Atogepant 60 mg q.d. (N = 186)	Placebo (N = 186)	Atogepant 60 mg q.d. (N = [redacted])	Placebo (N = [redacted])
Ureteritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	[redacted]	[redacted]
Ureterolithiasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	[redacted]	[redacted]
Ventricular tachycardia	NR	NR	NR	NR	NR	NR	NR	NR	[redacted]	[redacted]
Breast cancer, stage II	NR	NR	NR	NR	NR	NR	NR	NR	[redacted]	[redacted]
Invasive breast carcinoma	NR	NR	NR	NR	NR	NR	NR	NR	[redacted]	[redacted]
WDAEs, n (%)										
Overall	**9 (4.1)**	**4 (1.8)**	**6 (2.6)**	**6 (2.7)**	**4 (4.3)**	**11 (6.0)**	**6 (3.2)**	**5 (2.7)**	[redacted]	[redacted]
Ear pain	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	[redacted]	[redacted]
Vertigo	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	[redacted]	[redacted]
Constipation	1 (0.5)	2 (0.9)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	[redacted]	[redacted]
Nausea	1 (0.5)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	3 (1.6)	0 (0.0)	0 (0.0)	[redacted]	[redacted]
Abdominal pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	[redacted]	[redacted]
Abdominal discomfort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	1 (0.5)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	[redacted]	[redacted]
Decreased appetite	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	[redacted]	[redacted]
Diabetes mellitus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Muscle spasms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Preferred term	ADVANCE study (safety population)				CGP-MD-01 study (safety population)				ELEVATE study (safety population)	
	Atogepant 10 mg q.d. (N = 221)	Atogepant 30 mg q.d. (N = 228)	Atogepant 60 mg q.d. (N = 231)	Placebo (N = 222)	Atogepant 10 mg q.d. (N = 93)	Atogepant 30 mg q.d. (N = 183)	Atogepant 60 mg q.d. (N = 186)	Placebo (N = 186)	Atogepant 60 mg q.d. (N =)	Placebo (N =)
Musculoskeletal chest pain										
Brain injury										
Dizziness	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)		
Headache	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Migraine										
Optic neuritis										
Somnolence	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Agitation										
Insomnia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Abnormal dreams										
Bipolar disorder										
Suicidal ideation										
Hematuria										
Renal colic										
Pelvic pain										
NPPE										
Hyperhidrosis										
Pruritus, generalized	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Skin exfoliation										

Preferred term	ADVANCE study (safety population)				CGP-MD-01 study (safety population)				ELEVATE study (safety population)	
	Atogepant 10 mg q.d. (N = 221)	Atogepant 30 mg q.d. (N = 228)	Atogepant 60 mg q.d. (N = 231)	Placebo (N = 222)	Atogepant 10 mg q.d. (N = 93)	Atogepant 30 mg q.d. (N = 183)	Atogepant 60 mg q.d. (N = 186)	Placebo (N = 186)	Atogepant 60 mg q.d. (N = [redacted])	Placebo (N = [redacted])
Rash	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	[redacted]	[redacted]
Rash, papular	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	[redacted]	[redacted]
Affect lability	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Benign ovarian tumour	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Product use complaint	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood CPK, increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AST, increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALT, increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	[redacted]	[redacted]
Weight, increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nightmare	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	[redacted]	[redacted]
IBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperacusis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hodgkin disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GERD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Preferred term	ADVANCE study (safety population)				CGP-MD-01 study (safety population)				ELEVATE study (safety population)	
	Atogepant 10 mg q.d. (N = 221)	Atogepant 30 mg q.d. (N = 228)	Atogepant 60 mg q.d. (N = 231)	Placebo (N = 222)	Atogepant 10 mg q.d. (N = 93)	Atogepant 30 mg q.d. (N = 183)	Atogepant 60 mg q.d. (N = 186)	Placebo (N = 186)	Atogepant 60 mg q.d. (N =)	Placebo (N =)
Depressive symptoms										
Concussion										
Arthralgia										
Ventricular tachycardia										
Notable harms, n (%)										
Constipation										
Suicidal ideation										
ALT or AST ≥ 3 × ULN[b]										
Hy's law cases										

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatinine phosphokinase; GERD = gastroesophageal reflux disease; IBS = irritable bowel syndrome; NPPE = negative pressure pulmonary edema; NR = not reported; q.d. = once daily; SAE = serious adverse event; TEAE = treatment-emergent adverse event; ULN = upper limit of normal; WDAE = withdrawal due to adverse event.

[a]Event specific to females; percentages for sex-specific TEAEs are relative to the number of patients of the appropriate sex.

[b]Values were n of N1, where N1 = the number of patients with at least 1 nonmissing postbaseline value.

[c]One of these 3 patients had elevated liver function values that were not treatment-emergent values related to pre-existing rhabdomyolysis, and thus this case was not subject to adjudication.

Sources: ADVANCE Clinical Study Report,[13] CGP-MD-01 Clinical Study Report,[14] and ELEVATE Clinical Study Report.[15]

Acceptable methods to account for multiplicity were used in all trials. In the ADVANCE and ELEVATE studies, the primary end point and 6 key secondary end points (change from baseline in MHD, change from baseline in acute MUDs, a 50% or greater reduction in a 3-month average of MMDs, change from baseline in the MSQ version 2.1 role function-restrictive domain score, change from baseline in the performance of daily activities domain score of AIM-D, and change from baseline in the mean monthly physical impairment domain score of AIM-D) were controlled for multiplicity using the overall familywise error rate at the 0.05 level. Other secondary efficacy analyses in the ADVANCE and ELEVATE trials, including results for the HIT-6, MIDAS, WPAI:Migraine, and other migraine or headache severity measures, were performed at the nominal significance level, without adjusting for multiplicity or missing data. Thus, these secondary efficacy analyses must be interpreted in consideration of type I error and should be viewed as supportive evidence for the overall effect of atogepant.

A limited dose response was observed in the ADVANCE study for all efficacy end points, where higher doses demonstrated greater efficacy. Conversely, in study CGP-MD-01, an inverse dose response was observed, where lower doses of atogepant demonstrated greater efficacy compared to higher doses. The reason for the observed dose-response relationships in the ADVANCE and CGP-MD-01 studies remains unknown. As a result of the dose-response relationship in the ADVANCE trial, the 60 mg once daily dosing of atogepant was selected for the ELEVATE study.

In study CGP-MD-01, results for all outcomes generally favoured atogepant; however, secondary end points, including a 50% reduction in mean MMDs and change from baseline in mean monthly acute MUDs, did not reach statistical significance in any group compared to placebo. Consequently, the results for secondary end points should be viewed as supportive of the overall effect of atogepant.

One prespecified subgroup analysis of the ADVANCE study was conducted that included patients with or without prior exposure to migraine prevention medication with proven efficacy. An additional post hoc subgroup analysis was submitted to CADTH by request, for patients in the ADVANCE study with 1 or more and 2 or more prior migraine prevention treatment failures; this 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 have confounded the observed results and should be interpreted as supportive evidence only for the overall effect of atogepant. Moreover, missing data were unaccounted for, and the analyses did not adjust for multiplicity. Subgroups also had wider, more imprecise 95% CIs when reported. However, the population for this post hoc subgroup analysis was the target population for the ELEVATE study, which also featured 3 prespecified subgroups, including 2 of interest to this review (prior oral prophylactic treatment failure and migraine days at baseline).

External Validity

The clinical experts consulted by CADTH indicated that the inclusion and exclusion criteria for the ADVANCE, CGP-MD-01, and ELEVATE studies were appropriate. There was a high proportion of screening failures in all trials (60%, 53%, and [redacted] for the ADVANCE, CGP-MD-01, and ELEVATE studies, respectively), mostly due to patients not meeting eligibility criteria, though the specific reasons were not specified. There were no

Canadian sites in either the ADVANCE or CGP-MD-01 trial, though the ELEVATE trial included [redacted]. The clinical expert noted that historically, patients with aura were generally excluded from RCTs in migraine due to the increased possibility of vascular events; however, all studies enrolled patients with and without aura. Baseline demographic and clinical characteristics, including the average number of MMDs and MHDs at baseline, was observed to be a true reflection of what would be seen in Canadian clinical practice as noted by the clinical expert. However, the clinical expert stated that the proportion of Asian patients may be higher than what is seen in the trials, and that the proportion of Black patients would be lower in clinical practice than what was reported in the trials. In addition, it is worth noting that patients enrolled in the studies had to have a history of 4 migraine days per month to 14 migraine days per month on average in the 3 months before the first visit. Hence, all studies excluded patients with 1 migraine day per month to 3 migraine days per month, and it is uncertain if results from the ADVANCE, CGP-MD-01, and ELEVATE trials are generalizable to patients with fewer than 4 migraine days per month.

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. There were some instances in the ADVANCE trial where a few enrolled patients had previously failed CGRP inhibitors; however, this was unlikely to affect the outcomes of the study based on the limited number of patients enrolled. Conversely, the ELEVATE study enrolled patients who had failed 2 to 4 oral prophylactic migraine medications. 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 the ADVANCE study compared to [redacted] of patients in the CGP-MD-01 trial, and 100% of patients in the ELEVATE trial. The reimbursement request for atogepant is for patients with an inadequate response, an intolerance, or a contraindication to at least 2 oral prophylactic migraine medications, or — in other words — patients who had not received injectable CGRP mAbs; which is only reflected by the population in the ELEVATE trial. As noted in the post hoc subgroup analysis for the ADVANCE trial, only [redacted] patients had failed 2 or more prior preventive 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. The CGP-MD-01 study did not have a subgroup analysis for patients with 2 or more prior treatment failures and the ADVANCE study does not fully 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. As a result, the trials may overestimate the treatment effects. In all studies, there was a high placebo response, impacting the ability to interpret the efficacy of atogepant. No direct comparative effect was studied between atogepant versus other available migraine-preventive treatments. Study CGP-MD-01 included 2 additional doses of atogepant (30 mg and 60 mg twice daily); however, given that these doses are not Health Canada–approved, they were not discussed in the report.

Outcomes of the ADVANCE and ELEVATE trials were nearly identical, with similar outcomes included in the CGP-MD-01 study, all of which were aligned with other clinical trials for migraine and are reflective and

important in guiding treatment decisions in Canadian clinical practice. The most valuable outcomes to patients include decreases in headache intensity and frequency, which were assessed by changes in MMDs and MHDs, as well as the clinically important 50% reduction of mean MMDs, which was a key secondary outcome of these studies. Patients also cited improvements in quality of life as 1 of the most valuable outcomes for preventive medications. Multiple HRQoL and patient-reported outcomes (PROs) were assessed in the trials; however, the use of tools such as the MSQ version 2.1, AIM-D, PGIC, PGI-S, and WPAI:Migraine by physicians in clinical practice is limited. The clinical expert consulted by CADTH noted that the HIT-6 and MIDAS measures were most likely to be used to assess disease severity; however, these outcomes were secondary and were not controlled for multiplicity or missing data. Consequently, the results should be treated with caution.

The duration of the trials (12-week double-blind period) was also considered appropriate for assessing these outcomes over time given that the effects of CGRP inhibitors in migraine are rapidly seen. The duration of follow-up was only 4 additional weeks, and it remains uncertain if there is waning efficacy with atogepant, as seen with other CGRP inhibitors (i.e., the CGRP mAbs).

Indirect Evidence

Objectives and Methods for the Summary of Indirect Evidence

This section was redacted as requested by the sponsor.

Description of the NMA

This section was redacted as requested by the sponsor.

Methods of Sponsor-Submitted NMA

This section was redacted as requested by the sponsor.

Results of Sponsor-Submitted NMA

This section was redacted as requested by the sponsor.

Critical Appraisal of the Sponsor-Submitted NMA

The sponsor-submitted NMA was informed by an adequately conducted SLR that included planned searches of multiple databases. The SLR was recently updated to capture relevant comparators for the Canadian context. [redacted]. Screening was conducted based on standard methods, with studies selected independently in duplicate, according to prespecified criteria. A quality assessment of the included studies was conducted per the National Institute for Health and Care Excellence checklist for the original and updated SLR, for which the sponsor considered there to be a low risk of bias in the included studies for baseline comparability, imbalances in dropouts between the treatment groups, outcome selection and reporting, and randomization and statistical analysis. However, it noted a higher risk of bias in 33% of included studies due to the open-label designs. No sensitivity analysis based on quality of study was conducted. The population, interventions, and outcomes of the sponsor-submitted SLR were relevant to Canadian clinical practice. The interventions and outcomes

considered in the SLR were broader than those included in the NMA. A list of excluded publications, as well as trial groups excluded due to dose and reason for exclusion, was provided.

As previously mentioned, the original SLR and NMA were updated for the Canadian context, which included [redacted], deemed relevant to the Canadian context and the reimbursement request. A feasibility assessment to identify trials for inclusion in the NMA was undertaken in an iterative, stepwise manner. Studies from the SLR were assessed according to relevant treatments, end point data availability (relevant outcomes, time points, definitions), a comparison of trial design and inclusion and exclusion criteria, and a comparison of the patient population characteristics. As previously mentioned, the list of treatments for the NMA was narrower than that of the SLR. As noted by the clinical expert consulted by CADTH, the overall NMA did not include valproic acid or candesartan ([redacted]), which could be considered relevant comparators for the treatment of EM in the Canadian landscape. Overall, the outcomes assessed were appropriate; however, other important outcomes such as HRQoL were not considered based on a low availability of data. Based on the NMA report, the outcomes assessed in the included trials appeared similar with respect to the definitions used.

All networks were constructed based on the feasibility assessment and the availability of outcome data. In [redacted], comparisons for almost all competing interventions were based on single trials versus placebo, apart from data from older studies evaluating [redacted], where there were only a few closed loops. This allowed direct and indirect evidence to be compared, which demonstrated no evidence of inconsistency in this scenario, suggesting that relative treatment effects estimated within the NMA are in line with the trial results, and are not being influenced by treatment effect modifiers for those specific comparisons. However, given that there were very few closed loops in most analyses, inconsistency could not be assessed for the most part and may exist. [redacted]. In [redacted], there were no closed loops, and connections were only made via placebo. It was not possible to validate the transitivity assumption of the NMA and check for consistency between direct and indirect results.

[redacted] both fixed and random-effects models were conducted, with similar estimates produced and base-case analyses selected using model fit statistics by the lowest DIC. In [redacted], random-effects models for the analyses [redacted] were selected as the base-case analysis. Given the larger evidence base, random-effects models were appropriate to allow for the possibility of heterogeneity between studies. Conversely, in [redacted], fixed-effects models were selected as the base case due to the smaller number of trials and the lower DIC compared to the random-effects models. There was a high amount of evidence identified for [redacted]. In addition, these trial populations often only included small sample sizes, ranging from [redacted] patients per treatment group, [redacted]. [redacted]. The sponsor noted that the ELEVATE trial would provide more robust sample size for patients with 2 or more treatment failures for the atogepant 60 mg group [redacted]

Based on the feasibility assessment, clinical heterogeneity was assessed visually for baseline characteristics, including [redacted]. The sponsors reported that in general, the studies were similar, including [redacted]. 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. [redacted]. As such, there may have been several differences in study and baseline characteristics across the trials that remain unaccounted for, including study design. This comprised 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 none of the trials published before 2001 reported MMD or MHD inclusion criteria. The number of prior treatment failures was not considered as a potential prognostic factor or treatment effect modifier; however, it was considered a significant potential source of heterogeneity that was not explored. [redacted] 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. Moreover, though not confirmed to be a prognostic factor or treatment effect modifier, the presence of migraine with or without aura was not considered, though the clinical expert suggested it may have some clinical importance. However, this likely would not have confounded the results.

Follow-up duration of the included trials generally varied and was also a significant source of heterogeneity across trials, with treatment periods ranging from [redacted] weeks. [redacted] the clinical expert consulted by CADTH considered 12 weeks to generally be acceptable to observe the efficacy of treatments for EM; however, treatment waning, particularly for mAbs, must be considered. For [redacted], though it remains unclear how the different times of assessment may have impacted the results.

[redacted]. Though an important limitation, signifying heterogeneity across pairwise comparisons, I^2 values must also consider the direction and magnitude of effects. Overall, the 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.

[redacted] estimates were generally associated with wide CrIs, resulting in some uncertainty in the precision of the results, they most often did not include the null threshold, suggesting greater confidence in the results [redacted]. Moreover, there were wide CrIs that crossed the null threshold, further challenging the precision of the results. As previously noted, and despite the extent of evidence included in the network, the high amount of heterogeneity in [redacted] may result in this uncertainty and imprecision. Interestingly, and opposite to the results of the ADVANCE trial, [redacted]. No rationale for this observation was provided, and therefore the reason for this remains uncertain, [redacted].

Other Relevant Evidence

This section includes submitted long-term extension studies and additional relevant studies included in the sponsor's submission to CADTH that were considered to address important gaps in the evidence included in the systematic review.

Long-Term Extension Study: Study 309

One long-term, open-label extension study examining the long-term safety and tolerability of oral atogepant 60 mg once daily in patients with EM — Study 309[33] — was submitted by the sponsor and is summarized as follows.

Methods

A phase III, open-label extension study, Study 309,[33] was conducted to evaluate the long-term safety and tolerability of atogepant 60 mg once daily in adult patients with EM, defined as 4 migraine days per month to 14 migraine days per month, for up to 40 weeks of prophylactic treatment. Patients were eligible to enrol in Study 309 if they completed the lead-in Study 301[13] (the ADVANCE study), a randomized, double-blind, placebo-controlled, 12-week study that evaluated the safety and efficacy of atogepant 10 mg, atogepant 30 mg, and atogepant 60 mg once daily. Visit 7 (week 12) of the ADVANCE study functioned as visit 1 (day 1) of Study 309. For patients who completed visit 7 of the ADVANCE study before the initiation of Study 309, visit 8 of the ADVANCE study (end-of-study, including discontinuation of study intervention) or soon thereafter functioned as visit 1 (day 1) instead. Patients were evaluated every 4 weeks throughout the study. After completing 40 weeks of treatment or prematurely discontinuing, patients were evaluated for an additional 4 weeks for safety follow-up. The study was conducted between 2019 and 2021 in the US. There were no Canadian study sites in the study.

Populations

Patients with EM were eligible to enrol in Study 309 if they had completed the 12-week, double-blind treatment period (visit 7) and if applicable, the safety follow-up period (visit 8) of the ADVANCE study. Notably, patients had to have completed the lead-in study without any significant deviations from the protocol (i.e., noncompliance with procedures) and without experiencing an AE that may have indicated an unacceptable safety risk per investigator judgment. Refer to the systematic review section for a detailed description of study design and patient population in the ADVANCE study.

Briefly, patients were excluded from Study 309 if they required any medication (i.e., amitriptyline, topiramate, or propranolol) or diet item (i.e., grapefruit juice) that was prespecified in the list of prohibited concomitant medications and were unable to discontinue or switch to an alternative that was permitted. Patients were excluded if they were pregnant, lactating, or planning to become pregnant; patients of child-bearing potential were required to have a negative urine pregnancy test at visit 1 and use an effective contraceptive for the duration of the study. Further, patients were excluded if they presented with a clinically significant abnormality in their ECG, any clinically significant disease, hypertension, or a significant risk of self-harm or harm to others according to their clinical interview or their responses on the C-SSRS tool. Finally, patients were excluded if they had any condition or circumstance that could have interfered with or confounded the study based on investigator judgment.

A total of 685 patients received at least 1 dosage of open-label atogepant 60 mg once daily (the safety population). The mean age of patients in the study was [redacted]. [redacted] of patients were female ([redacted]) and white [redacted]). At baseline, the mean BMI was [redacted]). [redacted] ([redacted] patients were diagnosed with migraine without aura and the mean duration of the migraine disorder was [redacted]). The mean number of MMDs and MHDs in the last 3 months were [redacted], respectively. The [redacted] of patients had taken a medication for migraine prevention in the past. The [redacted] acute migraine treatment was NSAIDs [redacted] followed by triptans [redacted]. Refer to Table 24 for a summary of baseline characteristics of patients enrolled in Study 309.

Interventions

Beginning at visit 1, patients received atogepant 60 mg once daily in the form of oral tablets. The open-label treatment period was 40 weeks in duration.

The use of prespecified medications for the treatment of acute migraine was permitted during the study, including any triptans, ergots, opioids, alternative forms of analgesics, NSAIDs, and antiemetic drugs. Further, Aspirin (a maximum dose of 325 mg once daily) was permitted for cardiac prophylaxis. At the discretion of the investigator, any medications that were considered required for the welfare of the patient were permitted provided that prespecified conditions unique to the class of medication were met.

Table 24: Summary of Baseline Characteristics in Study 309 (Safety Population)

Characteristic	Atogepant 60 mg q.d. N = 685
Age, years, mean (SD)	[redacted]
Female, n (%)	[redacted]
Race or ethnicity, n (%)	
White	[redacted]
Black or African American	[redacted]
Asian	[redacted]
American Indian or Alaska Native	[redacted]
Multiple[a]	[redacted]
Missing	[redacted]
BMI,[b] kg/m^2, mean (SD)	[redacted]
Migraine diagnosis, n (%)	
With aura	[redacted]
Without aura	[redacted]
Both	[redacted]
Migraine disorder duration, years, mean (SD)	[redacted]
Migraine prevention medication in the past, n (%), yes	[redacted]
Number of migraine days per month in last 3 months, mean (SD)	[redacted]
Number of headache days per month in last 3 months, mean (SD)	[redacted]
Acute migraine treatment, n (%)	
NSAID	[redacted]
Triptan	[redacted]
Antiemetic drug	[redacted]
Opiate or opiate combination	[redacted]
Barbiturate	[redacted]
Ergot or ergot combination	[redacted]
Other	[redacted]

BMI = body mass index; NSAID = nonsteroidal anti-inflammatory drug; q.d. = once daily; SD = standard deviation.

[a]The Multiple category included patients who reported multiple races or ethnicities.

[b]Baseline values for safety variables, including physical characteristics and migraine history, were collected from the last nonmissing safety evaluation before the first dosage of treatment in the ADVANCE study.

Source: Study 309 Clinical Study Report.[33]

Medications that were strong and moderate CYP3A4 inhibitors or inducers, were strong OATP1B1 inhibitors, or were any drugs with a narrow therapeutic window and potential for CYP interaction (i.e., warfarin) were prohibited 30 days before visit 1 and for the duration of the study. The use of any medications indicated for the prevention of migraine and cannabidiol oil were also prohibited 30 days before visit 1 and for the duration of the study. Further, botulinum toxin injections and injectable mAbs that block the CGRP pathway were prohibited within 6 months of visit 1 and throughout the study.

Outcomes

The safety outcomes included AEs, clinical laboratory tests, vital sign measurements, physical examinations, and ECGs. Suicidal ideation and behaviour were assessed using the C-SSRS.

Statistical Analysis

Safety analyses were conducted on the safety population, which included all patients who had received at least 1 dosage of open-label atogepant 60 mg in Study 309. Descriptive statistics were used to summarize continuous safety variables while data for the number and percentage of patients were used to summarize categorical variables. The baseline values were defined as the baseline values obtained in the lead-in study ADVANCE.

Patient Disposition

A total of 695 patients from the lead-in ADVANCE study were screened; of these patients, 10 discontinued Study 309 before receiving the study drug. A total of 685 patients received at least 1 dosage of open-label atogepant (safety population), of which [redacted] received placebo, atogepant 10 mg, atogepant 30 mg, and atogepant 60 mg once daily, respectively, during their participation in the ADVANCE study. A total of [redacted] patients completed Study 309 and [redacted] patients entered safety follow-up. The reason for discontinuation during the open-label treatment period most frequently reported by patients (≥ 5% of patients) was [redacted] and withdrawal by patient or of consent [redacted]. A total of [redacted] patients prematurely discontinued due to AEs. Notably, [redacted] patients who prematurely discontinued the study for other reasons were due to reasons related to [redacted]. Refer to Table 25 for a summary of patient disposition in Study 309.

Table 25: Patient Disposition in Study 309 (Safety Population)

Characteristic	Atogepant 60 mg q.d.
Screened, N[a]	[redacted]
Open-label treatment period	
Number of patients completed, N (%)	[redacted]
Reason for discontinuation, N (%)	
Withdrawal criteria met at visit 1[b]	[redacted]
Withdrawal by patient or of consent	[redacted]
Adverse event	[redacted]

Characteristic	Atogepant 60 mg q.d.
Lost to follow-up	[redacted]
Protocol deviation or violation	[redacted]
Lack of efficacy	[redacted]
Noncompliance	[redacted]
Pregnancy	[redacted]
Site terminated by sponsor	[redacted]
Other[c]	[redacted]
Safety follow-up period	
Number of patients entered, N (%)	[redacted]
Number of patients completed, N (%)	[redacted]
Reason for discontinuation, N (%)	
Withdrawal by patient or of consent	[redacted]
Lost to follow-up	[redacted]
Safety, N	[redacted]
Number of patients from lead-in study treatment	
Placebo, N (%)	[redacted]
Atogepant 10 mg, N (%)	[redacted]
Atogepant 30 mg, N (%)	[redacted]
Atogepant 60 mg, N (%)	[redacted]

ALT = alanine aminotransferase; AST = aspartate aminotransferase; IgM = immunoglobulin M; q.d. = once daily; QTcF = QT interval corrected for heart rate using the Fridericia formula; ULN = upper limit of normal.

[a]Of the 10 screening failures, 2 patients did not meet inclusion and/or exclusion criteria, 1 patient met a protocol-specified withdrawal criterion at visit 1, 5 patients were lost to follow-up, and 2 patients were withdrawals by patient or withdrawals of consent.

[b]Of the 43 patients who discontinued due to withdrawal criteria met at visit 1, 42 patients met withdrawal criteria related to clinical laboratory results (i.e., ALT or AST > 1 × ULN, total bilirubin > 1 × ULN [with the exception of patients with Gilbert syndrome]; serum albumin < 2.8 g/dL; positive urine drug screening test; or positive anti–hepatitis A IgM antibody, hepatitis B surface antigen, anti–hepatitis C antibody testing, or anti–hepatitis E IgM antibody) and 1 patient met withdrawal criteria related to electrocardiogram results (i.e., QTcF > 450 milliseconds for males and QTcF > 470 milliseconds for females on the final central vendor electrocardiogram report or clinically significant cardiac rhythm or conduction abnormalities).

[c]A total of 19 (2.8%) patients prematurely discontinued the open-label treatment period due to reasons related to COVID-19.

Source: Study 309 Clinical Study Report.[33]

Exposure to Study Treatments

The mean duration of treatment exposure was [redacted]), and the median duration of treatment exposure was [redacted]. The total time at risk was [redacted]. A total of [redacted] patients were taking concomitant medications throughout the open-label treatment period. The concomitant medications most frequently used by patients (≥ 20% of patients) were ibuprofen [redacted] a combination medication that contains [redacted]. Mean overall adherence to open-label treatment was [redacted]. Median overall adherence was [redacted].

Efficacy

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

Harms

Only those harms identified in the review protocol are reported as follows. Refer to Table 26 for detailed harms data.

Table 26: Summary of Harms in Study 309 (Safety Population)

Characteristic	Atogepant 60 mg q.d.
TEAEs (≥ 5%), n (%)	
Overall	[redacted]
Upper respiratory tract infection	[redacted]
Urinary tract infection	[redacted]
SAEs, n (%)	
Overall	[redacted]
WDAEs, n (%)	
Overall	[redacted]
Notable harms, n (%)	
Constipation	[redacted]
Suicidal ideation	[redacted]
ALT or AST ≥ 3 × ULN[a, b]	[redacted]
Hy's law cases[c]	[redacted]

ALT = alanine aminotransferase; AST = aspartate aminotransferase; q.d. = once daily; SAE = serious adverse event; TEAE = treatment-emergent adverse event; ULN = upper limit of normal value; WDAE = withdrawal due to adverse event.

[a]Values were n of N1, where N1 = the number of patients with at least 1 nonmissing postbaseline value.

[b]An external independent clinical adjudication committee determined that 2 of the 4 cases of aminotransferase elevations were unlikely to be related to the study drug and the remaining 2 cases were possibly related to the study drug.

[c]Hy's law cases were defined as concurrent ALT or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN and alkaline phosphatase value < 2 × ULN.

Source: Study 309 Clinical Study Report.[33]

TEAEs were reported in [redacted] patients in the safety population during the open-label treatment. The TEAEs most commonly reported by patients (≥ 5% of patients) were [redacted].

SAEs were reported in [redacted] patients during the open-label treatment. The following SAEs were reported in more than 1 patient: [redacted].

No deaths were reported in the safety population.

Premature discontinuation due to at least 1 TEAE was reported in [redacted] patients during the open-label treatment. The following TEAEs that led to discontinuation were reported in more than 1 patient: [redacted]

patients discontinued due to nausea and [redacted] patients each discontinued due to abdominal pain, vomiting, decreased weight, dizziness, and migraine. Notably, [redacted] patient discontinued due to constipation.

For notable harms [redacted] patients reported constipation and [redacted] patients reported ALT or AST greater than or equal to 3 times the ULN value. An external independent clinical adjudication committee determined that [redacted]. No [redacted] suicidal ideation were reported.

Long-Term Safety Study: Study 302

One long-term, randomized, open-label study examining the long-term safety and tolerability of oral atogepant in patients with EM — Study 302[34] — was submitted by the sponsor and is summarized as follows.

Methods

Study 302 was a multicentre, randomized, open-label, 52-week, long-term safety study conducted at 111 sites in the US. No Canadian study sites or patients were included in Study 302. The objective of Study 302 was to evaluate the safety and tolerability of atogepant 60 mg once daily when administered over 52 weeks for the preventive treatment of migraine in patients with EM. Patients with EM were eligible to enrol in Study 302 if they had completed the 12-week, double-blind treatment and safety follow-up periods (visit 8) of the CGP-MD-01 trial or were new patients not previously enrolled in the CGP-MD-01 trial. A total of [redacted] patients were randomized in a 5:2 ratio to atogepant 60 mg once daily ([redacted]) or oral SOC migraine-preventive medication ([redacted]). This study enrolled 2 groups of patients:

- de novo patients — patients who did not participate in any previous study with atogepant who met the inclusion criteria and did not meet the exclusion criteria
- study CGP-MD-01 completers — patients who completed study CGP-MD-01 (visit 8) without significant protocol deviations (e.g., noncompliance with protocol-required procedures) and who met the inclusion criteria and did not meet the exclusion criteria.

The SOC treatment group only served to provide context for interpreting the safety results of atogepant. The oral migraine preventives were prescribed in a manner that reflected clinical practice. A flexible treatment paradigm was used that permitted the discontinuation of, or switching from, 1 drug to an alternative for migraine prevention as needed and per investigator judgment. Regardless of the type of change made, patients in the SOC group were permitted to continue with the study.

Notably, there was at least a 6-month gap between the end of the CGP-MD-01 trial and the initiation of Study 302; hence, study eligibility and baseline migraine days were re-established at screening.

The total study duration was 60 weeks, consisting of a 4-week screening and baseline period, a 52-week open-label treatment period, and a 4-week safety follow-up period. The last observation was May 29, 2020, and the study database was locked as of June 26, 2020.

Populations

Patients with EM were eligible to enrol in Study 302 if they had completed the 12-week, double-blind treatment and safety follow-up periods (visit 8) of the CGP-MD-01 trial. Notably, patients were required to

have completed the lead-in study without any significant deviations from the protocol (i.e., noncompliance with procedures) and without experiencing any AE that may have indicated an unacceptable safety risk per investigator judgment. Refer to the systematic review section for a detailed description of study design and patient population in the CGP-MD-01 trial.

Adult patients aged 18 years to 80 years without prior exposure to atogepant, with at least a 1-year history or diagnosis of migraine with or without aura, and with an age of migraine onset younger than 50 years were also eligible to enrol in Study 302. Further, new patients were required to have a history of 4 mean migraine days per month to 14 mean migraine days per month in the past 3 months of visit 1 per investigator judgment and 4 migraine days to 14 migraine days recorded in the electronic diary during the baseline period of 28 days. Notably, newly enrolled patients were excluded if they used opioids and/or barbiturates for more than 2 days per month, triptans or ergots for 10 or more days per month, or simple analgesics for 15 or more days per month in the past 3 months of visit 1 or during the baseline period per investigator judgment.

Briefly, patients were excluded from Study 302 if they required any medication (i.e., amitriptyline, topiramate, and propranolol), nonpharmacological treatment, or diet item (i.e., grapefruit juice) that was prespecified in the list of prohibited concomitant medications and could not be discontinued or switched to an alternative that was permitted. Patients were excluded if they were pregnant, lactating, or planning to become pregnant; patients of child-bearing potential were required to have a negative urine pregnancy test at visit 1 and visit 2 as well as use an effective contraceptive for the duration of the study. Further, patients were excluded if they presented with a clinically significant abnormality in their ECG, any clinically significant disease (i.e., cardiovascular, cerebrovascular, hepatic, and/or neurologic) or laboratory values, a history of malignancy in the past 5 years (with the exception of adequately treated basal or squamous cell skin cancer or in situ cervical cancer), hypertension, dialysis, or a significant risk of self-harm or harm to others according to their clinical interview or their responses on the C-SSRS. Finally, patients were excluded if they had any condition or circumstance that could have interfered with or confounded the study based on investigator judgment.

A total of [redacted] patients received at least 1 dosage of open-label atogepant 60 mg once daily and SOC, respectively (safety population). The mean age of patients was [redacted] in the atogepant group and [redacted] in the SOC group. Most patients were female [redacted] and white [redacted]. At baseline, the mean BMI was [redacted] and [redacted] in the atogepant and SOC groups, respectively.

[redacted] ([redacted]) were diagnosed with migraine without aura. The mean duration of the migraine disorder was [redacted] the atogepant and SOC groups, respectively. The mean number of MMDs and MHDs in the last 3 months was [redacted]), respectively, in the atogepant group. The mean number of MMDs and MHDs in the last 3 months was [redacted], respectively, in the SOC group. [redacted]) of patients have not taken a medication for migraine prevention in the past. The most commonly used acute migraine treatment was a [redacted] in the atogepant and SOC groups, respectively) followed by [redacted].

A total of 521 patients from the safety population in the atogepant group had evaluable data from completing the electronic diary during the baseline period and at least 1 4-week postbaseline period (mITT

population). At baseline, the mean number of MMDs was [redacted] and the mean number of MHDs was [redacted]. The mean number of monthly acute MUDs was [redacted]. The mean MSQ version 2.1 role function-restrictive domain score was [redacted]. The mean monthly performance of daily activities and physical impairment domain scores of the AIM-D were [redacted], respectively.

Refer to Table 27 for a summary of baseline characteristics of patients enrolled in Study 302 according to the intervention received.

Table 27: Summary of Baseline Characteristics in Study 302

Characteristic	Atogepant 60 mg q.d.	SOC
Demographic and disease characteristics (safety population)		
N	[redacted]	[redacted]
Age, years, mean (SD)	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]
Race or ethnicity, n (%)		
White	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]
Asian	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]
Native Hawaiian or Other Pacific Islander	[redacted]	[redacted]
Multiple[a]	[redacted]	[redacted]
Missing	[redacted]	[redacted]
BMI, kg/m^2, mean (SD)	[redacted]	[redacted]
Migraine diagnosis, n (%)		
With aura	[redacted]	[redacted]
Without aura	[redacted]	[redacted]
Both	[redacted]	[redacted]
Migraine disorder duration in years, mean (SD)	[redacted]	[redacted]
Migraine prevention medication, n (%), yes	[redacted]	[redacted]
Number of migraine days per month in last 3 months, mean (SD)	[redacted]	[redacted]
Number of headache days per month in last 3 months, mean (SD)	[redacted]	[redacted]
Acute migraine treatment, n (%)		
NSAID	[redacted]	[redacted]
Triptan	[redacted]	[redacted]
Antiemetic drug	[redacted]	[redacted]

Characteristic	Atogepant 60 mg q.d.	SOC
Opiate or opiate combination	[redacted]	[redacted]
Barbiturate	[redacted]	[redacted]
Ergot or ergot combination	[redacted]	[redacted]
Other	[redacted]	[redacted]
Baseline efficacy parameters (mITT population)		
N	[redacted]	[redacted]
Number of monthly migraine days, mean (SD)	[redacted]	[redacted]
Number of monthly headache days, mean (SD)	[redacted]	[redacted]
Number of monthly acute medication use days, mean (SD)	[redacted]	[redacted]
MSQ version 2.1 role function-restrictive domain score,[b] mean (SD)	[redacted]	[redacted]
Monthly performance of daily activities domain score of the AIM-D,[c] mean (SD)	[redacted]	[redacted]
Monthly physical impairment domain score of the AIM-D,[c] mean (SD)	[redacted]	[redacted]

AIM-D = Activity Impairment in Migraine–Diary; BMI = body mass index; mITT = modified intention to treat; MSQ = Migraine-Specific Quality-of-Life Questionnaire; NA = not applicable; NSAID = nonsteroidal anti-inflammatory drug; q.d. = once daily; SD = standard deviation; SOC = standard of care.

[a]The "multiple" category included patients who reported multiple races or ethnicities.

[b]n = 516.

[c]n = 445.

Source: Study 302 Clinical Study Report.[34]

Interventions

The open-label treatment period was 52 weeks in duration. Beginning at visit 2, patients randomized to the atogepant treatment group received atogepant 60 mg once daily in the form of oral tablets. Beginning at day 1, patients randomized to the SOC treatment group received an oral migraine-preventive medication that was recognized as safe and effective for migraine prevention, was on the list of acceptable treatments per protocol, and was provided per investigator judgment with input from the patient.

For both treatment groups, the use of prespecified medications for the treatment of acute migraine was permitted during the study, including any triptans, ergots, opioids, alternative forms of analgesics, NSAIDs, and antiemetic drugs. Further, Aspirin (a maximum dose of 325 mg once daily) was permitted for cardiac prophylaxis. At the discretion of the investigator, any medications that were considered required for the welfare of the patient were permitted, provided that prespecified conditions unique to the class of medication were met.

For the atogepant group only, medications that were strong and moderate CYP3A4 inhibitors or inducers, were strong OATP1B1 inhibitors, or were any medications with a narrow therapeutic window and potential for CYP interactions (i.e., warfarin) were prohibited 30 days before visit 1 and for the duration of the study. The use of any medications indicated for the prevention of migraine and cannabidiol oil were also prohibited 30 days before visit 1 and for the duration of the study. Further, botulinum toxin injections and injectable mAbs that block the CGRP pathway were prohibited within 6 months before visit 1 and throughout the study.

Prespecified nonpharmacological treatments for headaches were prohibited within 4 weeks of the baseline period and throughout the study.

Outcomes

The safety outcomes included AEs, clinical laboratory tests, vital sign measurements, and ECGs. Suicidal ideation and behaviour were assessed using C-SSRS.

For the atogepant group only, the efficacy outcomes included were not categorized as primary, secondary, or additional. In addition to improvement in MMDs at each monthly period (≥ 25%, ≥ 50%, ≥ 75%, and 100%), the efficacy end points included change in the following variables relative to baseline:

- MMDs at each monthly period
- MHDs at each monthly period
- monthly acute MUDs at each monthly period
- monthly cumulative headache hours at each monthly period
- monthly triptan use days at each monthly period
- monthly moderate to severe headache days at each monthly period
- monthly severe headache days at each monthly period
- MSQ version 2.1 role function-restrictive domain score at week 12, week 24, week 36, week 48, week 52, and week 56
- monthly performance of daily activities domain score of the AIM-D at each monthly period
- monthly physical impairment domain score of the AIM-D at each monthly period.

Other patient-reported health outcome measures for the atogepant treatment group were analyzed for health economics.

Statistical Analysis

Safety analyses were conducted on the safety population, which included all patients who received at least 1 dosage of open-label study intervention in Study 302. Descriptive statistics were used to summarize continuous safety variables while data for the number and percentage of patients were used to summarize categorical variables.

Efficacy analyses were conducted on the mITT population, which included all patients from the safety population in the atogepant treatment group and had evaluable data from completing the electronic diary during the baseline period and at least 1 4-week postbaseline period. Change in efficacy variables relative to baseline were analyzed using the MMRM and observed cases without imputation of missing values, while categorical variables were analyzed using summary statistics.

Subgroup analyses were conducted for patients in the atogepant group only by patient cohort according to exposure to atogepant and prior experience (yes or no) with a migraine-preventive treatment for change in monthly migraine, headache, and acute MUDs relative to baseline at each monthly period and for a 50% or greater improvement in MMDs at each monthly period.

Patient Disposition

A total of [redacted] patients ([redacted]) were screened, of which [redacted] discontinued from Study 302 before receiving the study intervention. Most ([redacted]) patients discontinued during screening due to screening failures or did not meet eligibility criteria. Of the [redacted] patients randomized to receive atogepant, [redacted] were new patients and [redacted] were study CGP-MD-01 completers. Of the [redacted] patients randomized to receive SOC, [redacted] were new patients and [redacted] were study CGP-MD-01 completers. A total of [redacted] patients received at least 1 dosage of the open-label study intervention (safety population) in the atogepant and SOC groups, respectively. A total of [redacted] patients from the safety population in the atogepant group had evaluable data from the baseline period and at least one 4-week postbaseline period (mITT population). A total of [redacted] patients completed the open-label treatment period in the atogepant and SOC groups, respectively, and [redacted] patients entered safety follow-up, respectively. The reason for discontinuation during the open-label treatment period in the atogepant group most frequently reported by patients (≥ 5% of patients) was [redacted]. The reason for discontinuation during the open-label treatment period in the SOC group most frequently reported by patients (≥ 5% of patients) was [redacted]. A total of [redacted]. Refer to Table 28 for a summary of patient disposition in Study 302.

Table 28: Patient Disposition in Study 302

Characteristic	Atogepant 60 mg q.d.	SOC
Screened, N[a]		[redacted]
Screening failure, N[b]		[redacted]
Randomized, N[c]	[redacted]	[redacted]
Open-label treatment period		
Number of patients completed, N (%)	[redacted]	[redacted]
Reason for discontinuation, N (%)		
Withdrawal by patient or of consent	[redacted]	[redacted]
AE	[redacted]	[redacted]
Protocol deviation or violation	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]
Pregnancy	[redacted]	[redacted]
Noncompliance	[redacted]	[redacted]
Other	[redacted]	[redacted]
Follow-up period		
Number of patients entered, N (%)	[redacted]	[redacted]
Number of patients completed, N (%)	[redacted]	[redacted]

Characteristic	Atogepant 60 mg q.d.	SOC
Reason for discontinuation, N (%)		
Withdrawal by patient or of consent	[redacted]	[redacted]
Protocol deviation or violation	[redacted]	[redacted]
AE	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Pregnancy	[redacted]	[redacted]
Other	[redacted]	[redacted]
ITT, N	[redacted]	[redacted]
mITT, N	[redacted]	[redacted]
Safety, N	[redacted]	[redacted]

AE = adverse event; ITT = intention to treat; mITT = modified intention to treat; NA = not applicable; q.d. = once daily; SOC = standard of care.

[a]Of the 1,727 patients screened, 1,589 were new patients and 138 were study CGP-MD-01 completers.

[b]The most common reason for patients discontinuing during screening was screening failures or not meeting eligibility criteria (n = 936).

[c]Of the 744 patients randomized, 637 were new patients and 107 were study CGP-MD-01 completers.

[d]Of the 198 patients randomized to receive SOC, 170 were new patients and 28 were study CGP-MD-01 completers.

[e]Of the 546 patients randomized to receive atogepant, 467 were new patients and 79 were study CGP-MD-01 completers.

[f]Patients randomized in the SOC group, by design, were permitted to change or withdraw SOC, but were not counted as having discontinued as long as the patient stayed in the study and completed the visits.

Source: Study 302 Clinical Study Report.[34]

Exposure to Study Treatments

The mean duration of treatment exposure to atogepant was [redacted], and the median duration of treatment exposure was 364 (range, 1 to 384) days. The total time at risk was 433.6 patient-years.

The mean duration of treatment exposure to SOC was [redacted], and the median duration of treatment exposure was [redacted] The total time at risk was 149.6 patient-years. The most commonly prescribed initial SOC were [redacted].

[redacted] in the safety population were taking concomitant medications during the open-label treatment period.

The concomitant medications most frequently used by patients in the atogepant and SOC groups (≥ 20% of patients) were [redacted]), a combination medication that contains [redacted].

The mean overall adherence to open-label atogepant was [redacted] The median overall adherence was [redacted].

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported as follows.

Monthly Migraine Days

For week 1 to week 4, the mean number of MMDs at baseline was [redacted] and the LSM change from baseline was [redacted]. For week 49 to week 52, the mean MMDs at baseline was [redacted] and the LSM change from baseline was [redacted].

In the subgroup of patients who had prior exposure to atogepant from the CGP-MD-01 trial, the LSM change from baseline in the number of MMDs at week 1 to week 4 was [redacted] and at week 49 to week 52 was [redacted]. In the subgroup of patients with no prior exposure to atogepant (new patients or study CGP-MD-01 completers from the placebo group), the LSM change from baseline in the number of MMDs at week 1 to week 4 was [redacted] and at week 49 to week 52 was [redacted].

In the subgroup of patients who had prior exposure to a migraine prevention therapy with proven efficacy, the LSM change from baseline in the number of MMDs at week 1 to week 4 was [redacted] and at week 49 to week 52 was [redacted]. In the subgroup of patients with no prior exposure to a migraine prevention therapy, the LSM change from baseline in the number of MMDs at week 1 to week 4 was [redacted] and at week 49 to week 52 was [redacted].

50% Reduction in MMDs and Additional Responder Analysis

The proportion of patients who achieved a 50% or more, 75% or more, and 100% reduction in MMDs at week 1 to week 4 was [redacted] respectively. The proportion of patients who achieved a 50% or more, 75% or more, and 100% reduction in MMDs at week 49 to week 52 was [redacted] respectively.

The proportion of patients who achieved a 50% or greater reduction in MMDs for the subgroup analyses in patients with or without prior exposure to atogepant were [redacted] for patients with previous experience with atogepant but by week 52, the results were [redacted] for both subgroups.

The proportion of patients who achieved a 50% or greater reduction in MMDs for the subgroup analyses in patients with or without prior exposure to a migraine-preventive medication with proven efficacy [redacted] for both subgroups throughout the treatment period.

Monthly Headache Days

For week 1 to week 4, the mean number of MHDs at baseline was [redacted] and the LSM change from baseline was [redacted]. For week 49 to week 52, the mean MHDs at baseline was [redacted] and the LSM change from baseline was [redacted].

In the subgroup of patients who had prior exposure to atogepant, the LSM change from baseline in the number of MHDs at week 1 to week 4 was [redacted] and at week 49 to week 52 was [redacted]. In the subgroup of patients with no prior exposure to atogepant, the LSM change from baseline in the number of MHDs at week 1 to week 4 was [redacted] and at week 49 to week 52 was [redacted]

In the subgroup of patients who had prior exposure to a migraine prevention therapy with proven efficacy, the LSM change from baseline in the number of MHDs at week 1 to week 4 was [redacted] and at week 49 to week 52 was [redacted]. In the subgroup of patients with no prior exposure to a migraine prevention

therapy, the LSM change from baseline in the number of MHDs at week 1 to week 4 was [redacted] and at week 49 to week 52 was [redacted]

Monthly Moderate to Severe Headache Days

The LSM change from baseline in the number of monthly moderate to severe headache days was [redacted] and [redacted] days at week 1 to week 4 and week 49 to week 52, respectively.

The LSM change from baseline in the number of monthly severe headache days was [redacted] and [redacted] days at week 1 to week 4 and week 49 to week 52, respectively.

Monthly Cumulative Headache Hours

The LSM change from baseline in the number of monthly cumulative headache hours was [redacted] and [redacted] hours at week 1 to week 4 and week 49 to week 52, respectively.

Monthly Acute Medication Use Days

For week 1 to week 4, the mean number of MUDs at baseline was [redacted] and the LSM change from baseline was [redacted]. For week 49 to week 52, the mean MUDs at baseline was [redacted] and the LSM change from baseline was [redacted].

In the subgroup of patients who had prior exposure to atogepant, the LSM change from baseline in the number of MUDs at week 1 to week 4 was [redacted] and at week 49 to week 52 was [redacted]. In the subgroup of patients with no prior exposure to atogepant, the LSM change from baseline in the number of MUDs at week 1 to week 4 was [redacted] and at week 49 to week 52 was [redacted].

In the subgroup of patients who had prior exposure to a migraine prevention therapy with proven efficacy, the LSM change from baseline in the number of MUDs at week 1 to week 4 was [redacted] and at week 49 to week 52 was [redacted] In the subgroup of patients with no prior exposure to a migraine prevention therapy, the LSM change from baseline in the number of MUDs at week 1 to week 4 was [redacted] and at week 49 to week 52 was [redacted].

Monthly Triptan Use Days

The LSM change from baseline in the number of monthly triptan use days was [redacted] and [redacted] days at week 1 to week 4 and week 49 to week 52, respectively.

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

The LSM change from baseline in the MSQ version 2.1 role function-restrictive domain score was [redacted] and [redacted] at week 12 and week 52, respectively.

Activity Impairment in Migraine–Diary

The LSM change from baseline in the AIM-D performance of daily activities domain score was [redacted] and [redacted] at week 1 to week 4 and week 49 to week 52, respectively.

The LSM change from baseline in the AIM-D physical impairment domain score was [redacted] and [redacted] at week 1 to week 4 and week 49 to week 52, respectively.

Harms

Only those harms identified in the review protocol are reported as follows. Refer to Table 29 for detailed harms data.

TEAEs were reported in [redacted] patients in the safety population during the open-label treatment with atogepant. The TEAEs most commonly reported by patients (≥ 5% of patients) were [redacted] For context, TEAEs were reported in [redacted] patients in the safety population during the open-label treatment with SOC. The TEAEs most commonly reported by patients (≥ 5% of patients) were [redacted].

SAEs were reported in [redacted] patients during the open-label treatment with atogepant; each event was reported by [redacted] patient. For context, SAEs were reported in [redacted] patients during the open-label treatment with SOC; each event was reported by [redacted] patient with the exception of noncardiac chest pain in [redacted] patients.

Two deaths were reported in the safety population of the atogepant treatment group. One death was due to homicide and 1 death was due to toxic shock syndrome (complications of a beta hemolytic streptococcal infection). Both reports were considered not related to atogepant per investigator judgment. For context, no deaths were reported in the SOC group.

Premature discontinuation due to at least 1 TEAE was reported in [redacted] patients during the open-label treatment with atogepant. The following TEAEs were reported in more than 1 patient that led to discontinuation [redacted] patients discontinued due to nausea and [redacted] patients each discontinued due to fatigue, dizziness, and rash. Notably, [redacted] patient discontinued due to constipation. For context, premature discontinuation due to at least 1 TEAE was reported in [redacted] patients during the open-label treatment with SOC. The following TEAEs were reported in at least [redacted] patient that led to discontinuation: dizziness, corneal degeneration, osteonecrosis, breast cancer, metastatic colon cancer, and alopecia.

Notable harms identified in the atogepant treatment group included constipation in [redacted] patients, suicidal ideation in [redacted] patients (one type 4 classification with no suicidal behaviour and 2 type 5 classifications with suicidal behaviour per C-SSRS), and elevations in ALT or AST that were greater than or equal to 3 times the ULN value in [redacted] patients. An external independent clinical adjudication committee determined that [redacted] cases of aminotransferase elevations were unlikely to be related to the study drug and the remaining [redacted] cases were possibly related to the study drug. [redacted].

Table 29: Summary of Harms in Study 302 (Safety Population)

Characteristic	Atogepant 60 mg q.d.	SOC
TEAEs (≥ 5%), n (%)		
Overall	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
SAEs, n (%)		
Overall	[redacted]	[redacted]
Deaths, n (%)		
Overall	[redacted]	[redacted]
Homicide	[redacted]	[redacted]
Toxic shock syndrome	[redacted]	[redacted]
WDAEs, n (%)		
Overall	[redacted]	[redacted]
Notable harms, n (%)		
Constipation	[redacted]	[redacted]
Suicidal ideation	[redacted]	[redacted]
C-SSRS type 4 with no suicidal behaviour[a]	[redacted]	[redacted]
C-SSRS type 5 with suicidal behaviour[b]	[redacted]	[redacted]
ALT or AST ≥ 3 × ULN[c]	[redacted]	[redacted]
Hy's law cases[d]	[redacted]	[redacted]

ALT = alanine aminotransferase; AST = aspartate aminotransferase; C-SSRS = Columbia-Suicide Severity Rating Scale; NA = not applicable; q.d. = once daily; SAE = serious adverse event; SOC = standard of care; TEAE = treatment-emergent adverse event; ULN = upper limit of normal; WDAE = withdrawal due to adverse event.

[a]Per the C-SSRS assessment, active suicidal ideation type 4 was with some intent but without a specific plan.

[b]Per the C-SSRS assessment, active suicidal ideation type 5 was with a specific plan and intent.

[c]Values were n of N1, where N1 = the number of patients with at least 1 nonmissing postbaseline value.

[d]Hy's law cases were defined as concurrent ALT or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN and alkaline phosphatase value < 2 × ULN.

Source: Study 302 Clinical Study Report.[34]

Critical Appraisal

The open-label study design of the long-term extension study, Study 309, may have biased the reporting of end points, particularly any subjective measures included in the safety parameters (and efficacy parameters in Study 302) 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 without experiencing any AE that could indicate an unacceptable safety risk per investigator judgment, the resultant population may have been more tolerant of atogepant,

potentially leading to an underreporting of AEs. In the absence of an active comparator or placebo group, the interpretation of the results was limited, which was further compounded by the use of descriptive statistics only.

These limitations could also be applied to Study 302. The enrolment of new patients without prior experience with atogepant and patients who had completed a lead-in study further limited the interpretation of the results. It should be noted that the SOC treatment group only served to provide context for interpreting the safety results of atogepant. The oral migraine preventives were prescribed in a manner that reflected routine clinical practice. A flexible treatment paradigm was used that permitted the discontinuation of, or switching from, 1 drug to an alternative for migraine prevention as needed and per investigator judgment. Regardless of the type of change made, patients in the SOC group were permitted to continue with the study. Thus, AE reporting in the SOC group could have been influenced by investigator choice as the AEs could have differed based on the oral migraine preventive selected.

Discussion

Summary of Available Evidence

Initially, 2 double-blind RCTs (the ADVANCE and CGP-MD-01 studies) were included in this review, and the ELEVATE study was provided by the sponsor before completion of this clinical report. All studies were a total of 20 weeks in duration, with 12-week double-blind periods. All studies included adult patients with a 1-year history of migraine consisting of 4 migraine days per month to 14 migraine days per month, with or without aura, and migraine onset before age 50 years. A total of 910 patients, 834 patients, and [redacted] patients were enrolled in the ADVANCE, CGP-MD-01, and ELEVATE trials, respectively. In the ADVANCE study, patients were randomized 1:1:1:1 to atogepant 10 mg, atogepant 30 mg, atogepant 60 mg, or placebo. In the CGP-MD-01 trial, patients were randomized 2:1:2:1:2:1 to receive placebo, atogepant 10 mg, atogepant 30 mg, atogepant 60 mg once daily, or atogepant 30 mg or atogepant 60 mg twice daily; however, the twice daily regimens were not reported upon. Patients in the ELEVATE study were randomized 1:1 to atogepant 60 mg once daily or matching placebo. The dose of 60 mg once daily for the ELEVATE trial was used based on the results of the ADVANCE study, in which the sponsor noted a dose-response relationship. The primary and secondary end points of all the studies were similar, sharing the primary end point of change from baseline in mean MMDs, and sharing 3 key secondary end points of change from baseline in mean MHDs, change from baseline in monthly acute MUDs, and at least a 50% reduction in a 3-month average of MMDs. The ADVANCE and ELEVATE studies included 3 additional secondary outcomes of change from baseline in MSQ version 2.1 role function-restrictive domain score, change from baseline in the mean monthly performance of daily activities domain score of AIM-D, and change from baseline in the mean monthly physical impairment domain score of AIM-D.

Baseline characteristics in the included studies were generally well balanced across groups and were generally applicable to the Canadian population. All studies enrolled mainly white patients (71.5% to 96.2%), though study CGP-MD-01 had a greater proportion of Black or African American patients. The median age

across studies was 38 years to 44 years, and all studies had a higher proportion of female patients (82.8% to 90.7%). The mean MMDs and MHDs were also similar at baseline across treatment groups, ranging from 7.2 days to 7.7 days and 9.1 days to 9.8 days, respectively. The main difference between the ADVANCE and CGP-MD-01 studies in terms of patient characteristics was with regard to prior migraine prevention therapy, where [redacted] of patients in the ADVANCE trial received prior migraine prevention therapy compared to [redacted] of patients in the CGP-MD-01 trial. However, it is worth noting that patients enrolled in the studies had to have a history of 4 migraine days per month to 14 migraine days per month on average in the 3 months before the first visit. Hence, all studies excluded patients with 1 migraine day per month to 3 migraine days per month, and it is uncertain if results from the ADVANCE, CGP-MD-01, and ELEVATE trials are generalizable to patients with fewer than 4 migraine days per month.

One sponsor-submitted NMA was summarized and critically appraised. Two analysis scenarios were conducted for atogepant for the Canadian context. The first compared atogepant to CGRP inhibitors and key oral preventives approved in the US as a treatment for EM. The second compared atogepant to CGRP inhibitors in patients who have experienced 2 or more prior preventive treatment failures.

Two additional studies submitted by the sponsor were appraised as other relevant evidence (Study 309 and Study 302). 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 EM for up to 40 weeks of treatment. The primary end point of Study 302 was the percentage of participants with at least 1 TEAE. 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 EM for up to 52 weeks of treatment. Patients were eligible to enrol in Study 302 if they had completed the lead-in study CGP-MD-01, and new patients who met the eligibility criteria were also eligible to enrol. Patients were randomized at visit 2 to receive atogepant 60 mg once daily or SOC (oral migraine-preventive medication) in a 5:2 ratio. The primary end point of Study 302 was the percentage of participants with at least 1 TEAE.

Interpretation of Results

Efficacy

The reimbursement request under review is for the prevention of migraine in adults with fewer than 15 migraine days per month who have experienced an inadequate response, an intolerance, or a contraindication to at least 2 oral prophylactic migraine medications. The clinical expert consulted by CADTH hypothesized that the criteria for 2 or more treatment failures before atogepant may be selected as this would allow for proper patient engagement, education, and implementation of lifestyle modifications and the use of earlier, more well-understood treatment options. As previously mentioned, the ADVANCE and CGP-MD-01 studies excluded patients with inadequate response to 4 prior migraine prevention therapies and 3 prior migraine prevention therapies, respectively. The sponsor provided CADTH with the results of the ELEVATE study at a later date; this included patients who had failed 2 to 4 oral migraine prophylaxis medications and was the only trial to reflect the reimbursement request. A post hoc analysis from the ADVANCE study of patients with 2 or more prior migraine prevention therapy failures was conducted, but only included 35 patients at the 60 mg once daily dose. Given that the results from the ADVANCE study

specific to the population of the reimbursement request were based on subgroup data, CADTH was unable to conclude that atogepant demonstrated improved efficacy in these patients as these subgroups were not powered to detect statistical differences. In general, the results for the primary end point of change from baseline in mean MMDs was [redacted] study population and the subgroup analysis results from the ADVANCE study, with LSM differences for the comparisons of atogepant 60 mg once daily and placebo of −2.43 days (95% CI, −3.27 to −1.59 days) and −3.12 (SE = 0.88) days in the ADVANCE study subgroup, respectively. Results for secondary end points (a 50% reduction in MMDs, MHDs, acute MUDs, and others) were also [redacted] and the ADVANCE study subgroup analysis, though the magnitude of effect versus placebo from the ADVANCE study subgroup analyses were [redacted].

Nearly all patients in the included studies were naive to CGRP inhibitor therapy based on the exclusion criteria for the trials. The clinical expert consulted by CADTH highlighted that in practice, most current patients with EM will likely have failed a CGRP mAb. There was some dispute between the clinical expert consulted by CADTH and the clinician group input as to when atogepant may be initiated in clinical practice. The clinical expert suggested that atogepant would be used following anti-CGRP mAbs as there is currently no evidence to suggest that it is superior to mAbs, while the clinician group expressed using atogepant ahead of the mAbs due to the preferable administration method and its potential use in primary care, though both stakeholders cited that cost would be an ultimate driver of these decisions. Hence, the place in therapy for atogepant either before or after anti-CGRP mAbs in Canada remains uncertain due to the naivety of the included population for anti-CGRP mAbs.

As highlighted by the drug program input, there was a low proportion of patients older than 65 years included in the trials. In total, only [redacted] and [redacted] patients were older than 60 years in the phase III ADVANCE and ELEVATE studies, respectively. The clinical expert consulted by CADTH noted that in general, these patients may have other comorbidities such as renal or hepatic issues that may render them ineligible for clinical studies. However, it was also noted that age alone should not preclude the use of atogepant in patients who are older adults, and that the upper limit for current CGRP inhibitors is 70 years.

Three doses of atogepant are approved by Health Canada (10 mg, 30 mg, or 60 mg once daily), and were evaluated in the ADVANCE and CGP-MD-01 studies, while only the 60 mg once daily dosage was evaluated in the ELEVATE study. Two additional doses of 30 mg and 60 mg twice daily were also evaluated in the CGP-MD-01 trial; however, given that these doses are not approved by Health Canada, they were omitted from this report. Overall, the ADVANCE trial generally demonstrated statistically significant treatment effects favouring atogepant on all primary and key secondary end points for all doses, with the exception of the AIM-D for the 10 mg dose. A limited dose response was observed for all efficacy end points in the ADVANCE study, with higher doses demonstrating greater benefit; however, an inverse relationship existed in the phase II/III CGP-MD-01 study, which is unexplainable. Based on the results of study CGP-MD-01, [redacted] of patients in the ADVANCE trial had to have taken a prior preventive medication. Additionally, the 1:1:1:1 randomization scheme and greater number of patients enrolled in each group of the ADVANCE study may have revealed the apparent relationship; however, the reason remains uncertain.

In all studies, all doses of atogepant resulted in greater absolute reductions in important headache-related outcomes such as change from baseline in MMDs, MHDs, or acute MUDs. Additionally, a greater proportion of patients achieved a 50% response with atogepant compared to placebo. In study CGP-MD-01, key secondary end points including a 50% reduction in mean MMDs and change from baseline in mean monthly acute MUDs did not reach statistical significance in any group compared to placebo; however, these outcomes were statistically significant in the ADVANCE and ELEVATE studies. There was a notable placebo response in all trials, though the [redacted]. Clinically important results were observed in the placebo group with a change from baseline in MMDs of −2.48 days in the placebo group of the ADVANCE study, −2.85 days in the CGP-MD-01 study, and [redacted] days in the ELEVATE study. Additionally, a clinically meaningful 50% response was observed in 29%, 40.4%, and [redacted] of patients who received placebo in the ADVANCE, CGP-MD-01, and ELEVATE trials, respectively. The clinical expert consulted by CADTH advised that this is the case with many other migraine therapies as well. Results were generally consistent across outcomes. The relative change from baseline across doses compared to placebo was not overtly meaningful with a change from baseline versus placebo for the atogepant 60 mg dose of −1.72 migraine days per month (95% CI, −2.28 migraine days per month to −1.15 migraine days per month) in the ADVANCE trial. Upon discussion with the clinical expert consulted by CADTH, based on the small to nonexistent dose response observed in the ADVANCE trial and the inverse relationship in the CGP-MD-01 trial, there is no rationale for the selection of dosages of atogepant as dose does not appear to influence the efficacy of atogepant, despite the sponsor selecting the 60 mg once daily dosage for the ELEVATE study based on these results.

In all studies, patients who were enrolled had to have a history of 4 migraine days per month to 14 migraine days per month on average in the 3 months before the first visit. Hence, all studies excluded patients with 1 migraine day per month to 3 migraine days per month, and it is uncertain if results from the ADVANCE, CGP-MD-01, and ELEVATE studies are generalizable to patients with fewer than 4 migraine days per month.

The results for the reduction in acute MUDs were considered important, favouring atogepant over placebo in all studies, though it is uncertain if a reduction of 1.11 days to 2.68 days is considered clinically meaningful in this population. By definition, patients with EM do not generally experience medication overuse; however, the reduction of MUDs is an important outcome in patients living with migraines as the chronification of disease generally results in greater use of acute medications to treat attacks.

Results for HRQoL measures and other PROs were consistent with the reductions in migraine frequency, generally favouring atogepant compared to placebo. The clinical expert consulted by CADTH considered the most useful PROs to be the HIT-6 and MIDAS measures, measuring the intensity and disability of headaches. It should be noted that absolute and relative changes are important in interpreting the results for measures such as the HIT-6. Though baseline and postbaseline scores at various time points were reported, it remains difficult to interpret the true effect of atogepant on HIT-6 scores due to the high placebo response and uncertainty in the clinically meaningfulness of the difference from placebo. There was a notable difference in baseline ([redacted]) and change from baseline scores ([redacted]) for the atogepant 30 mg group for MIDAS in the ADVANCE study compared to the atogepant 10 mg and atogepant 60 mg doses. The reason for these differences remains uncertain. Results for these measures were also exploratory in both studies; therefore, no generalizations should be made. The clinical expert also emphasized that HRQoL and PRO measures are

not frequently used in routine Canadian clinical practice, due to the highly subjective nature of pain intensity, and that measures of frequency and duration are most important to assess clinical efficacy.

All studies were of the same overall and double-blind treatment duration. The double-blind period of 12 weeks was considered appropriate to assess meaningful change in migraine frequency and intensity and was noted by the clinical expert to be in line with clinical practice and regular patient follow-up. The long-term efficacy of atogepant is currently being evaluated in Study 302. As with the CGRP mAbs, there may be the potential for waning efficacy at around 6 months of treatment; however, this remains uncertain.

In the absence of comparative evidence, the sponsor submitted a series of NMAs that compared atogepant to relevant comparators in the Canadian treatment landscape, including both CGRP inhibitors and key oral preventives in all patients with EM, and CGRP inhibitors only in patients with 2 or more migraine preventive failures. The results of the NMAs suggest that [redacted] There was both marked and unmarked clinical, methodological, and statistical heterogeneity, coupled with the wide CrIs in each network [redacted] which resulted in significant uncertainty in the comparative efficacy of atogepant. Moreover, [redacted] and the impact of this on treatment effect remains unknown and may impact the generalizability of the results. In addition, [redacted].

Harms

The overall incidence of harms in the included studies was generally well balanced between atogepant and placebo groups. There were some imbalances in specific incidences of TEAEs experienced with atogepant compared to placebo. However, there was no dose-response relationship observed for safety as there was for efficacy, where it may be expected that patients receiving higher doses of atogepant would experience more TEAEs, though this was not the case. There was a notably higher incidence of constipation and nausea in the atogepant groups in each study compared to placebo. As previously mentioned, constipation is a known complication of anti-CGRP mAbs and may be exacerbated in patients using other medications that affect the gastrointestinal system.[35] Patients with a history of clinically significant gastrointestinal disease were excluded from the included studies, which may have reduced the generalizability and underestimated the incidence of constipation in clinical practice. As noted by the clinical expert consulted by CADTH, patients with migraine with aura are at an increased risk for vascular disorders, including cardiovascular disease. Though patients with aura were included in the trials, no safety analyses for these patients in particular were provided; therefore, it remains unclear if there are any safety concerns specifically for patients with EM with aura. The incidence of vascular TEAEs was low in the included studies, and though the mechanism of action of CGRP remains unclear, it is thought to play a role in vasodilatation in the setting of tissue ischemia; thus, there is a concern that CGRP inhibitors may increase the risk of ischemic events.[36,37] Moreover, patients with a history of or current clinically significant cardiovascular or cerebrovascular disease were excluded from the trials; thus, the safety results may not be generalizable to these patients. Safety results for other subgroup analyses, including prior migraine prevention with proven efficacy, were not conducted.

Serious AEs and WDAEs were infrequent and were generally similar to the placebo groups. Mostly, TEAEs were mild to moderate in severity, and were consistent with other CGRP inhibitors according to the clinical expert consulted by CADTH. Suicidal ideation was a notable harm evaluated in the studies; however, the overall incidence of suicidal behaviours or actions was minimal.

The sponsor-submitted NMAs evaluated the occurrence of all-cause discontinuation and TEAEs in analysis scenario 2. There was generally [redacted] between any of the treatments evaluated in the NMA for these outcomes, with varying hazard rates and moderately wide 95% CrIs. Therefore, the safety results from the NMA were uncertain and imprecise and cannot be generalized to patients with EM.

Safety was the primary outcome from the 2 studies included in the Other Relevant Evidence section (Study 302 and Study 309). Overall, there were no additional safety concerns in the long-term studies, and results were consistent with the ADVANCE and CGP-MD-01 studies. However, Study 302 and Study 309 were both open-label, and no comparisons were made between atogepant and the SOC group. Moreover, some patients in Study 302 had prior exposure to atogepant through the CGP-MD-01 trial while others were atogepant-naive, and it is unclear what impact this may have had on the results. Therefore, the results of these studies should be viewed as supportive evidence only for the overall effect of atogepant.

Conclusions

Three randomized, double-blind studies were included in this review: the ADVANCE, CGP-MD-01, and ELEVATE studies. However, only the population from the ELEVATE study reflected the reimbursement request for patients who have experienced an inadequate response, an intolerance, or a contraindication to at least 2 oral prophylactic migraine medications. In the ADVANCE, CGP-MD-01, and ELEVATE studies, atogepant demonstrated a statistically significant change from baseline compared to placebo in mean MMDs, MHDs, and acute MUDs. Atogepant was also associated with clinically meaningful 50% reductions in average 3-month MMDs. Results for other key secondary end points, including change from baseline in MSQ version 2.1 and AIM-D scores, were generally in line with the primary outcome. Together, the migraine frequency, HRQoL, and patient-reported efficacy outcomes were appropriate and reflective of clinical practice in Canada; however, there was generally a high placebo response in these outcomes, limiting the interpretability and generalizability of the efficacy of atogepant. Overall, treatment with atogepant was well tolerated over the study period and did not appear to be associated with more TEAEs or SAEs compared to placebo. Known AEs for CGRP inhibitors, including constipation, were more frequent in the atogepant groups; however, there were no concerns.

The sponsor submitted a series of NMAs evaluating atogepant and appropriate comparators in the treatment of EM. However, the results of the indirect evidence on the comparative efficacy and safety of atogepant and relevant treatments was inconclusive, given that there was [redacted] between atogepant and other active comparators for important outcomes of interest, including the reduction of migraine frequency, and the results from the ELEVATE study were not included in the analysis.

Overall, the available evidence suggests that treatment with atogepant provides an additional treatment option for patients with EM, reducing the frequency and intensity of migraine headaches compared to placebo, and provides a meaningful clinical response in patients with EM. However, it is worth noting that patients enrolled in the studies had to have a history of 4 migraine days per month to 14 migraine days per month on average in the 3 months before the first visit. Hence, all studies excluded patients with 1 migraine day per month to 3 migraine days per month, and it is uncertain if results from the ADVANCE, CGP-MD-01, and ELEVATE studies are generalizable to patients with fewer than 4 migraine days per month.

References

1. Bigal ME, Lipton RB, Stewart WF. The epidemiology and impact of migraine. *Curr Neurol Neurosci Rep.* 2004;4(2):98-104. PubMed
2. Becker WJ, Findlay T, Moga C, Scott NA, Harstall C, Taenzer P. Guideline for primary care management of headache in adults. *Can Fam Physician.* 2015;61(8):670-679. PubMed
3. Goadsby PJ, Evers S. International Classification of Headache Disorders - ICHD-4 alpha. *Cephalalgia.* 2020;40(9):887-888. PubMed
4. Cooke LJ, Becker WJ. Migraine prevalence, treatment and impact: the canadian women and migraine study. *Can J Neurol Sci.* 2010;37(5):580-587. PubMed
5. Dodick DW, Loder EW, Manack Adams A, et al. Assessing Barriers to Chronic Migraine Consultation, Diagnosis, and Treatment: Results From the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study. *Headache.* 2016;56(5):821-834. PubMed
6. Evans RW. A rational approach to the management of chronic migraine. *Headache.* 2013;53(1):168-176. PubMed
7. Ramage-Morin PL, Gilmour H. Prevalence of migraine in the Canadian household population. *Health Rep.* 2014;25(6):10-16. PubMed
8. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology.* 2007;68(5):343-349. PubMed
9. Blumenfeld AM, Varon SF, Wilcox TK, et al. Disability, HRQoL and resource use among chronic and episodic migraineurs: results from the International Burden of Migraine Study (IBMS). *Cephalalgia.* 2011;31(3):301-315. PubMed
10. Buse DC, Manack AN, Fanning KM, et al. Chronic migraine prevalence, disability, and sociodemographic factors: results from the American Migraine Prevalence and Prevention Study. *Headache.* 2012;52(10):1456-1470. PubMed
11. American Headache Society. The American Headache Society Position Statement On Integrating New Migraine Treatments Into Clinical Practice. *Headache.* 2019;59(1):1-18. PubMed
12. Lipton RB, Silberstein SD. Episodic and chronic migraine headache: breaking down barriers to optimal treatment and prevention. *Headache.* 2015;55 Suppl 2:103-122; quiz 123-106. PubMed
13. Clinical Study Report: 3101-301-002. A Phase 3, Multicenter, Randomized, Double-Blind, Placebo controlled, Parallel-group Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Atogepant for the Prevention of Migraine in Participants With Episodic Migraine (ADVANCE) [internal sponsor's report]. Madison (NJ): Allergan Pharmaceuticals International Limited; 2020 Jul 6.
14. Clinical Study Report: CGP-MD-01. A Phase 2/3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy, Safety, and Tolerability of Multiple Dosing Regimens of Oral AGN-241689 in Episodic Migraine Prevention [internal sponsor's report]. Dublin (IE): Allergan Pharmaceuticals International Limited; 2018 Apr 23.
15. Clinical Study Report: 3101-304-002. A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Atogepant for the Prophylaxis of Migraine in Participants with Episodic Migraine Who Have Previously Failed 2 to 4 Classes of Oral Prophylactic Treatments (ELEVATE) [internal sponsor's report]. Madison (NJ): Allergan Pharmaceuticals International Limited; 2022 Dec 20.
16. Blumenfeld AM, Bloudek LM, Becker WJ, et al. Patterns of use and reasons for discontinuation of prophylactic medications for episodic migraine and chronic migraine: results from the second international burden of migraine study (IBMS-II). *Headache.* 2013;53(4):644-655. PubMed
17. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2018;392(10159):1789-1858. PubMed
18. Lanteri-Minet M. Economic burden and costs of chronic migraine. *Curr Pain Headache Rep.* 2014;18(1):385. PubMed
19. Martelletti P, Schwedt TJ, Lanteri-Minet M, et al. My Migraine Voice survey: a global study of disease burden among individuals with migraine for whom preventive treatments have failed. *J Headache Pain.* 2018;19(1):115. PubMed
20. PrQulipta (atogepant): 10 mg, 30 mg, 60 mg tablets [product monograph]. Markham (ON): Allergan Inc.; [2022].

21. CADTH Reimbursement Review: Galcanezumab (Emgality). *Can J Health Technol.* 2022;2(3). https://www.cadth.ca/sites/default/files/DRR/2022/SR0693-Emgality.pdf. Accessed 2022 May 27.
22. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 guideline statement. *J Clin Epidemiol.* 2016;75:40-46. PubMed
23. Ailani J, Lipton RB, Goadsby PJ, et al. Atogepant for the Preventive Treatment of Migraine. *N Engl J Med.* 2021;385(8):695-706. PubMed
24. Schwedt TJ, Lipton RB, Ailani J, et al. Time course of efficacy of atogepant for the preventive treatment of migraine: Results from the randomized, double-blind ADVANCE trial. *Cephalalgia.* 2022;42(1):3-11. PubMed
25. Goadsby PJ, Dodick DW, Ailani J, et al. Safety, tolerability, and efficacy of orally administered atogepant for the prevention of episodic migraine in adults: a double-blind, randomised phase 2b/3 trial. *Lancet Neurol.* 2020;19(9):727-737. PubMed
26. Drug Reimbursement Review sponsor submission: PrQulipta (atogepant) 10 mg, 30 mg, 60 mg tablets [internal sponsor's package]. Markham (ON): Allergan Inc.; 2022 Feb 23.
27. Cole JC, Lin P, Rupnow MF. Minimal important differences in the Migraine-Specific Quality of Life Questionnaire (MSQ) version. *Cephalalgia.* 2009;29(11):1180-1187. PubMed
28. Coeytaux RR, Kaufman JS, Chao R, Mann JD, Devellis RF. Four methods of estimating the minimal important difference score were compared to establish a clinically significant change in Headache Impact Test. *J Clin Epidemiol.* 2006;59(4):374-380. PubMed
29. Carvalho GF, Luedtke K, Braun T. Minimal important change and responsiveness of the Migraine Disability Assessment Score (MIDAS) questionnaire. *J Headache Pain.* 2021;22(1):126. PubMed
30. Lipton RB, Desai P, Sapra S, Buse DC, Fanning KM, Reed ML. How much change in headache-related disability is clinically meaningful? Estimating minimally important difference (MID) or change in MIDAS using data from the AMPP study [abstract PF52]. *Headache.* 2017;57(S3):165–166.
31. Reuter U, Goadsby PJ, Lanteri-Minet M, et al. Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study. *Lancet.* 2018;392(10161):2280-2287. PubMed
32. Network meta-analysis of treatments for prevention of episodic migraine [internal sponsor's report]. In: *Drug Reimbursement Review sponsor submission: PrQulipta (atogepant) 10 mg, 30 mg, 60 mg tablets.* Markham (ON): Allergan Inc.; 2022 Feb 23.
33. Clinical Study Report: 3101-309-002. A Phase 3, Multicenter, Open-Label 40-Week Extension Study to Evaluate the Long-Term Safety and Tolerability of Oral Atogepant for the Prevention of Migraine in Participants with Episodic Migraine [internal sponsor's report]. North Chicago (IL): AbbVie Inc.; 2021 Aug 19.
34. Clinical Study Report: 3101-302-002. A Phase 3, Multicenter, Randomized, Open-Label Study to Evaluate the Long-Term Safety and Tolerability of Oral Atogepant for the Prevention of Migraine in Participants with Episodic Migraine [internal sponsor's report]. Madison (NJ): Allergan Limited; 2020 Jun 26.
35. Haanes KA, Edvinsson L, Sams A. Understanding side-effects of anti-CGRP and anti-CGRP receptor antibodies. *J Headache Pain.* 2020;21(1):26. PubMed
36. Aradi S, Kaiser E, Cucchiara B. Ischemic Stroke Associated With Calcitonin Gene-Related Peptide Inhibitor Therapy for Migraine: A Case Report. *J Stroke Cerebrovasc Dis.* 2019;28(10):104286. PubMed
37. Mulder IA, Li M, de Vries T, et al. Anti-migraine Calcitonin Gene-Related Peptide Receptor Antagonists Worsen Cerebral Ischemic Outcome in Mice. *Ann Neurol.* 2020;88(4):771-784. PubMed
38. Bagley CL, Rendas-Baum R, Maglinte GA, et al. Validating Migraine-Specific Quality of Life Questionnaire v2.1 in episodic and chronic migraine. *Headache.* 2012;52(3):409-421. PubMed
39. Schober P, Boer C, Schwarte LA. Correlation coefficients: appropriate use and interpretation. *Anesth Analg.* 2018;126(5):1763-1768. PubMed

40. Speck RM, Yu R, Ford JH, Ayer DW, Bhandari R, Wyrwich KW. Psychometric validation and meaningful within-patient change of the Migraine-Specific Quality of Life questionnaire version 2.1 electronic patient-reported outcome in patients with episodic and chronic migraine. *Headache.* 2021;61(3):511-526. PubMed
41. Rendas-Baum R, Bloudek LM, Maglinte GA, Varon SF. The psychometric properties of the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ) in chronic migraine patients. *Qual Life Res.* 2013;22(5):1123-1133. PubMed
42. Dodick DW, Silberstein S, Saper J, et al. The impact of topiramate on health-related quality of life indicators in chronic migraine. *Headache.* 2007;47(10):1398-1408. PubMed
43. Kosinski M, Bayliss MS, Bjorner JB, et al. A six-item short-form survey for measuring headache impact: the HIT-6. *Qual Life Res.* 2003;12(8):963-974. PubMed
44. Kawata AK, Coeytaux RR, Devellis RF, Finkel AG, Mann JD, Kahn K. Psychometric properties of the HIT-6 among patients in a headache-specialty practice. *Headache.* 2005;45(6):638-643. PubMed
45. Yang M, Rendas-Baum R, Varon SF, Kosinski M. Validation of the Headache Impact Test (HIT-6) across episodic and chronic migraine. *Cephalalgia.* 2011;31(3):357-367. PubMed
46. Cohen J. A power primer. *Psychol Bull.* 1992;112(1):155-159. PubMed
47. Rendas-Baum R, Yang M, Varon SF, Bloudek LM, DeGryse RE, Kosinski M. Validation of the Headache Impact Test (HIT-6) in patients with chronic migraine. *Health Qual Life Outcomes.* 2014;12:117. PubMed
48. Houts CR, McGinley JS, Wirth RJ, Cady R, Lipton RB. Reliability and validity of the 6-item Headache Impact Test in chronic migraine from the PROMISE-2 study. *Qual Life Res.* 2021;30(3):931-943. PubMed
49. Smelt AF, Assendelft WJ, Terwee CB, Ferrari MD, Blom JW. What is a clinically relevant change on the HIT-6 questionnaire? An estimation in a primary-care population of migraine patients. *Cephalalgia.* 2014;34(1):29-36. PubMed
50. Houts CR, Wirth RJ, McGinley JS, Cady R, Lipton RB. Determining Thresholds for Meaningful Change for the Headache Impact Test (HIT-6) Total and Item-Specific Scores in Chronic Migraine. *Headache.* 2020;60(9):2003-2013. PubMed
51. Lipton RB, Gandhi P, Stokes J, et al. Development and validation of a novel patient-reported outcome measure in people with episodic migraine and chronic migraine: The Activity Impairment in Migraine Diary. *Headache.* 2022;62(1):89-105. PubMed
52. Bigal ME, Rapoport AM, Lipton RB, Tepper SJ, Sheftell FD. Assessment of migraine disability using the Migraine Disability Assessment (MIDAS) questionnaire: a comparison of chronic migraine with episodic migraine. *Headache.* 2003;43(4):336-342. PubMed
53. Stewart WF, Lipton RB, Dowson AJ, Sawyer J. Development and testing of the Migraine Disability Assessment (MIDAS) Questionnaire to assess headache-related disability. *Neurology.* 2001;56(6 Suppl 1):S20-28. PubMed
54. Stewart WF, Lipton RB, Kolodner K, Liberman J, Sawyer J. Reliability of the migraine disability assessment score in a population-based sample of headache sufferers. *Cephalalgia.* 1999;19(2):107-114; discussion 174. PubMed
55. Stewart WF, Lipton RB, Kolodner KB, Sawyer J, Lee C, Liberman JN. Validity of the Migraine Disability Assessment (MIDAS) score in comparison to a diary-based measure in a population sample of migraine sufferers. *Pain.* 2000;88(1):41-52. PubMed
56. Sauro KM, Rose MS, Becker WJ, et al. HIT-6 and MIDAS as measures of headache disability in a headache referral population. *Headache.* 2010;50(3):383-395. PubMed
57. Yang M, Rendas-Baum R, Varon SF, Kosinski M. Validation of the Headache Impact Test (HIT-6 TM) across episodic and chronic migraine. *Cephalalgia.* 2011;31(3):357-367. PubMed
58. Dunlop BW, Gray J, Rapaport MH. Transdiagnostic clinical global impression scoring for routine clinical settings. *Behav Sci (Basel).* 2017;7(3). PubMed
59. Forkmann T, Scherer A, Boecker M, Pawelzik M, Jostes R, Gauggel S. The Clinical Global Impression Scale and the influence of patient or staff perspective on outcome. *BMC Psychiatry.* 2011;11:83. PubMed
60. Kadouri A, Corruble E, Falissard B. The improved Clinical Global Impression Scale (iCGI): development and validation in depression. *BMC Psychiatry.* 2007;7:7. PubMed

Appendix 1: Literature Search Strategy

Note that this appendix has not been copy-edited.

Clinical Literature Search

Overview

Interface: Ovid

Databases:

- MEDLINE All (1946 to present)
- Embase (1974 to present)
- Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: March 22, 2022

Alerts: Biweekly search updates until project completion

Search filters applied: No filters were applied to limit the retrieval by study type.

Limits:

- No date or language limits were used
- Conference abstracts: excluded

Table 30: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Keyword heading word
.dq	Candidate term word (Embase)
.pt	Publication type
.rn	Registry number
.nm	Name of substance word (MEDLINE)

Syntax	Description
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

Multidatabase Strategy

1. (Qulipta* or atogepant* or MK8031 or MK-8031 or AGN-241689 or AGN241689 or 7CRV8RR151).ti,ab,kf,ot,hw,rn,nm.
2. 1 use medall
3. *atogepant/
4. (Qulipta* or atogepant* or MK8031 or MK-8031 or AGN-241689 or AGN241689).ti,ab,kf,dq.
5. 3 or 4
6. 5 not (conference review or conference abstract).pt.
7. 6 use oemezd
8. 2 or 7
9. remove duplicates from 8

Clinical Trials Registries

ClinicalTrials.gov

Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials.

[Search – Qulipta OR atogepant OR MK8031 OR “MK-8031” OR “AGN-241689” OR AGN241689]

WHO ICTRP

International Clinical Trials Registry Platform, produced by the WHO. Targeted search used to capture registered clinical trials.

[Search terms – Qulipta OR atogepant OR MK8031 OR “MK-8031” OR “AGN-241689” OR AGN241689]

Health Canada’s Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials.

[Search terms – Atogepant, qulipta, MK 8031, MK8031, AGN 241689, AGN241689]

EU Clinical Trials Register

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms – Qulipta* OR atogepant* OR MK8031 OR “MK-8031” OR “AGN-241689” OR AGN241689]

Grey Literature

Search dates: March 10 to 16, 2022

Keywords: Atogepant, Qulipta, CGRP, gepant, "calcitonin gene-related peptide," migraine

Limits: None

Updates: None

Relevant websites from the following sections of the CADTH grey literature checklist Grey Matters: A Practical Tool for Searching Health-Related Grey Literature were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trials Registries
- Internet Search

Appendix 2: Excluded Studies

Note this appendix has not been copy-edited.

Table 31: Excluded Studies

Reference	Reason for exclusion
Ailani J, Lipton RB, Goadsby PJ, et al. Atogepant for the Preventive Treatment of Migraine. N Engl J Med. 2021;385(8):695 to 706.	Duplicate
Schwedt TJ, Lipton RB, Ailani J, et al. Time course of efficacy of atogepant for the preventive treatment of migraine: Results from the randomized, double-blind ADVANCE trial. Cephalalgia. 2022;42(1):3 to 11.	Duplicate
Goadsby PJ, Dodick DW, Ailani J, et al. Safety, tolerability, and efficacy of orally administered atogepant for the prevention of episodic migraine in adults: a double-blind, randomized phase 2b/3 trial. Lancet Neurol. 2020;19(9):727 to 737.	Duplicate

Appendix 3: Detailed Outcome Data

Note this appendix has not been copy-edited.

Table 32: Redacted

Factor	Atogepant 10 mg q.d. (N = 214)	Atogepant 30 mg q.d. (N = 223)	Atogepant 60 mg q.d. (N = 222)	Placebo (N = 214)
Baseline				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Copy-reference approach				
LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
PMM, ANCOVA[a] atogepant vs. placebo				
LSM difference (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]
Robust regression[b]				
Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant vs. placebo				
Mean difference (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]
Within-group imputation under MAR				
LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
ANCOVA[c] atogepant vs. placebo				
LSM difference (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]

ANCOVA = analysis of covariance; CI = confidence interval; LSM = least squares mean; MAR = missing at random; PMM = pattern-mixture model; q.d. = once daily; SE = standard error; vs. = versus.

[a]Pattern-mixture model where the placebo group will be used as reference to impute missing values. For each imputed dataset, ANCOVA analysis is performed with treatment group and prior exposure to migraine prevention medications (yes or no) as fixed factors, and baseline value as a covariate. The estimates and P values are obtained from combining all the results from each individual analysis.

[b]Multiple imputation is used to create complete datasets at first. For each imputed dataset, robust regression (M-estimation) is used with treatment group and prior exposure to migraine prevention medications (yes or no) as fixed factors, and baseline value as a covariate. The robust analysis results from each imputed dataset are combined to obtain estimates and P values.

[c]Missing data are imputed under the MAR assumption using participants from the same treatment group. For each imputed dataset, ANCOVA analysis is performed with treatment group and prior exposure to migraine prevention medications (yes or no) as fixed factors, and baseline value as a covariate. The estimates and P values are obtained from combining all the results from each imputed dataset.

Source: ADVANCE Clinical Study Report.[13]

Table 33: Supportive Analysis, Change From Baseline in 3-Month Average of Monthly Migraine Days (ANCOVA) — mITT Population, ADVANCE Study

Factor	Atogepant 10 mg q.d. (N = 214)	Atogepant 30 mg q.d. (N = 223)	Atogepant 60 mg q.d. (N = 222)	Placebo (N = 214)
Baseline				
Mean (SD)	7.45 (2.463)	7.86 (2.316)	7.75 (2.307)	7.51 (2.388)
PMM				
ANCOVA[a]				
LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant vs. placebo				
LSM difference (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]

ANCOVA = analysis of covariance; CI = confidence interval; LSM = least squares mean; PMM = pattern-mixture model; q.d. = once daily; SE = standard error; vs. = versus.

[a]LSM difference was estimated from an ANCOVA model on change from baseline in the calculated average monthly migraine days during the 12-week treatment period for each participant with terms for treatment, prior exposure (Y/N) to a migraine prevention medication with proven efficacy, and baseline score.

Source: ADVANCE Clinical Study Report.[13]

Table 34: Sensitivity Analyses, Change From Baseline in Mean MMD — mITT Population, Study CGP-MD-01

Factor	Atogepant 10 mg q.d. (N = 92)	Atogepant 30 mg q.d. (N = 182)	Atogepant 60 mg q.d. (N = 177)	Placebo (N = 178)
Baseline				
Mean (SD)	7.63 (2.51)	7.64 (2.37)	7.74 (2.59)	7.81 (2.51)
PMM, ANCOVA[a]				
Atogepant vs. placebo				
LSM difference (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]

Factor	Atogepant 10 mg q.d. (N = 92)	Atogepant 30 mg q.d. (N = 182)	Atogepant 60 mg q.d. (N = 177)	Placebo (N = 178)
Robust regression[b]				
Atogepant vs. placebo				
Mean difference (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]

ANCOVA = analysis of covariance; CI = confidence interval; q.d. = once daily; SE = standard error; vs. = versus.

[a]PMM where the placebo group was used as reference to impute missing values. For each imputed dataset, ANCOVA analysis was performed with treatment group as a factor and baseline value as a covariate. The estimates and P values were obtained from combining all the results from each individual analysis.

[b]Multiple imputation was used to create complete datasets at first. For each imputed dataset, robust regression (M-estimation) was used with treatment group as a factor and baseline value as a covariate. The robust analysis results from each imputed dataset were combined to obtain estimates and P values.

Source: CGP-MD-01 Clinical Study Report.[14]

Table 35: Redacted

Factor	Atogepant 60 mg q.d. (N = 151)	Placebo (N = 154)
Baseline		
Mean (SD)	[redacted]	[redacted]
Within-group imputation under MAR[a]		
LSM (SE)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
ANCOVA atogepant vs. placebo		
LSM difference (SE)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
P value	[redacted]	[redacted]
Robust regression[b]		
Mean (SE)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Atogepant vs. placebo		
Mean difference (SE)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
P value	[redacted]	[redacted]
Copy-reference approach[c]		
LSM (SE)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]

Factor	Atogepant 60 mg q.d. (N = 151)	Placebo (N = 154)
PMM, ANCOVA atogepant vs. placebo		
LSM difference (SE)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
P value	[redacted]	[redacted]

ANCOVA = analysis of covariance; CI = confidence interval; LSM = least squares mean; MAR = missing at random; PMM = pattern-mixture model; q.d. = once daily; SE = standard error; vs. = versus.

[a]Missing data are imputed under the MAR assumption using participants from the same treatment group. For each imputed dataset, ANCOVA analysis is performed with treatment group, region and number of classes of failed prior prophylactic treatments (2 and > 2) as fixed factors, and baseline monthly migraine days as a covariate. The estimates and P value are obtained from combining all the results from each imputed dataset.

[b]Multiple imputation is used to create complete datasets at first. For each imputed dataset, robust regression (M-estimation) is used with treatment group, region and number of classes of failed prior prophylactic treatments (2 and > 2) as fixed factors, and baseline monthly migraine days as a covariate. The robust analysis results from each imputed dataset are combined to obtain estimates and P value.

[c]Pattern-mixture model where the placebo group will be used as reference to impute missing values. For each imputed dataset, ANCOVA analysis is performed with treatment group, region and number of classes of failed prior prophylactic treatments (2 and > 2) as fixed factors, and baseline monthly migraine days as a covariate. The estimates and P value are obtained from combining all the results from each individual analysis.

Source: ELEVATE Clinical Study Report.[15]

Table 36: Redacted

Factor	Atogepant 60 mg q.d. (N = 222)	Placebo (N = 214)
Baseline		
Mean (SD)	[redacted]	[redacted]
PMM		
ANCOVA[a]		
LSM (SE)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Atogepant vs. placebo		
LSM difference (SE)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
P value	[redacted]	[redacted]

ANCOVA = analysis of covariance; CI = confidence interval; LSM = least squares mean; PMM = pattern-mixture model; q.d. = once daily; SE = standard error; vs. = versus.

[a]LSM difference was estimated from an ANCOVA model on change from baseline in the calculated average monthly migraine days during the 12-week treatment period for each participant with treatment, region and number of classes of failed prior prophylactic treatments (2 and > 2) as fixed factors, and baseline monthly migraine days as a covariate.

Source: ELEVATE Clinical Study Report.[15]

Table 37: Redacted

Factor	Atogepant 10 mg q.d.	Atogepant 30 mg q.d.	Atogepant 60 mg q.d.	Placebo
Prior exposure, N	[redacted]	[redacted]	[redacted]	[redacted]
Baseline				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
MMRM[a]				
LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant vs. placebo				
LSM difference (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
No prior exposure, N	[redacted]	[redacted]	[redacted]	[redacted]
Baseline				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
MMRM[a]				
LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant vs. placebo				
LSM difference (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; LSM = least squares mean; MMRM = mixed model of repeated measures; q.d. = once daily; SD = standard deviation; SE = standard error; vs. = versus.

Note: Postbaseline (month 1 to month 3) = average of monthly migraine days across the 12-week treatment period.

[a]The MMRM for change from baseline included baseline monthly migraine days as a covariate, treatment group and visit (month) as fixed factors, and treatment-group-by-visit and baseline-by-visit as interaction terms, with an unstructured covariance matrix.

Source: ADVANCE Clinical Study Report.[13]

Table 38: Redacted

Factor	2 prior prophylactic treatment failures (N = 170)		≥ 3 prior prophylactic treatment failures (N = 135)	
	Atogepant 60 mg q.d. (N = 86)	Placebo (N = 84)	Atogepant 60 mg q.d. (N = 65)	Placebo (N = 70)
Baseline				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Postbaseline (month 1 to month 3)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
MMRM[a]				
LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant vs. placebo				
LSM difference (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; LSM = least squares mean; MMRM = mixed model of repeated measures; q.d. = once daily; SD = standard deviation; SE = standard error; vs. = versus.

[a]The MMRM for change from baseline included baseline MMD as a covariate, treatment group, and visit (month) as fixed factors, and treatment-group-by-visit and baseline-by-visit as interaction terms, with an unstructured covariance matrix.

Source: ELEVATE Clinical Study Report.[15]

Table 39: Redacted

Factor	4 to < 8 migraine days at baseline (N = 72)		≥ 8 migraine days at baseline (N = 233)	
	Atogepant 60 mg q.d. (N = 37)	Placebo (N = 35)	Atogepant 60 mg q.d. (N = 114)	Placebo (N = 119)
Baseline				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Postbaseline (month 1 to month 3)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
MMRM[a]				
LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant vs. placebo				
LSM difference (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; LSM = least squares mean; MMRM = mixed model of repeated measures; q.d. = once daily; SD = standard deviation; SE = standard error; vs. = versus.

[a]The MMRM for change from baseline included baseline includes baseline MMDs as a covariate, treatment group, visit (month), and number of classes of failed prior prophylactic treatments (2 and > 2) as fixed factors, and treatment-group-by-visit and baseline-by-visit as interaction terms, with an unstructured covariance matrix.

Source: ELEVATE Clinical Study Report.[15]

Table 40: Redacted

Factor	ADVANCE study[a]				ELEVATE study[b]	
	Atogepant 10 mg q.d. (N = 214)	Atogepant 30 mg q.d. (N = 223)	Atogepant 60 mg q.d. (N = 222)	Placebo (N = 214)	Atogepant 60 mg q.d. (N = 151)	Placebo (N = 154)
25% responders						
Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nonresponders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OR vs. placebo (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
75% responders						
Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Factor	ADVANCE study[a]				ELEVATE study[b]	
	Atogepant 10 mg q.d. (N = 214)	Atogepant 30 mg q.d. (N = 223)	Atogepant 60 mg q.d. (N = 222)	Placebo (N = 214)	Atogepant 60 mg q.d. (N = 151)	Placebo (N = 154)
Nonresponders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OR vs. placebo (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
100% responders						
Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nonresponders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OR vs. placebo (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; OR = odds ratio; q.d. = once daily; vs. = versus.

[a]The OR (95% CI) and P value are based on logistic regression with treatment group, baseline value, and prior exposure (yes/no) to a migraine prevention medication with proven efficacy as explanatory variables.

[b]The OR (95% CI) and P value are based on logistic regression with treatment group, region, baseline monthly migraine days, and number of classes of failed prior prophylactic treatments (2 and > 2) as explanatory variables.

Sources: ADVANCE Clinical Study Report[13] and ELEVATE Clinical Study Report.[15]

Table 41: Redacted

Factor	Atogepant 10 mg q.d.	Atogepant 30 mg q.d.	Atogepant 60 mg q.d.	Placebo
Prior exposure, N	145	159	152	152
Baseline				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
MMRM[a]				
LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant vs. placebo				
LSM difference (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
No prior exposure, N	[redacted]	[redacted]	[redacted]	[redacted]
Baseline				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
MMRM[a]				
LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant vs. placebo				
LSM difference (SE)	[redacted]	[redacted]	[redacted]	[redacted]

Factor	Atogepant 10 mg q.d.	Atogepant 30 mg q.d.	Atogepant 60 mg q.d.	Placebo
95% CI	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; LSM = least squares mean; MMRM = mixed model of repeated measures; q.d. = once daily; SD = standard deviation; SE = standard error; vs. = versus.

[a]MMRM for change from baseline. The model includes baseline as a covariate; prior exposure to migraine prevention medications (yes or no), treatment group, and visit (month) as fixed factors; and treatment-group-by-visit and baseline-by-visit as interaction terms, with an unstructured covariance matrix.

Source: ADVANCE Clinical Study Report.[13]

Table 42: Redacted

Factor	Atogepant 10 mg q.d.	Atogepant 30 mg q.d.	Atogepant 60 mg q.d.	Placebo
Prior exposure, N	[redacted]	[redacted]	[redacted]	[redacted]
Baseline				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
MMRM[a]				
LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant vs. placebo				
LSM difference (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
No prior exposure, N	[redacted]	[redacted]	[redacted]	[redacted]
Baseline				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
MMRM[a]				
LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant vs. placebo				
LSM difference (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; LSM = least squares mean; MMRM = mixed model of repeated measures; q.d. = once daily; SD = standard deviation; SE = standard error; vs. = versus.

[a]MMRM for change from baseline. The model includes baseline as a covariate, treatment group and visit (month) as fixed factors, and treatment-group-by-visit and baseline-by-visit as interaction terms, with an unstructured covariance matrix.

Source: ADVANCE Clinical Study Report.[13]

Table 43: Redacted

Factor	Atogepant 10 mg q.d.	Atogepant 30 mg q.d.	Atogepant 60 mg q.d.	Placebo
Prior exposure, N	**145**	**159**	**152**	**152**
50% responders				
Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
OR[a] vs. placebo (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
75% responders				
Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
OR vs. placebo (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
100% responders				
Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
OR[a] vs. placebo (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
No prior exposure, N	**69**	**64**	**70**	**62**
50% responders				
Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
OR[a] vs. placebo (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
75% responders				
Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
OR[a] vs. placebo (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
100% responders				
Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
OR vs. placebo (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; NA = not applicable; OR = odds ratio; q.d. = once daily; vs. = versus.

[a]The OR (95% CI) is based on logistic regression with treatment group and baseline value as explanatory variables.

Source: ADVANCE Clinical Study Report.[13]

Table 44: Redacted

Baseline to week 12	Atogepant 10 mg q.d.		Atogepant 30 mg q.d.		Atogepant 60 mg q.d.		Placebo	
	≥ 1 (N = 105)	≥ 2 (N = 19)	≥ 1 (N = 119)	≥ 2 (N = 38)	≥ 1 (N = 106)	≥ 2 (N = 35)	≥ 1 (N = 106)	≥ 2 (N = 27)
Mean MMD								
Baseline, mean (SD)	[redacted]							
LSM (SE) CFB	[redacted]							
LSM difference (SE) vs. placebo	[redacted]							
Mean MHD								
Baseline, mean (SD)	[redacted]							
LSM (SE) CFB	[redacted]							
LSM difference (SE) vs. placebo	[redacted]							
Mean monthly acute MUDs								
Baseline, mean (SD)	[redacted]							
LSM (SE) CFB	[redacted]							
LSM difference (SE) vs. placebo	[redacted]							
Percentage of reduction in 3-month average MMD								
≥ 50% reduction, n (%)	[redacted]							
OR vs. placebo (95% CI)	[redacted]							
MSQ version 2.1 role function-restrictive domain[a]								
LSM (SE) change	[redacted]							
LSM difference (SE) vs. placebo	[redacted]							
AIM-D performance of daily activities domain								
LSM (SE) change	[redacted]							
LSM difference (SE) vs. placebo	[redacted]							
AIM-D physical impairment domain								
LSM (SE) change	[redacted]							

Baseline to week 12	Atogepant 10 mg q.d.		Atogepant 30 mg q.d.		Atogepant 60 mg q.d.		Placebo	
	≥ 1 (N = 105)	≥ 2 (N = 19)	≥ 1 (N = 119)	≥ 2 (N = 38)	≥ 1 (N = 106)	≥ 2 (N = 35)	≥ 1 (N = 106)	≥ 2 (N = 27)
LSM difference (SE) vs. Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AIM-D = Activity Impairment in Migraine–Diary; CFB = change from baseline; CI = confidence interval; LSM = least squares mean; MHD = monthly headache day; mITT = modified intention to treat; MMD = monthly migraine days; MSQ = Migraine-Specific Quality-of-Life Questionnaire; OR = odds ratio; q.d. = once daily; SD = standard deviation; SE = standard error; vs. = versus.

[a]The MID for the MSQ version 2.1 role function-restrictive domain is 3.2 points for between-group comparisons and the meaningful within-patient change is at least 25 points. An MID for the AIM-D has not been published, but a meaningful within-patient change of at least 9 points in the AIM-D performance of daily activities domain and at least 6 points in the AIM-D physical impairment domain has been established.

Source: Sponsor's submission.[26]

Table 45: Redacted

Factor	Atogepant 10 mg q.d. (N = 214)			Atogepant 30 mg q.d. (N = 223)			Atogepant 60 mg q.d. (N = 222)			Placebo (N = 214)		
	4 weeks	8 weeks	12 weeks	4 weeks	8 weeks	12 weeks	4 weeks	8 weeks	12 weeks	4 weeks	8 weeks	12 weeks
Role function-restrictive domain score												
Baseline												
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMRM[a]												
LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant vs. placebo												
LSM difference (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Role function-preventive domain score												
Baseline												
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMRM[a]												
LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant vs. placebo												

Factor	Atogepant 10 mg q.d. (N = 214)			Atogepant 30 mg q.d. (N = 223)			Atogepant 60 mg q.d. (N = 222)			Placebo (N = 214)		
	4 weeks	8 weeks	12 weeks	4 weeks	8 weeks	12 weeks	4 weeks	8 weeks	12 weeks	4 weeks	8 weeks	12 weeks
LSM difference (SE)	[redacted]											
95% CI	[redacted]											
Emotional function domain score												
Baseline												
n (%)	[redacted]											
Mean	[redacted]											
MMRM[a]												
LSM (SE)	[redacted]											
95% CI	[redacted]											
Atogepant vs. placebo												
LSM difference (SE)	[redacted]											
95% CI	[redacted]											

CI = confidence interval; LSM = least squares mean; MMRM = mixed model of repeated measures; q.d. = once daily; SE = standard error; vs. = versus.

[a]The MMRM for change from baseline included baseline as a covariate; prior exposure to migraine prevention medications (yes or no), treatment group, and visit (month) as fixed factors; and treatment-group-by-visit and baseline-by-visit as interaction terms, with an unstructured covariance matrix. P values were from the test between the atogepant dose group and the placebo group.

Source: ADVANCE Clinical Study Report.[13]

Table 46: Redacted

Factor	Atogepant 60 mg q.d. (N = 151)			Placebo (N = 154)		
	4 weeks	8 weeks	12 weeks	4 weeks	8 weeks	12 weeks
Role function-restrictive domain score						
Baseline						
n (%)	[redacted]					
Mean	[redacted]					
MMRM[a]						
LSM (SE)	[redacted]					
95% CI	[redacted]					
Atogepant vs. placebo						
LSM difference (SE)	[redacted]					

Factor	Atogepant 60 mg q.d. (N = 151)			Placebo (N = 154)		
	4 weeks	8 weeks	12 weeks	4 weeks	8 weeks	12 weeks
95% CI	[redacted]					
Role function-preventive domain score						
Baseline						
n (%)	[redacted]					
Mean	[redacted]					
MMRM[a]						
LSM (SE)	[redacted]					
95% CI	[redacted]					
Atogepant vs. placebo						
LSM difference (SE)	[redacted]					
95% CI	[redacted]					
Emotional function domain score						
Baseline						
n (%)	[redacted]					
Mean	[redacted]					
MMRM[a]						
LSM (SE)	[redacted]					
95% CI	[redacted]					
Atogepant vs. placebo						
LSM difference (SE)	[redacted]					
95% CI	[redacted]					

CI = confidence interval; LSM = least squares mean; MMRM = mixed model of repeated measures; q.d. = once daily; SE = standard error; vs. = versus.

[a]The MMRM for change from baseline included baseline domain score as a covariate, treatment group, visit (month), region, number of classes of failed prior prophylactic treatments (2 and > 2) and number of migraine days during the screening or baseline period (4 to = 8) as fixed factors, and treatment-group-by-visit and baseline-by-visit as interaction terms, with an unstructured covariance matrix.

Source: ELEVATE Clinical Study Report.[13]

Table 47: Redacted

Factor	Atogepant 10 mg q.d. (N = 214)			Atogepant 30 mg q.d. (N = 223)	Atogepant 60 mg q.d. (N = 222)					Placebo (N = 214)		
	Week 1 to week 4	Week 5 to week 8	Week 9 to week 12	Week 1 to week 4	Week 5 to week 8	Week 9 to week 12	Week 1 to week 4	Week 5 to week 8	Week 9 to week 12	Week 1 to week 4	Week 5 to week 8	Week 9 to week 12
Performance of daily activities domain score												
Baseline												
N (%)												
Mean												
MMRM[a]												
LSM (SE)												
95% CI												
Atogepant vs. placebo												
LSM difference (SE)												
95% CI												
Physical impairment domain score												
Baseline												
N (%)												
Mean												
MMRM[a]												
LSM (SE)												
95% CI												

Factor	Atogepant 10 mg q.d. (N = 214)			Atogepant 30 mg q.d. (N = 223)	Atogepant 60 mg q.d. (N = 222)					Placebo (N = 214)		
	Week 1 to week 4	Week 5 to week 8	Week 9 to week 12	Week 1 to week 4	Week 5 to week 8	Week 9 to week 12	Week 1 to week 4	Week 5 to week 8	Week 9 to week 12	Week 1 to week 4	Week 5 to week 8	Week 9 to week 12
Atogepant vs. placebo												
LSM difference (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AIM-D = Activity Impairment in Migraine–Diary; CI = confidence interval; LSM = least squares mean; MMRM = mixed model of repeated measures; q.d. = once daily; SE = standard error; vs. = versus.

[a]The MMRM for change from baseline included baseline as a covariate; prior exposure to migraine prevention medications (yes or no), treatment group, and visit (month) as fixed factors; and treatment-group-by-visit and baseline-by-visit as interaction terms, with an unstructured covariance matrix.

Source: ADVANCE Clinical Study Report.[13]

Table 48: Redacted

Factor	Atogepant 60 mg q.d. (N = 151)			Placebo (N = 154)		
	Week 1 to week 4	Week 5 to week 8	Week 9 to week 12	Week 1 to week 4	Week 5 to week 8	Week 9 to week 12
Performance of daily activities domain score						
Baseline						
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMRM[a]						
LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant vs. placebo						
LSM difference (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Physical impairment domain score						
Baseline						
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMRM[a]						
LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant vs. placebo						
LSM difference (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AIM-D = Activity Impairment in Migraine–Diary; CI = confidence interval; LSM = least squares mean; MMRM = mixed model of repeated measures; q.d. = once daily; SE = standard error; vs. = versus.

[a]The MMRM for change from baseline included baseline monthly domain score as a covariate, treatment group, visit (month), region, number of classes of failed prior prophylactic treatments (2 and > 2) and number of migraine days during the screening or baseline period (4 to = 8) as fixed factors, and treatment-group-by-visit and baseline-by-visit as interaction terms, with an unstructured covariance matrix.

Source: ELEVATE Clinical Study Report.[15]

Appendix 4: Description and Appraisal of Outcome Measures

Note this appendix has not been copy-edited.

Aim

To describe the following outcome measures and review their measurement properties (validity, reliability, responsiveness to change, and MID):

- MSQ version 2.1
- AIM-D
- HIT-6
- PGIC
- WPAI:Migraine version 2.0
- MIDAS
- PGI-S

Findings

The validity, reliability, responsiveness, and the MID of each outcome measure were summarized and evaluated in Table 49.

Table 49: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MID
MSQ version 2.1	A 14-item questionnaire used to rate the impact of migraine on physical and emotional functioning across 3 domains using a 6-point scale. Raw scores are rescaled from 0 to 100, with higher scores indicating better HRQoL. The recall period is 4 weeks.	**Validity:** Construct, convergent, discriminant, and known-groups validity were adequate when compared to other headache-related and HRQoL instruments in patients with EM and CM. **Reliability:** Internal consistency and test-retest reliability were adequate in patients with EM and CM. **Responsiveness:** Responsiveness to change was adequate in patients with EM and CM.	Estimated group-level MIDs for patients with < 15 HDPM were 3.2 for RR, 4.6 for RP, and 7.5 for EF. Estimated individual-level MIDs for patients with < 15 HDPM ranged from 4.8 to 8.6 for RR, 5.0 to 9.9 for RP, and 8.0 to 12.4 for EF.
HIT-6	A 6-item questionnaire used to quantify the impact of headaches on a patient's daily life. Each item is rated on a 5-point Likert scale based on the following responses: never, rarely, sometimes, very often, or always, which are assigned 6, 8, 10, 11, or 13 points, respectively, with	**Validity:** Construct validity was adequate when compared to other headache-related assessments in patients with EM and CM. **Reliability:** Internal consistency and test-retest reliability were adequate in patients with CM and EM.	Estimated within-group MID was 2.5 points based on the mean change approach and 6 points based on the receiver operating characteristic curve approach in patients with EM.

Outcome measure	Type	Conclusions about measurement properties	MID
	higher scores indicating a greater degree of impact.	**Responsiveness:** Responsiveness to change was adequate in patients with CM. Not identified for EM.	Estimated between-group MID was 1.5 points in patients with EM.
AIM-D	An 11-item diary used to assess the impact of migraine on activity across 2 domains. Each item is rated on a 6-point scale. The total score and each domain score are transformed to a 0- to 100-scale, with higher scores indicating greater degree of impairment. The recall period is the previous 24 hours. AIM-D includes supplementary items (level and limitations of activity) that patients can rate on a 5-point scale.	**Validity:** Construct, convergent, and known-groups validity were adequate when compared to other headache-related and HRQoL instruments in patients with EM and CM. **Reliability:** Internal consistency and test-retest reliability were adequate in patients with EM and CM. **Responsiveness:** Responsiveness to change was adequate in patients with EM but conflicting results were found for CM.	Not identified for migraine.
MIDAS	A 5-item (2 additional items are not included in the scoring) questionnaire used to assess disability due to headaches. Each item corresponds to the number of days missed or with reduced productivity in 3 domains: work or school; housework or chores; and family, social, or leisure activities. The recall period is 3 months. The total score was calculated by summing the first 5 items.	**Validity:** Concurrent validity was adequate when compared to other headache-related assessments in patients with CM and EM. **Reliability:** Internal consistency and test-retest reliability were adequate in patients with CM and EM. **Responsiveness:** Responsiveness to change was limited in patients with CM and EM (based on nonpharmacological intervention and modified recall period of 1 month).	Estimated MID for patients with at least 4 HDPM (migraines) was 3.7 points. Estimated MID for patients with EM and CM was 4.5 points (based on nonpharmacological intervention and modified recall period of 1 month).
PGIC	A single item rating scale used to assess a patient's impression of the overall change experienced in migraine following initiation of treatment. Patients were asked to rate their impression on a 7-point scale that ranged from "very much better" to "very much worse."	**Validity:** Not identified for migraine. **Reliability:** Not identified for migraine. **Responsiveness:** Not identified for migraine.	Not identified for migraine.
PGI-S	A single item used to assess the impression patients have of the overall severity of their migraine-related symptoms at the time of evaluation. Patients were asked to rate the severity on a 5-point scale ranging from "none" to "very severe."	**Validity:** Not identified for migraine. **Reliability:** Not identified for migraine. **Responsiveness:** Not identified for migraine.	Not identified for migraine.
WPAI:Migraine version 2.0	A 6-item questionnaire used to assess the impact of migraine on work productivity, absenteeism, presenteeism, and activity impairment. The recall period was 1 week. Four scores were calculated	**Validity:** Not identified for migraine. **Reliability:** Not identified for migraine. **Responsiveness:** Not identified for migraine.	Not identified for migraine.

Outcome measure	Type	Conclusions about measurement properties	MID
	and expressed as percentages of impairment that ranged from 0% to 100%, with higher percentages indicating greater impairment and reduced productivity.		

AIM-D = Activity Impairment in Migraine–Diary; EM = episodic migraine; HDPM = headache days per month; HIT-6 = 6-item Headache Impact Test; HRQoL = health-related quality of life; MID = minimal important difference; MIDAS = Migraine Disability Assessment; MSQ = Migraine-Specific Quality-of-Life Questionnaire; PGI-S = Patient Global Impression–Severity; PGIC = Patient Global Impression of Change; RP = role preventive; RR = role restrictive; VAS = visual analogue scale; WPAI:Migraine version 2.0 = Work Productivity and Activity Impairment Questionnaire: Migraine, version 2.0.

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

The MSQ version 2.1 is a 14-item questionnaire used to assess HRQoL across 3 domains: role function – restrictive (RR; 7 items assessing how migraines limit daily activities related to social and work life), role function – preventive (RP; 4 items assessing how migraines prevent said activities), and EF (EF; 3 items assessing the emotions associated with migraines).[38] The recall period is 4 weeks and items are rated on a 6-point Likert scale where 1 = none of the time, 2 = a little bit of the time, 3 = some of the time, 4 = a good bit of the time, 5 = most of the time, and 6 = all of the time. The overall score for each domain is obtained by summing the item responses then rescaling to a 0- to 100-point scale with higher scores indicative of better HRQoL.

Bagley et al.[38] provided evidence for the validity and reliability of MSQ version 2.1 in patients with EM and CM. The study was a web-based, cross-sectional survey conducted in 8,726 patients with EM (< 15 headache days per month) or CM (15 headache days per month) from 9 countries. Construct validity was assessed using Pearson's correlation coefficients, r, of the MSQ version 2.1 scores and other HRQoL instruments. Based on the overall study population (both CM and EM), correlations were moderate to strong between MSQ version 2.1 and the HIT-6 (r = −0.60 to −0.71), weak to moderate for MSQ version 2.1 and the 4-item Patient Health Questionnaire (r = −0.31 to −0.42), and weak for MSQ version 2.1 and the MIDAS (r = −0.38 to −0.39) and headache days per month (r = −0.17 to −0.24).[38,39] Overall, this provided some support for convergent and discriminant validity of MSQ version 2.1. Similar results were also obtained for the CM and EM groups separately.[38] Known-groups validity was also demonstrated using the same HRQoL measures, as a statistically significant difference was observed for the mean MSQ version 2.1 scores across migraine frequency groups. Internal consistencies were measured with the Cronbach alpha for the overall study population for role function-restrictive, role function-preventive, and EF (0.96, 0.90, and 0.87, respectively), and was acceptable based on a threshold of 0.70. Internal consistency was also adequate for either of the EM and CM populations with the Cronbach alpha of 0.86 or greater for each domain.

Speck et al.[40] assessed the validity and reliability of the electronic MSQ version 2.1 using data from EVOLVE-1, EVOLVE-2, and REGAIN which were studies of adult patients with EM and CM. For convergent validity, they found moderate to strong correlations between each of the 3 domains when compared to MIDAS and the PGI-S. Spearman rank correlations ranged from 0.46 to 0.57 for the role function-restrictive, from 0.35 to 0.57 for the role function-preventive, and from 0.38 to 0.51 for the EF domains and the

correlations were stronger with MIDAS than with PGI-S. The correlations between each domain and the number of monthly migraine headache days at baseline were determined to be weak. The correlations ranged from 0.22 to 0.27 for role function-restrictive, 0.13 to 0.22 for role function-preventive, and 0.17 to 0.22 for EF. Internal consistency and test-retest reliability (assessed 1 month apart) were adequate for all 3 domains of MSQ version 2.1 (the Cronbach alpha ranged from 0.83 to 0.93 and intraclass correlation coefficient [ICC] ranged from 0.77 to 0.92). Responsiveness was demonstrated where patients who demonstrated a 1 or higher level of improvement on MIDAS, PGI-S, or the Patient Global Impression of Improvement and/or at least 50% fewer headache days per month during the first 3 months of treatment also showed a significant improvement in all 3 MSQ version 2.1 domains compared to those who did not demonstrate such improvements. Spearman rank correlations across domains compared to headache days per month were also stronger for patients with CM versus those with EM (−0.60, −0.48, and −0.47 versus −0.47, −0.35, and −0.35), respectively. Lastly, the investigators observed no significant floor or ceiling effects from the data in any of the studies.

Rendas-Baum et al.[41] provided further evidence for the validity and reliability of MSQ version 2.1 in patients with CM undergoing prophylactic treatment. Data were pooled from 2 clinical trials of onabotulinumtoxin A, PREEMPT-1 and PREEMPT-2, and included 1,376 patients. MSQ version 2.1 and HIT-6 scores were moderately to strongly correlated[39], Pearson values ranged from −0.59 (EF) to −0.75 (RR) at baseline and −0.74 (EF and role function-preventive) and −0.86 (RR) at week 24 demonstrating adequate validity.[41] Internal consistency at baseline was acceptable according to the Cronbach alpha of 0.80 for all 3 domains, varying between 0.80 (EF) and 0.93 (RR). At 24 weeks, the Cronbach alpha remained acceptable and ranged from 0.90 to 0.97 across all domains in both studies. MSQ version 2.1 change scores showed large and moderate effect sizes for patients who experienced a 50% or greater improvement and improvement between 30% and 50%, respectively, indicating acceptable responsiveness.

Cole et al.[27] calculated group- and individual-level MIDs for each MSQ version 2.1 domains. The analyses were performed on pooled data from 2 clinical trials of topiramate for migraine prophylaxis (N = 916) and the QualityMetric National Headache Survey (N = 1,016). The trials were randomized, double-blind, and placebo-controlled from Canada and US. Patients were 12 to 65 years of age and experienced 3 to 12 migraines per month (but not more than 15 headache days per month during the 28-day baseline period). Patients were randomized to placebo or topiramate 50, 100, or 200 mg per day and continued treatment for 18 weeks. The QualityMetric database included adults aged 18 to 65 years residing in the contiguous 48 states of the US and experienced a headache at least once in the past 4 weeks before the phone interview. No study intervention was administered to the survey participants. Using a distribution-based method with Cohen D effect sizes from the pooled topiramate trial data, group-level MIDs were estimated to be 3.2, 4.6, and 7.5 for role function-restrictive, role function-preventive, and EF, respectively.

Cole et al.[27] also calculated individual-level MIDs with anchor-based versus distribution-based methods. Anchors included average monthly migraine rate (30%, 40%, or 50% reduction), migraine status (yes/no), MIDAS, a difference in the frequency of headaches compared to 3 months prior (yes/no), bothered by headaches more now compared to 3 months prior (yes/no), and impact of migraine on day-to-day life (daily

physical activities, feelings of frustration or irritability, limitations in daily activities, and overall quality of life). The individual-level MIDs according to the anchor-based techniques were 4.9 and 5.0 for role function-restrictive, 5.0 and 7.9 for role function-preventive, and 8.0 and 10.6 for EF and were generally smaller than those reported by Dodick et al. (2007)[42] It is important to note that the MIDs proposed by Dodick et al.[42] were based on patients with CM, whereas the datasets used by Cole et al.[27] included patients with a maximum of 15 headache days per month, meaning patients would be below the threshold for the classification of CM.

Using a distribution-based method, the MIDs were calculated from one-half of the SD of each MSQ version 2.1 domain from the pooled topiramate trial dataset and the QualityMetric dataset separately.[27] In a second distribution-based technique, the MIDs were calculated from the SE of the mean of the MSQ version 2.1 domains in the pooled clinical trial dataset. The estimated MIDs were 4.8, 8.3 and 8.6 (RR), 7.9, 8.5, and 9.9 (RP), and 10.6, 11.5, and 12.4 (EF). The anchor-based MIDs were similar to the distribution-based MIDs using the SE of the mean, however, were less than the distribution-based MIDs using one-half SD.

Six-Item Headache Impact Test Questionnaire

The HIT-6 is a 6-item questionnaire used to quantify the impact of headaches on a patient's daily life.[43] The items relate to pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress.[44] Each item is rated on a 5-point Likert scale based on the following responses: never, rarely, sometimes, very often, or always, which are assigned 6, 8, 10, 11, or 13 points, respectively. Total HIT-6 scores range from 36 to 78 where a higher score indicates a greater impact of headache on daily life.[28,44] The scores may also be interpreted using 4 groupings: 36 to 49 points indicate little or no impact, 50 to 55 points for some impact, 56 to 59 indicate substantial impact, and 60 to 78 points reflect severe impact.[44]

The validity and reliability of HIT-6 was assessed by Yang et al.[45] in 2,049 patients with EM, CM, or nonmigraine headaches. Adult patients who had been participants of the National Survey of Headache Impact study and the HIT-6 validation study were selected. Both studies had similar inclusion and exclusion criteria, and data were pooled. A total of 6.4% of respondents had CM, 42.1% of respondents had EM, and 51.5% of respondents had nonmigraine headaches. The instrument showed strong[46] internal consistency (Cronbach alpha = 0.83 and 0.90 for the first and second interview, respectively, in the total sample) and test-retest reliability (ICC = 0.77 for HIT-6 validation study respondents). Correlations between HIT-6 scores and other scores (MIDAS, headache pain severity, and number of headache days per month) were also obtained. A moderate correlation was observed between HIT-6 scores and total MIDAS scores (r = 0.56), demonstrating construct validity. Correlation was moderate (r = 0.46) and weak (r = 0.29) with headache pain intensity and number of headache days per month, respectively. For discriminant validity, HIT-6 scores differed significantly between subgroups of CM (mean score was 62.5 [SD = 7.8]), EM (mean score was 60.2 [SD = 7.8]), and nonmigraine headaches (mean score was 49.1 [SD = 8.7]) ($P < 0.01$); however, the sample size of the CM subgroup was much smaller in comparison to the other subgroups, and this may have affected the findings. The authors stated that patients with CM were more likely to have an increased impact severity level than patients with EM and nonmigraine headaches, in that order.[45]

Rendas-Baum et al. (2014)[47] further validated the HIT-6 in 1,384 patients with CM using pooled data from 2 studies, PREEMPT-1 and PREEMPT-2, that investigated onabotulinumtoxin A for the treatment of migraine. The correlation between HIT-6 and MSQ was determined; if correlation coefficients were less than −0.40, then HIT-6 was deemed as having convergent validity. Construct validity was examined by comparing mean scores across subgroups known to differ in the number of headache days within a 28-day period (< 10, 10 to 14, and ≥ 15) and cumulative hours of headache within a 28-day period (< 140, 140 to 279, 280 to 419, and ≥ 420) at week 24. Test-retest reliability was assessed with the ICC among a stable subsample at weeks 8 and 12. Internal consistency was assessed with the Cronbach alpha, the average interitem correlation, and the item-total correlation at baseline and week 24. Ability to detect change was evaluated by the difference in HIT-6 scores among patients who were "much improved" (≥ 50% decrease in headache frequency), "moderately improved" (≥ 30% to < 50% decrease in headache frequency), or "not improved or worsening" (< 30% decrease in headache frequency or worsening). HIT-6 correlated moderately to strongly[39] with MSQ (−0.86 to −0.59) and discriminated between prespecified known subgroups, demonstrating convergent and construct validity. Test-retest reliability was demonstrated with an ICC of 0.76 to 0.80. HIT-6 also demonstrated internal consistency with a Cronbach alpha of 0.75 to 0.92, and average interitem correlation and item-total correlation above the threshold of 0.40. HIT-6 scores were significantly higher for patients with greater improvement in headache frequency and cumulative hours of headache, demonstrating responsiveness to change.

Houts et al. (2021)[48] further validated the HIT-6 in 1,072 patients with CM using data from the PROMISE-2 study. This was a randomized, double-blind, placebo-controlled, phase III clinical trial conducted to determine the safety and efficacy of eptinezumab for the prevention of CM. For convergent validity, Pearson correlations were reported for HIT-6 total score and reference measures with continuous variables, while Spearman correlations were reported for categorical/ordinal variables at baseline and week 12. At baseline, correlation was weak (r = 0.12 to 0.29) with 5-Level EQ-5D (EQ-5D-5L) mobility and usual activities and the number of MMDs. At baseline, correlation was moderate (r = −0.34 to −0.42) with Short Form (36) Health Survey (SF-36) bodily pain, physical role functioning, and emotional role functioning. At week 12, correlation was weak (r = 0.14) with EQ-5D-5L mobility; moderate (r = 0.38 to −0.40) with EQ-5D-5L usual activities and SF-36 emotional role functioning; and strong (r = 0.51 to −0.56) with SF-36 physical role functioning and bodily pain and the number of MMDs. Known-groups validity was determined at week 12 for HIT-6 total scores according to the following subgroups of patients. The "improved group" was based on PGIC item responses with "very much improved" and "much improved." The "not improved group" was based on PGIC item responses with "minimally improved," "no change," "minimally worse," and "much worse." Additionally, subgroups were defined by the frequency of headaches according to 15 or more headache days per month versus < 15 headache days per month. The "improved group" and < 15 headache days per month group demonstrated lower HIT-6 total scores in comparison to the "non-improved group" and 15 or more headache days per month (effect sizes were 1.09 and 0.88, respectively). Internal consistency at baseline was acceptable (Pearson correlation was 0.82, above the prespecified threshold of 0.70) for the total score, while the item-total correlations were variable (Pearson correlation ranged from 0.42 to 0.72). Test-retest reliability between screening and baseline did not meet the prespecified threshold of 0.70 (ICC = 0.65)

for the total score. Change in HIT-6 total score was weakly[46] correlated with change scores for EQ-5D-5L mobility and usual activities (r = 0.12 and 0.20, respectively) between baseline to week 12. Change in HIT-6 total score was moderately[46] correlated with change scores for the number of MMDs and SF-36 emotional role functioning, physical role functioning, and bodily pain (r = 0.48, −0.35, −0.49, and −0.47, respectively). Change in HIT-6 total score was strongly[46] correlated with change scores for PGIC (r = 0.57).

The MID in the HIT-6 score was estimated by Coeytaux et al. based on a study of 71 patients with chronic daily headaches, defined as 15 or more headache days per month, and who had participated in a randomized clinical trial comparing usual medical care plus acupuncture treatments to usual care alone. The mean age was 46 years (range = 19 to 83) and 80% (n = 57) were female. Patients reported a mean of 24.2 (SD = 5.8) headache days in the month before study enrolment. Before randomization, HIT-6 was administered at baseline and again at week 6. The follow-up test included 1 additional question to determine the patient's perceived clinical change to define a meaningful clinical change: "Compared with six weeks ago, my headache condition is a) much better; b) somewhat better; c) about the same; d) somewhat worse; or e) much worse."[28] The MID was established using an anchor-based approach that compared HIT-6 scores of patients who reported clinical improvement to HIT-6 scores of patients who reported no clinical change. Four different anchors were used: Method 1 related HIT-6 change scores to levels of perceived improvement in clinical status; method 2 compared HIT-6 change scores associated with some perceived clinical change to scores associated with no change; method 3 compared HIT-6 follow-up scores between 2 levels of clinical improvement; and method 4 compared HIT-6 change scores associated with each level of change to scores associated with no perceived clinical change, using a linear regression model.

Baseline HIT-6 scores were 64.9 (95% CI, 62.7 to 67.1) in the acupuncture group and 64.1 (95% CI, 62.2 to 66.1) in the medical care only group. At 6 weeks, HIT-6 scores were 61.4 (95% CI, 59.2 to 63.5) in the acupuncture group and 63.7 (95% CI, 62.0 to 65.5) in the medical care only group.[28] Similar MID mean estimates were obtained using different anchors, which ranged from −2.7 (95% CI, −4.4 to −1.0) based on method 2 to −2.3 (95% CI, −4.3 to −0.3) based on method 4. Based on these results, the authors concluded that a between-group difference of HIT-6 change scores of 2.3 units suggests an improvement in a patient's headache condition that may be considered clinically important. Accuracy of recall may have been a limitation in the study given that patients had to recall their headache condition of 6 weeks before.

Smelt et al.[49] estimated the within-group and between-group MIDs for HIT-6 in patients with EM. The dataset consisted of 490 patients with migraine who participated in a randomized trial that compared a proactive approach by general practitioners with usual SOC in the Netherlands. The average age of patients was 48 years, 86% were female, and patients experienced an average of 6 headache days per month. The diagnosis of migraine, however, was not based on the International Headache Society criteria. Change scores on HIT-6 from baseline to month 3 (n = 368) were compared with 2 anchor questions: "(1) Compared to three months ago, how is your headache condition? a) much better; b) somewhat better; c) about the same; d) somewhat worse; e) much worse" and "(2) Compared to three months ago, how often do headaches limit your usual daily activities? a) a lot less often now; b) somewhat less often now; c) about the same; d) somewhat more often now; e) a lot more often now." A within-group MID was suggested by a mean change approach, which

defines the MID as the mean change in HIT-6 score of the group of patients who reported being "somewhat better." The between-group MID was proposed by subtracting the mean change score in the group that reported to be "about the same" from the mean change score of the group that reported to be "somewhat better." An additional, receiver operating characteristic curve analysis was conducted to determine within-group MID. The within-group MID was estimated to be –2.5 points based on the mean change approach and –6 points based on the receiver operating characteristic curve approach. The between-group MID was estimated to be –1.5 points.

Houts et al.[50] determined the meaningful differences within patients for the HIT-6 total and item-specific scores in patients with CM. The dataset consisted of adult patients (n = 1,072) with CM who participated in the PROMISE-2 study. The majority (88.2%) of patients were females and the mean age was 40.5 (SD = 11.2) years. Distribution- and anchor-based approaches were used to determine the threshold for a meaningful change within patients over time for the HIT-6 total score and anchor-based approaches were used for the item-specific scores. Distribution-based approaches used 2 typical values of the HIT-6 total scores based on one-half SD of baseline scores and the SE of measurement at baseline. The anchor-based approaches were based on "improved" and "not improved" at week 12 relative to baseline according to PGIC, EQ-5D-5L, and the number of MMDs. To determine the final clinically meaningful change in HIT-6 total score and item-specific score, the cumulative distribution function of change from baseline to week 12 were plotted against the anchor groups. In addition to the data from PROMISE-2 trial, values from existing literature were considered as well. According to the distribution-based approach, a clinically meaningful change in the HIT-6 total score was approximately –3.0 points and according to the anchor-based approach, it ranged from –10.0 to –11.0 points. Based on both PROMISE-2 data analyses and previous literature findings, a clinically meaningful change in the HIT-6 total score to discriminate between patients with CM who have experienced a meaningful change over time versus patients who have not was estimated to be –6.0 points. According to the anchor-based approaches, a clinically meaningful change was found to be a reduction of 1 severity step in items 1 to 3 ("severe pain," "limits daily activities," and "lie down") and a reduction of 2 severity steps in items 4 to 6 ("too tired," "felt fed up or irritated," and "limits concentration").[50]

Activity Impairment in Migraine–Diary

The AIM-D is an 11-item diary used to assess the impact of migraine on activity in patients with EM or CM.[51] The 11 items are (1) household chores, (2) errands, (3) leisure activities at home, (4) leisure or social activities outside of home, (5) strenuous physical activities, (6) walking, (7) moving body, (8) bending forward, (9) moving head, (10) concentrating, and (11) thinking clearly. Two domains are assessed: performance of daily activities (items 1 to 5, 10, and 11) and physical impairment (items 6 to 9). Each item is rated on a 6-point scale ranging from 0 ("not difficult at all") to 5 ("I could not do it at all"). Select items (errands, leisure outside home, and strenuous activities) offer an additional response option to indicate the activity was not planned. The total score and domain scores are transformed to a 0- to 100-scale, with higher scores indicative of a greater degree of impairment. The recall period is the previous 24 hours. AIM-D was developed as an electronic diary and is available in 2 different versions that use the same set of items and rating scale: headache (patient only considers functional impairment in the context of time spent with headache) and nonheadache (patient only considers functional impairment in the context of time spent

without headache). Additionally, AIM-D has supplementary items (level and limitations of activity) that patients can respond to daily.[51] Activity level is rated on a 5-point scale ranging from "no activity – spent all day lying down" to "exercised – brisk walk, running, jogging, biking or other activity for 30 minutes or more." Activity limitation is rated on a 5-point scale ranging from "not at all limited – I could do everything" to "extremely limited."

Lipton et al.[51] evaluated the psychometric properties of the AIM-D in a prospective, noninterventional observational study in 316 adult patients with EM (n = 186) or CM (n = 130). EM was defined as 4 to 14 migraine days per month in the previous 3 months. CM was defined as 15 or more headache days per month (with migraine headaches on ≥ 8 days) in the previous 3 months.

Convergent validity was demonstrated by the Spearman's rank-order correlations between AIM-D (total and domain scores) and the following PRO measures at baseline for both EM and CM. [51] Moderate correlations were shown with HIT-6 total score (0.36 to 0.38), MSQ domain scores (−0.36 to −0.50), and activity level (−0.41 to −0.45). Moderate to strong correlations were shown with number of headache days (0.49 to 0.58). Strong correlations were shown with PGI-S (0.53 to 0.55), Patient-Reported Outcome Measure Information System Pain Interference total score (0.54 to 0.57), Functional Impact of Migraine Questionnaire total score (0.56 to 0.60), number of migraine days (0.59 to 0.69), and activity limitations (0.80 to 0.86). Similar results for construct validity were reported for EM and CM separately. Known-groups validity was demonstrated in patients with EM; mean AIM-D total and domain scores at baseline were higher for patients with 10 to 14 migraine days per month versus 4 to 5 migraine days per month ($P < 0.003$). Similarly, known-groups validity was demonstrated in patients with CM; mean AIM-D total and domain scores at baseline were higher for patients with 23 to 28 migraine days per month versus 0 to 7 migraine days per month ($P < 0.003$). However, statistically significant differences were not found for every comparison when AIM-D baseline scores were analyzed according to the number of migraine days experienced in both EM and CM. Further, known-groups validity was reported in both EM and CM when AIM-D baseline scores were analyzed according to MSQ version 2.1 role function-restrictive and HIT-6 score categories.

Internal consistency for AIM-D (headache version) was found to be good (greater than the prespecified threshold of 0.70) in EM and CM; the Cronbach alpha was 0.97 for the performance of daily activities domain, 0.95 for the physical impairment domain, and 0.98 for the total score.[51] Similar results demonstrating good internal consistency were reported for EM and CM separately for both headache and nonheadache versions of the diary. Test-retest reliability for AIM-D was found to be substantial in EM and CM; ICC was greater than 0.60 for total and domain scores in stable patients according to their PGI-S scores between baseline and week 2. Similar results were reported for EM and CM separately as well as between baseline and week 4.

Evidence for responsiveness to change was demonstrated for migraine frequency and severity.[51] For patients with EM, changes in the AIM-D total and domain scores from baseline to month 3 were statistically significantly higher in patients who achieved an improvement of 1 or more points in the PGI-S score in comparison to patients whose score worsened by ≥ 1-point (effect size ranged from −0.59 to −0.65). For patients with CM, changes in the AIM-D total and domain scores from baseline to month 3 were numerically

higher in patients who achieved an improvement of 1 or more points in the PGI-S score in comparison to patients whose score worsened by 1 or more points. Changes in total and domain scores between baseline and month 3 were reported as higher in patients who achieved a 30% or greater reduction in the number of MMDs and in patients whose activity limitations improved in comparison to patients with no change or worsened. Changes in the total and domain scores between baseline and month 3 were reported as not significant according to change in HIT-6 scores. It should be noted, however, that data pertaining to responsiveness to change using the AIM-D should be interpreted with caution as the analyses were based on an observational, noninterventional study.

Evidence for a MID in AIM-D total and domain scores were not identified in the literature.

Migraine Disability Assessment Scale

The MIDAS is a self-reported, 5-item (2 additional items are not included in the scoring) questionnaire used to assess disability associated with headaches.[52] Each item corresponds to the number of days missed or with reduced productivity in 3 domains: work or school; housework or chores; and family, social, or leisure activities. Responses are based on a 3-month recall period which allows the questionnaire to capture information on patients' long-term experience with headaches.[53] The total score was calculated by summing the first 5 items.[13] Absenteeism was determined by summing items 1, 3, and 5, while presenteeism was determined by summing the items 2 and 4. Two additional questions are not included in the scoring that inquire about the frequency of headaches and the intensity of headache pain.[53] These are used to provide clinicians with additional information for managing treatment decisions.

The MIDAS is considered valid and reliable in patients experiencing headaches and migraines; however, the proportion of patients with CM versus EM in these studies is unknown.

Stewart et al.[53-55] provided evidence for the concurrent validity of MIDAS by comparing the MIDAS score with a 90-day headache diary, both of which were completed by 144 patients with physician-confirmed migraine diagnosis. The individual items and overall MIDAS score showed a moderate to strong correlation[39] between the questionnaire and daily headache diary (Pearson's r = 0.50 to 0.77, Spearman's ρ = 0.53 to 0.76) demonstrating concurrent validity.[53,55] Two studies by Stewart et al.[53,54] assessed the reliability of MIDAS by collecting data using phone interviews and a clinically-validated, computer-assisted telephone interview that asked respondents about their headaches, which was used to define cases of migraine in combination with International Headache Society criteria. A total of 124 respondents with migraines and 100 nonmigraine headache controls completed the MIDAS twice.[54] Spearman's and Pearson's correlations were used to assess test-retest reliability between responses to the first and second questionnaires, and internal consistency for the overall score was evaluated using a Cronbach alpha. There was substantial agreement based on a Pearson's correlation, ranging from 0.60 to 0.75 for each question, and Spearman's correlation, ranging from 0.67 to 0.84, demonstrating adequate test-retest reliability. The MIDAS also demonstrated acceptable internal consistency (Cronbach alpha = 0.83). Similar methods were used to evaluate reliability in the second study by Stewart et al.[53] Questionnaires were collected from 197 patients living with migraine (97 from the US and 100 from the UK), which were completed a median of 21.5 days apart. Each MIDAS item

score showed a moderate to strong correlation based on Pearson's correlation coefficient (r = 0.52 to 0.82) and moderate to substantial correlation according to Spearman's correlation coefficient (ρ = 0.46 to 0.71), demonstrating variable test-retest reliability. Furthermore, the overall MIDAS score demonstrated acceptable test-retest reliability with high Pearson's (r = 0.80 to 0.83) and Spearman's correlations (ρ = 0.77 to 0.78).

Sauro et al.[56] used data from the Canadian Headache Outpatient Registry and Database to compare MIDAS and HIT-6 scores for 798 patients. Those who were part of the Registry were new patients at 1 of 5 affiliated neurology clinics in Canada and most were diagnosed with migraines. The Spearman rank correlation coefficient was 0.52 for the MIDAS and HIT-6 showing moderate correlation between the instruments. A similar strength of the correlation (r = 0.56) was also demonstrated with data from adults who recently reported headaches and participated in the National Survey of Headache Impact study and the HIT-6 validation study.[57] The investigators found that HIT-6 was more likely to categorize patients in a higher (more severe) category than the MIDAS: 79% had very severe impact on the HIT-6 whereas 57% had severe disability on the MIDAS.[56] Headache intensity also showed a stronger correlation with the HIT-6 (r = 0.46) compared to the MIDAS (r = 0.26). The recall period for the HIT-6 is typically 4 weeks versus 3 months for the MIDAS. It was also noted that the HIT-6 questions may be more subjective in nature with patients responding qualitatively (e.g., never, always). Alternatively, the MIDAS has patients quantify the number of days of lost or 50% reduced productivity, though there is still some subjectivity in patients' opinions. Furthermore, it was suggested that the content of the HIT-6 is more emotional in nature compared to the MIDAS with the former asking how patients felt during the recall period. The MIDAS may be more easily interpreted since the score refers to the number of days that a patient recalled having lost productivity, but this could depend on employment or school status since work/school and home are considered separate domains. Responses to the HIT-6 range from never to always which may be subjective and nonlinear in nature. Based on the differences, the investigators suggested that the 2 instruments are not interchangeable, but complementary.

A MID was estimated based on data from 2,442 patients who reported at least 4 headache days per month and had participated in the 2005 and 2006 American Migraine Prevalence and Prevention Study.[30] Using anchor-based methods, Lipton et al.[30] found that a 25% increase in headache days per month (N = 54) corresponded to an increase of 1.6 (SD = 30.9) points in mean MIDAS score while a 25% decrease in headache days per month (N = 82) corresponded to a decrease of 5.0 (SD = 16.5) points in mean MIDAS score. A weighted average was calculated and resulted in an estimated MID of 3.7 points.

Carvalho et al.[29] further investigated the minimal important change and responsiveness to change based on data from 103 patients with EM or CM who participated in a preference-based clinical trial. The trial was conducted to determine the effectiveness of physiotherapy and aerobic exercise as an add-on to their pharmacological treatment. The mean age of patients was 39.9 (SD = 13.5) years with a mean headache frequency of 12.6 (SD = 7.6) days per month. Responsiveness and minimal important change were anchored to the Global Rating of Self-perceived Change scale with a score of 3 or more indicating significant improvement and a score of −2 or + 2 indicating "unchanged." The MID was estimated by selecting the point on the curve that had the lowest overall misclassification of patients who "improved" versus "unchanged" (top left corner of the receiver operating characteristic curve). Since the prespecified area under the receiver

operating characteristic curve of 0.70 or more indicating satisfactory responsiveness was not met, MIDAS demonstrated limited (area under the curve ranged from 0.63 to 0.68) responsiveness to change and was moderately correlated with the reference scale. The minimal important change of MIDAS was estimated to be 4.5 points (sensitivity and specificity values ranged from 0.58 to 0.67 and 0.61 to 0.62, respectively). However, change was based on nonpharmacological treatment and a modified version of MIDAS was used such that a recall period of 1 month instead of 3 months was used. The psychometric properties of this modified version have not been determined and therefore the results should be interpreted with caution.

Patient Global Impression of Change

The PGIC consisted of a single item used to assess the impression that patients have of the overall change experienced with respect to migraines following initiation of treatment. Patients were asked to rate their impression on a 7-point scale that ranged from "very much better" to "very much worse."[13]

The Clinical Global Impression scales are among the most widely used, rapidly administered, and accessible measures for evaluating psychiatric outcomes in clinical trials. Despite wide acceptance, little psychometric validation of these scales has been performed, especially outside of specific disorders such as schizophrenia, depression, and social anxiety. The scales have been criticized for lacking consistency, reliability, validity, scoring anchors, and responsiveness. It has been argued that Clinical Global Impression measures may not lend themselves to the establishment of a clinically important change as they are too simple to precisely measure treatment effects, especially as new drugs may only offer incremental benefits.[58-60]

Evidence for the validity, reliability, responsiveness to change, and MID for patients with migraine were not identified.

Patient Global Impression–Severity

PGI-S consisted of a single item used to assess the impression patients have of the overall severity of their migraine-related symptoms at the time of evaluation. Patients were asked to rate the severity on a 5-point scale that ranged from "none" to "very severe."[13]

Evidence for the validity, reliability, responsiveness to change, and MID for patients with migraine were not identified.

Work Productivity and Activity Impairment Questionnaire: Migraine, Version 2.0

The WPAI:Migraine version 2.0 was a 6-item questionnaire used to assess the impact of migraine on work productivity. The recall period was 1 week. The 6 items were (1) employment status, (2) work hours missed due to migraine, (3) work hours missed due to other reasons, (4) hours worked, (5) impact of migraine on productivity at work, and (6) impact of migraine on daily activity. Four scores were calculated and expressed as percentages of impairment that ranged from 0% to 100%, with higher percentages indicating greater impairment and reduced productivity. Scores were calculated for "percentage of work time missed due to migraine (absenteeism)," "percentage of impairment while working due to migraine (presenteeism),"

"percentage of overall work impairment due to migraine (overall work productivity loss)," and "percentage of activity impairment due to migraine (regular activity impairment)."[13]

Evidence for the validity, reliability, responsiveness to change, and MID for patients with migraine were not identified.

Pharmacoeconomic Review

List of Tables

List of Figures

Abbreviations

AE	adverse event
BIA	budget impact analysis
BSC	best supportive care
CGRP	calcitonin gene–related peptide
EM	episodic migraine
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
MMD	monthly migraine day
MSQ	Migraine-Specific Quality-of-Life Questionnaire
NIHB	Non-Insured Health Benefits
NMA	network meta-analysis
ODB	Ontario Drug Benefit
pCPA	pan-Canadian Pharmaceutical Alliance
QALY	quality-adjusted life-year
WTP	willingness to pay

Executive Summary

The executive summary comprises 2 tables (Table 1 and Table 2) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Atogepant (Qulipta), 10 mg, 30 mg, and 60 mg oral tablets
Submitted price	Atogepant, 10 mg, 30 mg, and 60 mg: $18.44 per tablet
Indication	For the prevention of episodic migraine (< 15 migraine days per month) in adults
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	December 22, 2022
Reimbursement request	For the prevention of episodic migraine in adults with < 15 migraine days per month who have experienced an inadequate response, an intolerance, or a contraindication to at least 2 oral prophylactic migraine medications
Sponsor	AbbVie
Submission history	Previously reviewed: No

NOC = Notice of Compliance.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Semi-Markov model
Target populations	• Health Canada–indicated population: Adults with EM who have < 15 MMDs • Reimbursement population: Adults with EM who have < 15 MMDs and an inadequate response, an intolerance, or a contraindication to at least 2 oral prophylactic migraine medications (≥ 2 previous therapies)
Treatments	Atogepant: 10 mg, 30 mg, or 60 mg

Comparators	• Health Canada–indicated population:
	  ◦ BSC (comprising 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]

Component	Description
	◦ 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, with the effectiveness of atogepant informed by the ADVANCE trial and the discontinuation of active comparators informed by Study 302
Submitted results	• In the Health Canada–indicated population (patients with EM regardless of the number of prior therapies), all doses of atogepant were dominated by propranolol (i.e., atogepant was more costly and less effective than propranolol) as well as several other comparators. • In the reimbursement population (≥ 2 previous therapies), atogepant 30 mg was dominated by galcanezumab and atogepant 10 mg was dominated by galcanezumab and fremanezumab 225 mg. Atogepant 60 mg was associated with an ICER of $2,091,554 per QALY gained (incremental costs = $1,001; incremental QALYs = 0.0005) compared to fremanezumab 675 mg.
Key limitations	• The full Health Canada and reimbursement populations were not modelled. The effectiveness of atogepant was based on the ADVANCE trial, which enrolled patients with 4 MMDs to 14 MMDs. The cost-effectiveness of atogepant among patients with fewer than 4 MMDs is unknown. • The comparative clinical effectiveness of atogepant to other preventive therapies (i.e., galcanezumab, fremanezumab, eptinezumab, and oral preventive 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 [redacted] 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. • 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. The 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–indicated and reimbursement populations reflect the cost-effectiveness of atogepant for patients with between 4 MMDs and 14 MMDs. Owing to a lack of clinical data, the cost-effectiveness of atogepant among EM patients with 1 MMD to 3 MMDs is unknown, as is the cost-effectiveness of atogepant in

Component	Description

	the full Health Canada–indicated or reimbursement populations (i.e., among patients with 1 MMD 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-maker's WTP threshold.
	  ◦ In the reimbursement population (patients with EM and ≥ 2 previous therapies), atogepant 10 mg and atogepant 60 mg were dominated by fremanezumab 225 mg and fremanezumab 675 mg, respectively, and atogepant 30 mg was extendedly dominated by a mix of BSC and fremanezumab 225 mg.
	• 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; NMA = network meta-analysis; QALY = quality-adjusted life-year; WTP = willingness to pay.

[a]This includes ibuprofen, Excedrin (acetaminophen, ASA, caffeine), sumatriptan, and acetaminophen.

Conclusions

Based on the CADTH clinical review, atogepant may reduce migraine frequency and improve quality of life among patients with episodic migraine (EM) compared to placebo. There are no direct head-to-head trials comparing atogepant to anti–calcitonin gene–related peptides (CGRPs) (i.e., eptinezumab, fremanezumab, and galcanezumab) or to oral preventive migraine medications. Results of the sponsor's network meta-analysis (NMA) suggest that atogepant may be associated with [redacted] in monthly migraine days (MMDs) relative to some comparators and [redacted] compared to others; [redacted], indicating that there may be [redacted] between atogepant and other drugs used to treat migraine.

The sponsor-submitted pharmacoeconomic analyses for atogepant were conducted in the reimbursement population (patients with EM and ≥ 2 prior therapies) and in the Health Canada–indicated population (patients with EM). In both populations, the efficacy of atogepant was informed by the sponsor's NMAs, which included atogepant data from the ADVANCE trial for patients with 4 MMDs to 14 MMDs. As such, the sponsor's pharmacoeconomic analyses reflect the cost-effectiveness of atogepant among patients with 4 MMDs to 14 MMDs. 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. CADTH was also unable to address uncertainty in the health state utility values, limitations related to the sponsor's modelling approach (i.e., model structure, subsequent treatments, and transparency), uncertainty in the long term effectiveness of atogepant, and the lack of clinical data for patients with fewer than 4 MMDs.

While the findings of CADTH's reanalysis were generally aligned with those submitted by the sponsor (i.e., atogepant is not a cost-effective treatment option for EM in adults), the sponsor-submitted NMAs suggests that there may be [redacted] between atogepant and relevant comparators in terms of reducing MMDs. As such, there is insufficient evidence to suggest that atogepant should be priced higher than other treatments

for EM. Thus, to ensure cost-effectiveness, atogepant should be priced no more than the lowest-cost active comparator that is funded in the population to be reimbursed.

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups, registered clinicians, and drug plans that participated in the CADTH review process.

CADTH received 1 joint patient input submission from Migraine Canada and Migraine Quebec, collected via 2 online surveys, along with a statement of support from the Women's Health Coalition of Alberta Society. The first survey included 1,165 respondents from Canada (19% with low-frequency migraine, 28% with 8 MMDs to14 MMDs, and 52% with chronic migraine), while the second included 300 respondents from Canada (15% with low-frequency migraine, 26% with 8 MMDs to 14 MMDs, and 59% with chronic migraine). An additional 8 patients (2 Canadians and 6 Americans) with atogepant experience provided input. Respondents indicated that their migraines impact their quality of life, not only due to pain but also via disrupted sleep, mental health issues (e.g., depression, anxiety), family concerns (e.g., parenting, partner burdens), and difficulties attaining or maintaining full employment, leading to financial strain. Respondents indicated that the outcomes most important to them in a preventive medication are decreased headache intensity, decreased frequency, and decreased nonpain symptoms (e.g., light and sound sensitivity, nausea, brain fog). Many respondents reported being unsatisfied with the current preventive treatment options available in Canada. Some reported that the care they had received had not improved their quality of life, while others reported a mild or marked improvement. Many respondents indicated they had discontinued a preventive therapy due to side effects, although some reported having side effects but tolerating them. More than half of respondents to the second survey indicated they had tried 5 or more preventive treatments and almost half of respondents reported they had not found an effective and tolerated way to control the majority of their migraine attacks. More than half of respondents indicated they did not fill their migraine prescription in the previous 6 months due to cost and lack of coverage. Of the 8 patients with atogepant experience, 6 reported an improved frequency and/or intensity of migraines, as well as side effects that were generally described as "slight" and improving or resolving over time.

Clinician input was received from the Canadian Headache Society. The group noted that currently available treatment options are not effective for all patients, that they may lose effectiveness over time, that some options have significant side effects or contraindications, that currently available oral medications are not disease specific, and that injectables are not ideal for all patients. Clinicians also noted that, while monoclonal antibodies may be seen as a specialist option, primary care physicians may feel more confident prescribing atogepant, which would be beneficial owing to limited access to migraine specialists in Canada. Clinicians indicated that the short half-life of atogepant would be advantageous for patients planning a pregnancy. Clinicians indicated that atogepant may be a first-line treatment option for preventing migraine, yet its place in therapy may partly be determined by its cost relative to oral preventive treatments. The clinician group also noted that, in theory, atogepant could be used in combination with other treatments with

a different mechanism of action (e.g., oral preventive treatments), although there is a lack of evidence to support this approach.

CADTH-participating drug plans indicated that it may be desirable to align the patient criteria for atogepant with that recommended for fremanezumab (i.e., in terms of the number of headache days per month for initiation and > 50% reduction from baseline in MMDs for renewal). The drug plans noted the absence of safety and efficacy information in the pediatric population and an insufficient number of study participants older than 65 years. Drug plans also noted the presence of confidential prices for comparators, given that fremanezumab has completed the pan-Canadian Pharmaceutical Alliance (pCPA) negotiations, while galcanezumab negotiations are ongoing.

Several of these concerns were addressed in the sponsor's model:

- The clinical effectiveness of preventive migraine therapies was based on the number of MMDs, with higher frequency associated with lower health-related quality of life (HRQoL) and higher health care costs.
- Loss of productivity was considered in scenario analyses.

Some aspects were not directly addressed in the sponsor's model and could not be adequately addressed by CADTH owing to structural or data limitations, such as:

- the iterative nature of treatment (i.e., patients are unlikely to remain off treatment after discontinuing a preventive therapy that is ineffective or not tolerated)
- migraine features other than frequency that patients noted as being important (i.e., intensity, light and sound sensitivity, nausea, and brain fog)
- the potential use of atogepant in combination with other oral preventive migraine treatments.

Economic Review

The current review is for atogepant (Qulipta) for the prevention of EM (< 15 MMDs) in adults.

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

Atogepant is indicated for the prevention of EM (defined as < 15 MMDs) in adults,[1] while the sponsor's reimbursement request is for the prevention of migraine in adults with EM who have experienced an inadequate response, an intolerance, or a contraindication to at least 2 oral preventive migraine medications (hereafter referred to as ≥ 2 prior therapies).[2] The sponsor submitted 2 cost-utility analyses: 1 to assess the cost-effectiveness of atogepant in the Health Canada–indicated population compared to best supportive care [BSC] and to active preventive comparators (i.e., anti-CGRP monoclonal antibodies [galcanezumab, fremanezumab, and eptinezumab] and oral preventive treatments [amitriptyline, propranolol, and topiramate]) and 1 to assess the cost-effectiveness of atogepant in the reimbursement population (compared to BSC and

anti-CGRPs). The reimbursement request is aligned with, but is narrower than, the Health Canada–indicated population. For both, the modelled populations in the sponsor's analyses are based on patients enrolled in the ADVANCE trial.[3,4]

Atogepant is available as 10 mg, 30 mg, and 60 mg oral tablets, with a recommended dose of 10 mg, 30 mg, or 60 mg once daily. The submitted price of atogepant is $18.44 per tablet, regardless of strength, which corresponds to an annual per-patient cost of $6,735.[5] The annual per-patient cost of fremanezumab (225 mg monthly or 675 mg every 3 months) was $6,429, the annual per-patient cost of eptinezumab was $7,240 for 100 mg every 12 weeks and $21,719 for 300 mg every 12 weeks, and the annual per-patient cost of galcanezumab was $7,213 in the first year and $6,659 each year thereafter. The sponsor's estimated costs for oral preventive treatments were amitriptyline at $112, propranolol at $149, and topiramate at $167. No drug acquisition costs were included for BSC in the model. All patients, including those receiving BSC, were assumed to receive acute treatments (i.e., triptans, ergot derivatives, opioids, analgesics, nonsteroidal anti-inflammatory drugs, and antiemetic drugs), although rates differed between treatments. Acute medication costs were modelled separately from drug acquisition costs.

The clinical outcome of interest was quality-adjusted life-years (QALYs). The sponsor adopted a 5-year time horizon, with the analyses conducted from the perspective of a publicly funded health care payer. Future costs and benefits were discounted at a rate of 1.5% per year, and the model cycle length was 28 days.

Model Structure

The sponsor's model consisted of a semi-Markov model with 6 health states (Figure 1): 2 health states before initial response assessment (on treatment, off treatment), 3 health states after response assessment (on-treatment responder, off-treatment nonresponder, off treatment after response assessment), and death. All patients entered the model in the on-treatment state and underwent initial treatment response assessment at 12 weeks, with response defined as at least a 50% reduction in the number of MMDs from baseline. Patients deemed to be treatment responders at 12 weeks entered the on-treatment responder state, while those with less than a 50% reduction in MMDs entered the off-treatment nonresponder state. At the time of response assessment (i.e., 12 weeks), the sponsor additionally assumed that patients had a 1-time probability of transitioning to the off treatment before response assessment state, due to the possibility of preassessment discontinuation (e.g., because of an adverse event [AE] or lack of efficacy). Patients who entered a state of off treatment (i.e., before or after response assessment) were assumed to remain off treatment until death or the end of the model horizon. From 12 weeks onward, a per-cycle discontinuation rate was assigned to the on-treatment responder state, adopted from Study 302,[6] with the rate of discontinuation for all active comparators assumed to be equal to the discontinuation due to AE rate observed for atogepant 60 mg. For BSC, patients who initially had a treatment response had a risk of returning to their baseline number of MMDs at a rate assumed to be equivalent to the discontinuation rate for the placebo group in Study 302.

Model Inputs

The baseline population characteristics used to inform the model were based on the ADVANCE trial, which included patients aged 18 years to 80 years with 4 MMDs to 14 MMDs.[4] BSC was represented by the placebo

group of the ADVANCE trial. Patients in all groups within the trial were permitted to take acute treatments for migraine attacks including triptans, ergot derivatives, opioids, analgesics, nonsteroidal anti-inflammatory drugs, and antiemetic drugs, but received no preventive treatments with the exception of atogepant for those randomized to receive it.[4]

The primary measures of efficacy in the model were the probability of a treatment response at 12 weeks (i.e., at least a 50% reduction in MMDs) and the mean change from baseline in the number of MMDs per 28-day period. The efficacy estimates were derived from the sponsor-conducted NMAs.[7] Separate NMAs were used to inform inputs for the Health Canada–indicated and reimbursement populations. Mean change from baseline in the number of MMDs was stratified by treatment (active or BSC) and by response status and was converted to a mean number of MMDs with a Poisson distribution for each treatment. The mean number of MMDs at baseline and after discontinuation was 7.645 for the Health Canada–indicated population and 8.103 for the reimbursement population. The NMAs did not include data for eptinezumab for the reimbursement population, and model inputs regarding eptinezumab for this analysis were imputed in an unspecified manner.[5] Response rates and mean MMDs for responders to each treatment can be found in Table 13.

Mortality was based on Statistics Canada[8] estimates of age-specific and gender-specific mortality rates, weighted by the proportion of male and female patients in the ADVANCE trial. The risk of death was assumed to be independent of the number of MMDs experienced and treatment received.

Health state utility values were determined by the number of MMDs experienced per 28-day cycle. Utility values were derived from a regression model based on Migraine-Specific Quality-of-Life Questionnaire[9] (MSQ) version 2.1 estimates from the ADVANCE trial, mapped to the 3-Level EQ-5D.[10] All active comparators were assumed to have utility values equal to the pooled atogepant values by MMD level, while utility values for patients receiving BSC were derived from the ADVANCE trial's placebo group.

Grade 3 and higher AEs that occurred in at least 2% of patients who received either atogepant or placebo in the ADVANCE trial were included in the model. Overall AE rates for each treatment group were derived from the sponsor's NMA,[7] and applied in the model as a hazard ratio versus placebo to each type of AE. A disutility derived from Matza et al. (2019)[11] was assigned to each AE and assumed to last for 7 days.

The economic model included costs related to drug acquisition, treatment of AEs, and health care resource use. Drug acquisition costs for atogepant were based on the sponsor's submitted price.[5] The acquisition costs for fremanezumab and galcanezumab were based on Saskatchewan Formulary and wholesale prices from IQVIA DeltaPA, respectively,[12,13] and the cost of eptinezumab was based on that which was submitted to CADTH for the review of eptinezumab for migraine.[14] The cost of oral medications for migraine prevention was obtained from the Ontario Drug Benefit (ODB) Formulary, as was the cost of acute medications (ibuprofen, acetaminophen, and sumatriptan).[15] Health care resource use for the treatment of AEs was assumed to include the cost of a repeat consultation visit with a physician and acute medication.[16] Costs for regular general practitioner, nurse practitioner, neurologist, and emergency department visits were based on the MMD level, with the frequency of each obtained from the assessment of galcanezumab conducted by the National Institute for Health and Care Excellence,[17] and costs derived from the Ontario *Schedule of Benefits*

physician services,[16] the Ontario Nurses' Association collective agreement,[18] and the Ontario Case Costing Initiative.[19] All costs are presented in 2022 Canadian dollars.[5]

Summary of Sponsor's Economic Evaluation Results

The sponsor submitted 2 probabilistic base-case analyses, intended to represent the Health Canada indication (adults with EM) and the reimbursement request (adults with EM and ≥ 2 prior therapies). The sponsor's probabilistic analyses were based on 4,000 iterations. The probabilistic findings are presented as follows. The results of the deterministic analyses were similar to the probabilistic results, except where indicated in the following. The submitted analyses are based on the publicly available prices of the comparators. Additional results from the sponsor's economic evaluation are presented in Appendix 3.

Base-Case Results

Among patients with EM (Health Canada–indicated population), atogepant 10 mg, atogepant 30 mg, and atogepant 60 mg were dominated by propranolol (i.e., atogepant was more costly and less effective than propranolol) as well as other comparators (Table 3), such that atogepant would not be chosen as the optimal treatment strategy regardless of a decision-maker's willingness-to-pay (WTP) threshold.

The sponsor's model estimates that atogepant will generate 3.538 QALYs to 3.541 QALYs over a 5-year horizon, with 94% of the incremental benefits accrued after the first 3 months (i.e., beyond the treatment duration of the ADVANCE trial). In the sponsor's sequential analysis, all doses of atogepant had a 0% chance of being cost-effective at a WTP threshold of $50,000 per QALY. At the end of the 5-year horizon, more than 99% of patients in the modelled cohort remained alive.

Table 3: Summary of the Sponsor's Economic Evaluation Results for the Health Canada–Indicated Population (Patients With Episodic Migraine)

Drug	Total costs ($)	Total QALYs	Sequential ICER ($/QALY)
Propranolol	6,534	3.548	Reference
Galcanezumab	21,016	3.574	576,103 vs. propranolol
Dominated therapies			
Amitriptyline	6,612	3.540	Dominated by propranolol
BSC	6,649	3.356	Dominated by propranolol, amitriptyline
Topiramate	6,668	3.546	Dominated by propranolol
Eptinezumab 100 mg	19,085	3.526	Dominated by propranolol, amitriptyline, topiramate
Atogepant 30 mg	**19,142**	**3.538**	**Dominated by propranolol, amitriptyline, topiramate**
Fremanezumab 225 mg	19,381	3.568	Extendedly dominated by mix of propranolol and galcanezumab
Fremanezumab 675 mg	19,532	3.568	Extendedly dominated by mix of propranolol and galcanezumab
Atogepant 10 mg	**19,549**	**3.541**	**Dominated by propranolol, topiramate, fremanezumab 225 mg, fremanezumab 675 mg**

Drug	Total costs ($)	Total QALYs	Sequential ICER ($/QALY)
Atogepant 60 mg	**19,792**	**3.541**	**Dominated by propranolol, topiramate, fremanezumab 225 mg, fremanezumab 675 mg**
Eptinezumab 300 mg	48,451	3.541	Dominated by propranolol, topiramate, fremanezumab 225 mg, fremanezumab 675 mg

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus.
Note: Table 3 presents the results of the sponsor's discounted probabilistic analyses. Episodic migraine includes patients with fewer than 15 migraine days per month.
Source: Sponsor's pharmacoeconomic submission.[5]

Among patients with EM and 2 or more previous therapies (reimbursement request), atogepant 30 mg was more costly and less effective compared to galcanezumab (i.e., atogepant 30 mg was dominated by galcanezumab) while atogepant 10 mg was dominated by galcanezumab and fremanezumab 225 mg. These doses of atogepant would not be chosen as the optimal treatment strategy regardless of a decision-maker's WTP threshold (Table 4).

In the sequential analysis for this population, atogepant 60 mg was associated with an incremental cost-effectiveness ratio (ICER) of $2,091,554 (incremental costs = $1,001; incremental QALYs = 0.0005) compared to fremanezumab 675 mg. At a threshold of $50,000 per QALY, the sponsor's model predicted an 8%, 14%, and 8% chance of atogepant 10 mg, atogepant 30 mg, and atogepant 60 mg being cost-effective, respectively, with 94% of the incremental benefits accrued beyond the treatment duration of the ADVANCE trial. At the end of the 5-year horizon, more than 99% of patients in the modelled cohort remained alive.

The deterministic results of the sponsor's model were similar; however, some differences were noted, owing to the small differences in accumulated QALYs between treatments. In deterministic analyses, atogepant 60 mg was associated with an ICER of $516,713 compared with fremanezumab 675 mg, while atogepant 30 mg was extendedly dominated by a mix of BSC and galcanezumab.

Table 4: Summary of the Sponsor's Economic Evaluation Results for the Reimbursement Population (Episodic Migraine, ≥ 2 Previous Therapies)

Drug	Total costs ($)	Total QALYs	Sequential ICER ($/QALY)
BSC	7,327	3.282	Reference
Galcanezumab	18,956	3.518	49,327 vs. BSC
Fremanezumab 225 mg	20,099	3.532	83,964 vs. galcanezumab
Fremanezumab 675 mg	21,211	3.535	396,626 vs. fremanezumab 225 mg
Atogepant 60 mg	**22,212**	**3.535**	**2,091,554 vs. fremanezumab 675 mg**
Dominated therapies			
Eptinezumab 100 mg	18,829	3.467	Extendedly dominated by mix of BSC and galcanezumab
Atogepant 30 mg	**19,017**	**3.487**	**Dominated by galcanezumab**
Atogepant 10 mg	**21,067**	**3.500**	**Dominated by galcanezumab, fremanezumab 225 mg**

Drug	Total costs ($)	Total QALYs	Sequential ICER ($/QALY)
Eptinezumab 300 mg	46,169	3.488	Dominated by galcanezumab, fremanezumab 225 mg, fremanezumab 675 mg, atogepant 60 mg, atogepant 10 mg

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus.
Note: Table 4 presents the results of the sponsor's discounted probabilistic analyses. Episodic migraine includes patients with fewer than 15 migraine days per month.
Source: Sponsor's pharmacoeconomic submission.[5]

Sensitivity and Scenario Analysis Results

The sponsor conducted several scenario analyses. These analyses examined adopting a lifetime horizon; altering the discount rate; adopting a societal perspective; introducing a natural increase in MMDs over time; equalizing the time taken for treatment effect to wear off after discontinuation; considering relative dose intensity, including costs related to hospitalizations; and adopting alternative utility values.

In the Health Canada–indicated population, atogepant 10 mg, atogepant 30 mg, and atogepant 60 mg remained dominated in all scenarios. In the reimbursement population (EM and ≥ 2 prior therapies), atogepant 10 mg and atogepant 30 mg remained dominated or extendedly dominated in all scenarios, and results for atogepant 60 mg ranged from being dominated to sequential ICERs of $395,095 to $8,949,470 compared to fremanezumab 675 mg.

The sponsor conducted an additional scenario in the reimbursement request population using data from the ELEVATE study, a randomized clinical trial comparing atogepant 60 mg to BSC in patients with 4 MMDs to 14 MMDs who had previously failed 2 classes of oral preventives to 4 classes of oral preventives. The ICER for atogepant 60 mg was $58,898 per QALY compared to BSC in this analysis; however, no other comparators were included in this scenario, limiting the interpretation of this finding.

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications for the economic analysis.

- **Full Health Canada–indicated population was not modelled:** The sponsor submitted 2 base-case analyses — 1 intended to reflect the Health Canada indication (EM patients regardless of the number of previous treatments) and 1 intended to reflect the reimbursement request (EM and ≥ 2 prior therapies). The clinical evidence used to inform the pharmacoeconomic model for both populations was obtained from the ADVANCE trial, which included patients with 4 MMDs to 14 MMDs.[4,7] Given that the Health Canada indication and reimbursement request are not restricted to patients with at least 4 MMDs, the modelled populations do not reflect the full Health Canada–indicated population or the full reimbursement population. As such, the sponsor's analyses reflect the cost-effectiveness of atogepant in a subset of the indicated population and the requested reimbursement population (i.e., those with 4 MMDs to 14 MMDs).
    - CADTH was unable to address this limitation, owing to a lack of clinical data. The cost-effectiveness of atogepant in patients with fewer than 4 MMDs is unknown, as is the cost-

effectiveness of atogepant for the full Health Canada and reimbursement populations. CADTH reanalyses thus reflect patients with 4 MMDs to 14 MMDs.

- **Comparative effectiveness of atogepant to other preventive migraine treatments is uncertain:** There was no direct head-to-head evidence comparing atogepant to galcanezumab, fremanezumab, or eptinezumab, or to oral preventive migraine treatments. To inform the pharmacoeconomic model, the sponsor conducted a series of NMAs[7] to estimate the relative efficacy and safety of atogepant compared to relevant comparators in the Health Canada–indicated population (anti-CGRPs, oral preventive treatments) and the reimbursement population (anti-CGRPs). As noted in the CADTH clinical review, based on the results of the sponsor's submitted NMAs, there was [redacted] between atogepant and other active comparators for important outcomes of interest, including the reduction of migraine frequency. CADTH noted uncertainty in the comparative efficacy of atogepant relative to comparators, owing to clinical, methodological, and statistical heterogeneity among the trials included in the NMAs, as well as wide credible intervals with the associated estimates. In the pharmacoeconomic model for the reimbursement population, the sponsor imputed the efficacy data for eptinezumab because no trials for eptinezumab were included in the sponsor's NMA for this population; CADTH notes that the derivation of these values was not adequately described such that the validity could be appraised. Finally, as noted in the CADTH clinical review, there was a high placebo response (for migraine frequency and HRQoL) in the atogepant trials, which limits the interpretability and generalizability of the findings to clinical practice and increases uncertainty when comparing the effectiveness of atogepant to other treatments. CADTH additionally notes that HRQoL was not assessed in the sponsor-submitted NMAs.
    - Given the lack of direct evidence and limitations with the sponsor's NMAs, the comparative effectiveness of atogepant to galcanezumab, fremanezumab, and eptinezumab, as well as to oral preventive migraine medications, is uncertain. As the sponsor-submitted NMAs suggests that there may be [redacted] effectiveness or safety between atogepant and other available treatments, it is uncertain whether atogepant provides a net benefit relative to other currently funded treatments.
- **Utility values associated with the number of migraine days are uncertain:** In the sponsor's submission, utility values were based on the number of migraine days per 28-day period,[5] estimated based on data from the ADVANCE trial. There are several sources of uncertainty related to the utility values adopted by the sponsor. First, in the sponsor's base case, the health state utilities were based on the MSQ version 2.1 questionnaire, mapped to the 3-Level EQ-5D scale. The use of mapping increases the uncertainty associated with the utility values. The mapping algorithm established by Gillard et al. (2012)[10] used a UK value set; therefore, the utility values used in the model do not reflect Canadian preferences. CADTH notes that 5-Level EQ-5D data were collected in the ADVANCE trial and would not have required mapping for use in the economic model; however, these data were not used by the sponsor, which the sponsor indicated was because of increased granularity and the longer recall period of the MSQ version 2.1 instrument relative to the 5-Level EQ-5D instrument.[5] Second, the sponsor used a regression-based approach, which was not transparently described

in the sponsor's submission. Third, in their base-case analysis, the sponsor adopted treatment-specific utilities, such that utility values for all MMD levels were lower for patients receiving BSC compared to those receiving atogepant or other active comparators. The use of treatment-specific utilities is inappropriate as differences in clinical effects and costs should be reflected in the model health states. While the sponsor justified its use of treatment-specific utilities based on the HRQoL difference between atogepant and placebo in the ADVANCE trial and as an attempt to account for factors not captured by MMDs alone (e.g., migraine severity, headache days not classified as MMDs), the method used by the sponsor does not adequately differentiate the mechanism by which patients experience quality-of-life differences, and therefore there is meaningful uncertainty around the extent to which such differences are explained by MMD frequency versus other factors.

  - In the CADTH base case, all treatments, including BSC, were assumed to have the same utility value for each MMD level.

- **Model structure does not adequately reflect the management of migraine in clinical practice:** The health states used by the sponsor to assess the cost-effectiveness of atogepant classify patients as being on treatment or off treatment, with effectiveness defined as reduction in mean migraine days per 28 days. The model assumed that patients who are off treatment (i.e., patients with an inadequate treatment response at 12 weeks or who discontinue treatment after an initial response) would receive BSC (acute migraine treatment) for the remainder of the time horizon, with no additional preventive therapy. According to the clinical expert consulted by CADTH for this review, patients who discontinue an active preventive treatment would continue to receive preventive migraine treatment, which may comprise another anti-CGRP, depending on prior treatment experience, or an oral preventive treatment. This is consistent with patient group input, where patients described having tried many lines of preventive therapies.

  Clinical effects in the sponsor's model were based on the number of migraine days experienced by the patients and do not capture other clinically meaningful aspects of the condition such as headache intensity. According to patient input received by CADTH for this review, patients may find a reduction in the intensity of their headaches to be a meaningful outcome. The sponsor submitted 2 severity-based scenario analyses exploring this issue; however, the resulting utilities were higher than expected for the Canadian population,[20] and the cost-effectiveness of atogepant 10 mg, atogepant 30 mg, and atogepant 60 mg did not change substantially from the submitted base case when these were adopted.

  - CADTH was unable to address this limitation. The direction and magnitude of the impact on the cost-effectiveness results for atogepant are unknown.

- **Uncertainty in long-term treatment efficacy of atogepant:** In the sponsor's model, patients who remained on treatment were assumed to maintain the improved frequency of MMDs achieved in the first 12 weeks for the remainder of the time horizon (5 years). This assumption was not explicitly justified. The ADVANCE trial assessed the effectiveness of atogepant over a 12-week treatment period, and it is uncertain whether the short-term results are maintained indefinitely. As noted in the CADTH clinical review, although 2 long-term extension studies of atogepant have been undertaken

(Study 309 and Study 302), neither has reported on the effectiveness of atogepant (i.e., these studies were undertaken to assess the long-term safety and tolerability only). While the sponsor's model includes an option to allow MMDs for all patients to increase over time, this does not consider the impact of waning treatment effect relative to BSC or potentially different waning effects among active comparators. As noted in a prior CADTH review, up to 20% of patients may stop benefiting from prophylactic treatment over time.[21]

- CADTH was unable to address this limitation. Should patients receiving atogepant experience a reduction in efficacy over time, the ICERs associated with atogepant relative to BSC would be higher than estimated. The direction and magnitude of the impact of this assumption is unknown when comparing atogepant to anti-CGRPs and oral preventive migraine treatments, to which patients may also experience a reduction in efficacy over time.

- **Model lacked transparency:** The sponsor's submitted model included numerous IFERROR statements, which lead to situations in which the parameter value is overwritten with an alternative value without alerting the user to the automated overwriting. The systematic use of IFERROR statements makes thorough auditing of the sponsor's model impractical, as it remains unclear whether the model is running inappropriately by overriding errors.
  - CADTH was unable to address this limitation and notes that a thorough validation of the sponsor's model was not possible.

Additionally, the following key assumptions were made by the sponsor and have been appraised by CADTH (see Table 5).

Table 5: Key Assumptions of the Submitted Economic Evaluation (Not Noted as Limitations to the Submission)

Sponsor's key assumption	CADTH comment
Erenumab and onabotulinumtoxin A were not considered as comparators.	Acceptable. Onabotulinumtoxin A is indicated for patients with chronic migraine (≥ 15 MMDs) and thus the indicated population does not overlap with that of atogepant. While erenumab is indicated for patients with at least 4 MMDs, CADTH's review of erenumab resulted in a recommendation to limit reimbursement to patients with chronic migraine (≥ 15 MMDs).[22] Subsequently, negotiations with pCPA regarding erenumab concluded without an agreement;[23] thus, erenumab is unlikely to become a funded option for patients within the indicated population of atogepant.
Discontinuation rates before the 12-week assessment were obtained using all-cause discontinuation from the NMA, while post-assessment discontinuation rates were obtained from discontinuation due to AE rates in Study 302.	Uncertain. Modelled patients had a 1-time probability of discontinuation at the 12-week response assessment, representing the possibility of discontinuation before assessment due to AEs, lack of efficacy, or patient-specific factors. As this probability was modelled using hazard ratios from the sponsor-conducted NMA,[7] it is subject to the clinical, methodological, and statistical heterogeneity limitations with the NMA described in the comparative effectiveness key limitation. Postresponse assessment was based on discontinuation due to AEs from Study 302,[6] with active comparators assumed equal

Sponsor's key assumption	CADTH comment
	to the atogepant 60 mg group and BSC assumed equal to the placebo group. It is unclear if discontinuation rates will be similar for all active treatments in clinical practice. The decision to use discontinuation due to AE rather than all-cause discontinuation was not justified by the sponsor.
Health utility declines with age.	Appropriate. Due to increasing comorbidities and other age-related factors, utility norms decrease with age on a population level.[20]
Administration costs were not applied for galcanezumab, fremanezumab, or triptans, but were applied for eptinezumab.	Appropriate for fremanezumab, galcanezumab, and triptans. The sponsor assumed that injectable anti-CGRPs and triptans would be self-administered by the patient and would not incur additional costs. The inclusion of administration costs for eptinezumab is likely acceptable given its IV infusion mode of administration; however, depending on the outcome of reimbursement negotiations,[24] it is possible that the use of eptinezumab may not be associated with additional administration costs. The inclusion of such costs would not be expected to have a substantial impact on modelled results.
No migraine-related mortality was assumed.	Appropriate. According to the experts consulted by CADTH in this and previous reviews, patients living with migraine are not at higher risk of death than the general population.
Migraine frequency does not change except due to treatment effect.	Uncertain. The sponsor's base case does not consider changes in the frequency of migraine that are unrelated to treatment (i.e., no patients naturally improve or decline). According to the clinical expert consulted by CADTH for this review, some patients — regardless of treatment — may show a natural improvement or worsening in the frequency of migraines over time, transitioning between EM and chronic migraine. While the sponsor provided an option within the model to consider the natural history of migraine, the sponsor assumed that MMDs would increase over time, which does not reflect the full complexity of the expected natural history of this condition. The effect of this assumption on the model results is unknown but is not expected to meaningfully affect the ICER as this phenomenon would be biased neither for nor against any particular treatment.
Hazard ratios of overall AEs relative to placebo (as a proxy for BSC) were based on the sponsor's NMAs and were applied to each individual AE.	Inappropriate. The comparators within the model were associated with different AE profiles such that applying the hazard ratio of overall AEs relative to placebo derived from the NMAs does not reflect the relative rates of individual AEs between comparators. For example, all 3 atogepant groups experienced numerically more constipation and nausea than placebo in the ADVANCE trial, but similar numbers of overall AEs. The sponsor's method thus estimates that nausea and constipation rates are similar between atogepant and placebo. This issue was not considered a key limitation as changes to individual AE rates have minimal effect on modelled ICERs.
The use of acute medication was based on treatment group rather than number of MMDs.	Inappropriate. Given that a patient's need for acute medication is likely based on the number of migraines experienced, it would be more appropriate to model the use of acute medications based on MMDs rather than based on treatment group. This was not

Sponsor's key assumption	CADTH comment
	considered a key limitation as changes to acute medication costs have little impact on modelled ICERs.
Resource use per MMD was based on UK data.	Uncertain. While the absolute use of resources per MMD may differ in Canada compared to UK data,[17] general trends in resource use (i.e., increasing health practitioner visits with increasing migraine days) were deemed reasonable by the clinical expert consulted by CADTH. Altering the frequency of these visits did not have a substantial impact on modelled ICERs.

AE = adverse event; BSC = best supportive care; CGRP = calcitonin gene–related peptide; EM = episodic migraine; ICER = incremental cost-effectiveness ratio; MMD = monthly migraine day; NMA = network meta-analysis; pCPA = pan-Canadian Pharmaceutical Alliance.

CADTH Reanalyses of the Economic Evaluation

Base-Case Results

CADTH reanalyses addressed a key limitation of the submitted economic model (i.e., the use of treatment-specific utilities) (Table 6). CADTH addressed this limitation by assuming that all treatments would be associated with the same utility value for a given number of monthly migraines. Additionally, because galcanezumab is listed for reimbursement in some jurisdictions, the publicly available list price for galcanezumab was adopted in CADTH reanalyses.[13,25] CADTH was unable to address the other limitations of the model.

Table 6: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
1. Price of galcanezumab	$554.88 per pen, as per galcanezumab CADTH review[26]	$560.98 per pen, as per the publicly available list price in Ontario and Saskatchewan[13,25]
Changes to derive the CADTH base case		
1. Health state utility values	Treatment specific: Utilities for all active treatments[a] were based on pooled data for atogepant (10 mg, 30 mg, and 60 mg) from the ADVANCE trial. Utilities for BSC were 0.0289 lower than those for active treatments at all MMD levels.	The same utility value was assigned for all treatments at each MMD level, regardless of whether the treatment was BSC or an active treatment. Utility values were based on pooled data from the ADVANCE trial, for all treatment arms (atogepant 10 mg, atogepant 30 mg, atogepant 60 mg, and placebo).
CADTH base case	Reanalysis 1	

BSC = best supportive care; MMD = monthly migraine day.

[a]This includes atogepant, eptinezumab, fremanezumab, galcanezumab, and oral prophylactic treatments (propranolol, amitriptyline, and topiramate).

CADTH's base-case results are presented in Table 7 (Health Canada–indicated population) and Table 8 (reimbursement population). Full and disaggregated results as well as additional reanalyses are presented in Appendix 4.

Among patients with EM (Health Canada–indicated population), all doses of atogepant were dominated by propranolol (higher costs and fewer QALYs) and other comparators (refer to Table 14), which is consistent with the sponsor's base case. All doses of atogepant had a 0% chance of being cost-effective at a WTP threshold of $50,000 per QALY gained. As in the sponsor's submitted analysis, 94% of QALYs associated with atogepant were accrued in the post-trial period, and more than 99% of patients were still alive at the end of the 5-year time horizon.

Table 7: Summary of the CADTH Reanalysis Results for the Health Canada–Indicated Population (Patients With Episodic Migraine)

Drug	Total costs ($)	Total QALYs	Sequential ICER
Propranolol	6,536	3.547	Reference
Galcanezumab	21,168	3.572	577,840
Dominated treatments			
Atogepant 30 mg	**19,173**	**3.537**	**Dominated by propranolol**
Atogepant 10 mg	**19,507**	**3.540**	**Dominated by propranolol**
Atogepant 60 mg	**19,796**	**3.540**	**Dominated by propranolol**

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Note: Only nondominated treatments are presented. Dominated atogepant is presented as the drug under review. Full results are provided in Appendix 4.

Among patients with EM and 2 or more prior therapies (reimbursement population), atogepant 10 mg was more costly and less effective (dominated) by fremanezumab 225 mg (Table 8) and galcanezumab (Table 14). Atogepant 60 mg was dominated by fremanezumab 675 mg, while atogepant 30 mg was extendedly dominated by a mix of fremanezumab 225 mg and BSC. All doses of atogepant had a 0% chance of being cost-effective at a WTP threshold of $50,000 per QALY gained. Similar to the sponsor's submission, 94% of accrued QALYs associated with atogepant were accrued in the post-trial period, and more than 99% of patients were still alive at the end of the model.

Table 8: Summary of the CADTH Reanalysis Results for the Reimbursement Population (Episodic Migraine, ≥ 2 Previous Therapies)

Drug	Total costs ($)	Total QALYs	Sequential ICER ($/QALY)
BSC	7,330	3.421	Reference
Fremanezumab 225 mg	20,166	3.530	117,395 vs. BSC
Fremanezumab 675 mg	21,317	3.533	398,461 vs. fremanezumab 225 mg
Dominated treatments			
Atogepant 30 mg	18,996	3.484	Extendedly dominated by mix of BSC and fremanezumab 225 mg
Atogepant 10 mg	21,083	3.498	Dominated by fremanezumab 225 mg
Atogepant 60 mg	22,208	3.532	Dominated by fremanezumab 675 mg

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus.

Note: Only nondominated treatments are presented. Dominated atogepant is presented as the drug under review. Full results are provided in Appendix 4.

Scenario Analysis Results

Scenario analyses were conducted using the CADTH base case for the reimbursement population (EM and ≥ 2 prior therapies) to investigate the impact of adopting a 10-year time horizon and adopting alternate utility values. All doses of atogepant remained dominated or extendedly dominated in both scenarios. Details and results of these scenarios are presented in Appendix 4 (Table 17 and Table 18). CADTH also undertook price reduction analyses based on the sponsor-submitted analysis and CADTH's base case for the reimbursement population. Among patients with EM (4 MMDs to 14 MMDs) and 2 or more prior therapies, a 61% price reduction would be required for atogepant 60 mg to be considered cost-effective compared to BSC at a WTP threshold of $50,000 per QALY gained. No formal price reduction analyses were undertaken for the Health Canada–indicated population, as all doses of atogepant were less effective than propranolol, and at least a 98% price reduction would be required for the drug cost of atogepant to be equivalent to that of propranolol.

Issues for Consideration

- **Availability and pricing of anti-CGRP comparators:** Galcanezumab, fremanezumab, and eptinezumab have all received positive recommendations from the CADTH Canadian Drug Expert Committee for the prevention of EM, conditional on price reduction.[14,27,28] Galcanezumab and fremanezumab have begun to be listed on public formularies after successful negotiations with the pCPA.[25,29-31] It is therefore likely that both products are reimbursed by jurisdictional drug plans at confidential prices that are less than publicly available list prices. Eptinezumab (Vyepti) is currently under consideration for negotiation with the pCPA.[24]
- **Different mode of administration and half-life:** Some patients may prefer an oral treatment, such as atogepant, over injectable treatments (i.e., fremanezumab and galcanezumab) or infusions (i.e., eptinezumab). Additionally, clinician group input and the clinical expert consulted by CADTH for this review emphasized that the shorter half-life of atogepant compared to injectable or infusible anti-CGRPs may be preferred for patients considering pregnancy.
- **Comparison to the erenumab, fremanezumab, galcanezumab, and eptinezumab pharmacoeconomic reviews:** CADTH has previously reviewed erenumab, galcanezumab, eptinezumab, and fremanezumab for migraine prophylaxis.[14,21,26,32] The cost-effectiveness results from these evaluations may not be directly comparable to those in the current review, owing to differences in model structure, clinical effectiveness parameters, health state utility values, and cost inputs.

Table 9: CADTH Price Reduction Analyses for the Reimbursement Population (Episodic Migraine, ≥ 2 Previous Therapies)

Analysis	ICERs for atogepant vs. comparators ($/QALY)	
Price reduction	**Sponsor base case**	**CADTH reanalysis**
Atogepant submitted price	WTP < $49,327 = BSC $49,327 < WTP < $83,964 = galcanezumab $83,964 < WTP < $396,626 = fremanezumab 225 mg $396,626 < WTP < $2,091,554 = fremanezumab 675 mg **$2,091,554 < WTP = atogepant 60 mg**	WTP < $117,395 = BSC $117,395 < WTP < $398,461 = fremanezumab 225 mg $398,461 < WTP = fremanezumab 675 mg
10%		WTP < $117,395 = BSC $117,395 < WTP < $226,836 = fremanezumab 225 mg **$226,836 < WTP < $924,641 = atogepant 60 mg** $924,641 < WTP = fremanezumab 675 mg
14%	WTP < $48,775 = BSC **$48,775 < WTP < $52,934 = atogepant 30 mg** $52,934 < WTP < $60,867 = galcanezumab **$60,867 < WTP = atogepant 60 mg**	
20%	WTP < $45,177 = BSC **$45,177 < WTP < $51,171 = atogepant 30 mg** **$51,171 < WTP = atogepant 60 mg**	WTP < $105,646 = BSC **$105,646 < WTP < $3,104,726 = atogepant 60 mg** $3,104,726 < WTP = fremanezumab 675 mg
30%	WTP < $39,181 = BSC **$39,181 < WTP < $43,596 = atogepant 30 mg** **$43,596 < WTP = atogepant 60 mg**	
40%		
50%		
60%	WTP < $21,132 = BSC $21,132 < WTP = atogepant 60 mg	
61%		WTP < $48,715 = BSC **$48,715 < WTP < $12,043,076 = atogepant 60 mg** $12,043,076 < WTP = fremanezumab 675 mg

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus; WTP = willingness to pay.

Note: Only nondominated comparators are presented. Reported points were chosen based on the price reduction at which atogepant entered the cost-effectiveness frontier and the price reduction at which it became cost-effective at a WTP threshold of $50,000 per QALY gained.

Overall Conclusions

Based on the CADTH clinical review, atogepant may reduce migraine frequency and improve quality of life among patients with EM compared to placebo. There are no direct head-to-head trials comparing atogepant to anti-CGRPs (e.g., eptinezumab, fremanezumab, galcanezumab) or to oral preventive migraine medications, and the NMAs submitted by the sponsor suggests that there may be [redacted] in effectiveness or safety between atogepant and other active comparators for important outcomes of interest, including migraine frequency, [redacted] the Health Canada–indicated population or the reimbursement population. However, as noted in the CADTH clinical review, there remains uncertainty in the comparative efficacy of atogepant relative to other currently available treatments for EM, owing to clinical, methodological, and statistical heterogeneity among the trials included in the NMAs, as well as wide credible intervals with the associated estimates, indicating a lack of precision. Notably, HRQoL was not assessed in the sponsor's NMAs, and the relative impact of atogepant and comparators on this outcome remains unknown.

The sponsor-submitted pharmacoeconomic analyses comparing atogepant with eptinezumab, fremanezumab, and galcanezumab in the reimbursement population (patients with EM and ≥ 2 prior therapies) and with eptinezumab, fremanezumab, galcanezumab, and oral preventive migraine medications in the Health Canada–indicated population (patients with EM). In both populations, the efficacy of atogepant was informed by data from the ADVANCE trial, which enrolled patients with between 4 MMDs and 14 MMDs. As such, the sponsor's pharmacoeconomic analyses reflect the cost-effectiveness of atogepant among patients with 4 MMDs to 14 MMDs. 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.

CADTH undertook reanalyses to address limitations in the sponsor's pharmacoeconomic evaluation, which included adopting the same health state utility value for a given MMD level regardless of treatment. CADTH was unable to address uncertainty in the comparative clinical data, uncertainty in the health state utility values, limitations related to the sponsor's modelling approach (i.e., model structure, subsequent treatments, and transparency), uncertainty in the long term effectiveness of atogepant, and the lack of clinical data for patients with fewer than 4 MMDs.

The findings of CADTH's reanalysis were generally aligned with those submitted by the sponsor: atogepant was not a cost-effective treatment option for EM in adults. In the Health Canada–indicated population, atogepant (all doses) was dominated by propranolol (i.e., atogepant was less effective and more costly than propranolol) and in the reimbursement population, atogepant was dominated (atogepant 10 mg and atogepant 30 mg) by fremanezumab or extendedly dominated (atogepant 60 mg) by fremanezumab and BSC, such that it would not be the optimal treatment choice. In both populations, a price reduction would be required for atogepant to be considered cost-effective relative to currently available treatments.

The cost-effectiveness of atogepant relative to other treatments for EM, in both the Health Canada–indicated population and the reimbursement population, is uncertain owing to a lack of robust comparative data and limitations in the sponsor's analysis that could not be addressed in CADTH's reanalyses. Notably, the sponsor-submitted NMAs suggests that there may be [redacted] clinical outcomes (e.g., migraine frequency) between atogepant and anti-CGRPs or oral treatments, and HRQoL was not assessed in the sponsor's

NMAs. As such, there is insufficient evidence to suggest that atogepant should be priced higher than other treatments for EM. Thus, to ensure cost-effectiveness, atogepant should be priced no more than the lowest-cost active comparator that is funded in the population to be reimbursed.

References

1. .PrQulipta (atogepant): 10 mg, 30 mg, 60 mg tablets [product monograph]. Markham (ON): Allergan; [2022].
2. Drug Reimbursement Review sponsor submission: PrQulipta (atogepant) 10 mg, 30 mg, 60 mg tablets [internal sponsor's package]. Markham (ON): Allergan Inc.; 2022 Feb 23.
3. Clinical Study Report: 3101-301-002. A Phase 3, Multicenter, Randomized, Double-Blind, Placebo controlled, Parallel-group Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Atogepant for the Prevention of Migraine in Participants With Episodic Migraine (ADVANCE) [internal sponsor's report]. Madison (NJ): Allergan Pharmaceuticals International Limited; 2020 Jul 6.
4. Ailani J, Lipton RB, Goadsby PJ, et al. Atogepant for the Preventive Treatment of Migraine. *N Engl J Med.* 2021;385(8):695-706. PubMed
5. Pharmacoeconomic evaluation [internal sponsor's report]. In: *Drug Reimbursement Review sponsor submission: PrQulipta (atogepant) 10 mg, 30 mg, 60 mg tablets.* Markham (ON): Allergan Inc.; 2022 Feb 23.
6. Clinical Study Report: 3101-302-002. A Phase 3, Multicenter, Randomized, Open-Label Study to Evaluate the Long-Term Safety and Tolerability of Oral Atogepant for the Prevention of Migraine in Participants with Episodic Migraine [internal sponsor's report]. Madison (NJ): Allergan Limited; 2020 Jun 26.
7. Network meta-analysis of treatments for prevention of episodic migraine [internal sponsor's report]. In: *Drug Reimbursement Review sponsor submission: PrQulipta (atogepant) 10 mg, 30 mg, 60 mg tablets.* Markham (ON): Allergan Inc.; 2022 Feb 23.
8. Table: 13-10-0114-01. Life expectancy and other elements of the life table, Canada, all provinces except Prince Edward Island. Ottawa (ON): Statistics Canada; 2022: https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310011401. Accessed 2022 Jan 14.
9. Bagley CL, Rendas-Baum R, Maglinte GA, et al. Validating Migraine-Specific Quality of Life Questionnaire v2.1 in episodic and chronic migraine. *Headache.* 2012;52(3):409-421. PubMed
10. Gillard PJ, Devine B, Varon SF, Liu L, Sullivan SD. Mapping from disease-specific measures to health-state utility values in individuals with migraine. *Value Health.* 2012;15(3):485-494. PubMed
11. Matza LS, Deger KA, Vo P, Maniyar F, Goadsby PJ. Health state utilities associated with attributes of migraine preventive treatments based on patient and general population preferences. *Qual Life Res.* 2019;28(9):2359-2372. PubMed
12. DeltaPA. [Ottawa (ON)]: IQVIA; 2023: https://www.iqvia.com/. Accessed 2023 Jan 30.
13. Saskatchewan Drug Plan: search formulary. 2023; https://formulary.drugplan.ehealthsask.ca/SearchFormulary. Accessed 2023 Feb 06.
14. CADTH Reimbursement Recommendation: Eptinezumab (Vyepti). *Can J Health Technol.* 2023;3(1). https://www.cadth.ca/sites/default/files/DRR/2023/SR0743%20Vyepti%20-%20Final%20CADTH%20Recommendation%20(with%20redactions)%20final%20-%20KH%20-%20DM%20-%20KH2-meta%20(1).pdf. Accessed 2023 Jan 30.
15. Ontario Ministry of Health, Ontario Ministry of Long-Term Care. Ontario drug benefit formulary/comparative drug index. 2023; https://www.formulary.health.gov.on.ca/formulary/. Accessed 2023 Jan 30.
16. Schedule of benefits for physician services under the Health Insurance Act: effective October 1, 2021. Toronto (ON): Ontario Ministry of Health; 2021: https://www.health.gov.on.ca/en/pro/programs/ohip/sob/physserv/sob_master.pdf. Accessed 2022 Apr 14.
17. Single Technology Appraisal: Galcanezumab for preventing migraine [ID1372] - Committee Papers. London (GB): National Institute for Health and Care Excellence; 2020: https://www.nice.org.uk/guidance/ta659/evidence/committee-papers-pdf-8902011421. Accessed 2022 May 11.
18. Ontario Nurses' Association - Hospital Central Collective Agreement. Toronto (ON): Ontario Nurses' Association; 2021: https://www.ona.org/wp-content/uploads/6-20230331_hospcentralagreement-draft.pdf. Accessed 2022 Apr 14.
19. Ontario Case Costing Initiative (OCCI). Toronto (ON): Ontario Health and Long-Term Care; 2017: https://data.ontario.ca/dataset/ontario-case-costing-initiative-occi. Accessed 2021 Sep 19.

20. Guertin JR, Feeny D, Tarride JE. Age- and sex-specific Canadian utility norms, based on the 2013-2014 Canadian Community Health Survey. *CMAJ.* 2018;190(6):E155-E161. PubMed

21. CADTH Common Drug Review Pharmacoeconomic Review Report: erenumab (Aimovig) for prevention of migraine in adults who have had at least four migraine days monthly. Ottawa (ON): CADTH; 2020: https://www.cadth.ca/sites/default/files/cdr/pharmacoeconomic/sr0578-aimovig-pharmacoeconomic-review-report.pdf. Accessed 2021 Sep 01.

22. CADTH Drug Reimbursement Expert Review Committee final recommendation: erenumab (Aimovig — Novartis Pharmaceuticals Canada Inc.). Ottawa (ON): CADTH; 2020: https://cadth.ca/sites/default/files/cdr/complete/SR0578%20Aimovig%20-%20CDEC%20Final%20Recommendation%20July%2024%2C%202020%20%28redacted%29_For%20Posting.pdf. Accessed 2022 May 06.

23. pan-Canadian Pharmaceutical Alliance. Aimovig (erenumab). 2021; https://www.pcpacanada.ca/negotiation/21286. Accessed 2022 May 06.

24. pan-Canadian Pharmaceutical Alliance. Vyepti (eptinezumab). 2023; https://www.pcpacanada.ca/negotiation/22136. Accessed 2023 Jan 30.

25. Exceptional Access Program (EAP). Toronto (ON): Ontario Ministry of Health; Ontario Ministry of Long-Term Care; 2023: https://www.health.gov.on.ca/en/pro/programs/drugs/odbf/odbf_except_access.aspx. Accessed 2023 Jan 30.

26. CADTH Reimbursement Review Combined Clinical and Pharmacoeconomic Report: Galcanezumab (Emgality) for the prevention of migraine in adults who have at least 4 migraine days monthly. *Can J Health Technol.* 2022;2(3). https://www.cadth.ca/sites/default/files/DRR/2022/SR0693-Emgality.pdf. Accessed 2022 May 15.

27. CADTH Drug Reimbursement Expert Review Committee final recommendation: Fremanezumab (Ajovy – Teva Canada Innovation). Ottawa (ON): CADTH; 2021: https://cadth.ca/sites/default/files/cdr/complete/SR0641%20Ajovy%20-%20CDEC%20Final%20Recommendation%20April%201%2C%202021_For%20Posting.pdf. Accessed 2021 Apr 07.

28. CADTH Drug Reimbursement Recommendation: Galcanezumab (Emgality - Eli Lilly Canada Inc.). *Can J Health Technol.* 2022;2(1). https://www.cadth.ca/sites/default/files/DRR/2021/SR0693%20Emgality%20-%20CADTH%20Final%20Rec.pdf. Accessed 2022 Apr 11.

29. Saskatchewan Drug Plan: search formulary. 2022; https://formulary.drugplan.ehealthsask.ca/SearchFormulary. Accessed 2022 May 04.

30. pan-Canadian Pharmaceutical Alliance. Ajovy (fremanezumab). 2021; https://www.pcpacanada.ca/negotiation/21431. Accessed 2022 May 06.

31. pan-Canadian Pharmaceutical Alliance. Emgality (galcanezumab). 2022; https://www.pcpacanada.ca/negotiation/21690. Accessed 2022 May 06.

32. CADTH Drug Reimbursement Review Pharmacoeconomic Report: Fremanezumab (Ajovy) for the prevention of migraine in adults who have at least 4 migraine days monthly. Ottawa (ON): CADTH; 2021: https://www.cadth.ca/sites/default/files/cdr/complete/sr0641-ajovy-pharmacoeconomic-review-report.pdf. Accessed 2022 May 15.

33. Pringsheim T, Davenport W, Mackie G, et al. Canadian Headache Society guideline for migraine prophylaxis. *Can J Neurol Sci.* 2012;39(2 Suppl 2):S1-59. PubMed

34. Osman N, Worthington I, Lagman-Bartolome AM. Headache in adults. In: Compendium of therapeutic choices. Ottawa (ON): Canadian Pharmacists Association; 2021: https://www.pharmacists.ca. Accessed 2021 Aug 16.

35. Table: 17-10-0057-01 Projected population, by projection scenario, age and sex, as of July 1 (x 1,000). Ottawa (ON): Statistics Canada; 2022: https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1710005701. Accessed 2022 Apr 11.

36. Blumenfeld AM, Bloudek LM, Becker WJ, et al. Patterns of use and reasons for discontinuation of prophylactic medications for episodic migraine and chronic migraine: results from the second international burden of migraine study (IBMS-II). *Headache.* 2013;53(4):644-655. PubMed

37. Dodick DW, Loder EW, Manack Adams A, et al. Assessing Barriers to Chronic Migraine Consultation, Diagnosis, and Treatment: Results From the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study. *Headache.* 2016;56(5):821-834. PubMed

38. Ford JH, Jackson J, Milligan G, Cotton S, Ahl J, Aurora SK. A Real-World Analysis of Migraine: A Cross-Sectional Study of Disease Burden and Treatment Patterns. *Headache.* 2017;57(10):1532-1544. PubMed

39. Lipton RB, Serrano D, Holland S, Fanning KM, Reed ML, Buse DC. Barriers to the diagnosis and treatment of migraine: effects of sex, income, and headache features. *Headache.* 2013;53(1):81-92. PubMed

40. Ramage-Morin PL, Gilmour H. Prevalence of migraine in the Canadian household population. *Health Rep.* 2014;25(6):10-16. PubMed

41. Budget Impact Analysis [internal sponsor's report]. In: *Drug Reimbursement Review sponsor submission: PrQulipta (atogepant) 10 mg, 30 mg, 60 mg tablets.* Markham (ON): Allergan Inc.; 2022 Feb 23.

42. Allergan response to 21 April, 2022 CADTH request for additional information regarding atogepant (Qulipta) CADTH review [internal sponsor's report]. Markham (ON): Allergan (an Abbvie Company); 2022 Apr 28.

43. Non-Insured Health Benefits program: First Nations and Inuit Health Branch: Annual report 2019 to 2020. Ottawa (ON): Indigenous Services Canada; 2021: https://www.sac-isc.gc.ca/eng/1624462613080/1624462663098. Accessed 2023 Feb 16.

44. Non-Insured Health Benefits program: First Nations and Inuit Health Branch: Annual report 2020 to 2021. Ottawa (ON): Indigenous Services Canada; 2022: https://www.sac-isc.gc.ca/eng/1645718409378/1645718500555. Accessed 2023 Feb 16.

45. Saskatchewan Drug Plan. Appendix A: Exception Drug Status Program. 2022: https://formulary.drugplan.ehealthsask.ca/PDFs/APPENDIXA.pdf. Accessed 2022 May 13.

46. Exceptional Access Program Reimbursement Criteria for Frequently Requested Drugs. Toronto (ON): Ontario Ministry of Health; 2022 Sep 29: https://www.health.gov.on.ca/en/pro/programs/drugs/docs/frequently_requested_drugs.pdf. Accessed 2023 Feb 17.

Appendix 1: Cost Comparison Table

Note this appendix has not been copy-edited.

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical expert and drug plans. Comparators may be recommended (appropriate) practice or actual practice. Existing Product Listing Agreements are not reflected in the table and as such, the table may not represent the actual costs to public drug plans.

Table 10: CADTH Cost Comparison Table for Prevention of Episodic Migraine

Treatment	Strength / concentration	Form	Price	Recommended dosage	Average daily cost ($)	Average annual cost ($)
Atogepant (Qulipta)	10 mg 30 mg 60 mg	Tablets	$18.4400[a]	10 mg, 30 mg, or 60 mg once daily	$18.44	$6,735
Anti–calcitonin gene–related peptide monoclonal antibodies						
Eptinezumab (Vyepti)	100 mg	Solution for IV infusion	$1,665.00[b]	100 mg or 300 mg infused every 12 weeks	19.82 to 59.46[b]	7,240 to 21,719[b]
Erenumab (Aimovig)	70 mg/mL 140 mg/mL	Autoinjector	532.0000[c]	70 mg or 140 mg subcutaneously monthly	17.48	6,384
Fremanezumab (Ajovy)	225 mg/ 1.5 mL	Prefilled syringe	535.7240	225 mg once a month or 675 mg every 3 months	17.60	6,429
Galcanezumab (Emgality)	120 mg/mL	1 mL prefilled syringe or pen	560.9800	240 mg initial loading dose, then 120 mg once monthly	Maintenance = 18.43	First year = 7,293 Subsequent years = 6,732
Other treatments indicated for migraine prophylaxis						
Flunarizine (generics)	5 mg	Cap	0.7348	10 mg daily	1.47	537
Pizotyline/pizotifen (Sandomigran)	1 mg	Tab	0.9588	1.0 to 6 mg daily	0.96 to 5.75	350 to 2,101
Topiramate (generics)	25 mg 100 mg 200 mg	Tab	0.2433 0.4583 0.6748	100 mg per day[d]	0.46	167

Cap = capsule; Tab = tablet.

Note: All prices are from the Ontario Drug Benefit Formulary or Exceptional Access Program (accessed January 2023)[15,25] unless otherwise indicated and do not include dispensing fees. All recommended doses sourced from respective product monographs. An average year is assumed to comprise 365.25 days.

[a]Sponsor's submitted price.[5]

[b]Price submitted during the CADTH Reimbursement Review of Vyepti for migraine.[14] Cost of 300 mg dose assumes linear pricing (i.e., the use of three 100 mg vials).

[c]IQVIA DeltaPA wholesale price, accessed January 2023.[12]

[d]Daily and annual drug costs assume post-titration maintenance dose.

Table 11: CADTH Cost Comparison Table for Prophylaxis of Migraine (Nonindicated)

Drug/comparator	Strength	Dosage form	Price ($)	Recommended dosage	Daily drug cost ($)	Annual drug cost ($)
Antiepileptics						
Divalproex sodium[a, b] (generics)	125 mg 250 mg 500 mg	Ent tab	0.1539 0.2767 0.5537	500 mg to 1,500 mg per day[a, b]	0.55 to 1.66	202 to 607
Valproic acid[a, b] (generics)	250 mg	Cap	0.2905	500 mg to 1,500 mg per day[a, b]	0.58 to 1.74	212 to 637
	50 mg/mL	Oral sol	0.0398		0.40 to 1.19	145 to 436
	500 mg	Ent cap	0.8102		0.81 to 2.43	296 to 887
Gabapentin[a] (generics)	100 mg 300 mg 400 mg	Cap	0.0416 0.1012 0.1206	1,200 mg to 1,800 mg per day in 3 doses[a]	0.36 to 0.61	132 to 222
Antidepressants						
Amitriptyline[a, b] (generics)	10 mg 25 mg 50 mg	Tab	0.0435 0.0829 0.1540	20 mg to 150 mg per day[a, b]	0.09 to 0.46	32 to 169
Doxepin[b] (Sinequan)	10 mg 25 mg 50 mg 75 mg 100 mg	Cap	0.3877 0.4757 0.8824 1.1648[c] 1.5319[c]	25 mg to 100 mg per day[b]	0.48 to 1.53	174 to 560
Nortriptyline[a, b] (Aventyl)	10 mg 25 mg	Cap	0.2850 0.5760	20 mg to 150 mg per day[a, b]	0.57 to 3.46	208 to 1,262
Venlafaxine[a, b] (generics)	37.5 mg 75 mg 150 mg	ER cap	0.0913 0.1825 0.1927	150 mg per day[a, b]	0.19	70
Antihypertensives						
Atenolol (generics)	50 mg 100 mg	Tab	0.0938 0.1543	100 to 150 mg per day[b]	0.15 to 0.0.25	56 to 91
Metoprolol (generics)	50 mg 100 mg	Tab	0.0624 0.1361	100 mg to 200 mg per day[a, b]	0.12 to 0.25	46 to 91
	100 mg 200 mg	SR tab	0.1415 0.2568		0.14 to 0.26	52 to 94
Nadolol (generics)	40 mg 80 mg 160 mg	Tab	0.2375 0.3410 1.2046	80 mg to 160 mg per day[a, b]	0.34 to 0.68	125 to 249

Drug/comparator	Strength	Dosage form	Price ($)	Recommended dosage	Daily drug cost ($)	Annual drug cost ($)
Propranolol (generics)	10 mg 20 mg 40 mg 80 mg	Tab	0.0689 0.1107 0.1225 0.2034	80 mg to 160 mg per day in 2 doses[a, b]	0.24 to 0.41	89 to 149
Verapamil (generics)	80 mg 120 mg	Tab	0.2735 0.4250	240 mg to 320 mg per day[a, b]	0.82 to 1.09	300 to 400
	120 mg 180 mg 240 mg	SR tab	0.5078[c] 0.5204 1.7143		1.71[d]	626
Candesartan (generics)	4 mg 8 mg 16 mg 32 mg	Tab	0.1700 0.2281 0.2281 0.2281	Up to 16 mg per day[a, b]	0.17 to 0.23	62 to 83
Lisinopril (generics)	5 mg 10 mg 20 mg	Tab	0.1347 0.1619 0.1945	20 mg per day[a]	0.19	71
Antimanic/mood stabilizer						
Lithium carbonate (generics)	150 mg 300 mg 600 mg	Cap	0.0667 0.0657 0.1988[c]	300 mg 3 times daily[b]	0.20	72
Lithium carbonate (Lithmax)	300 mg	SR tab	0.2880[c]		0.86	316

Cap = capsule; Ent cap = enteric coated capsule; Ent tab = enteric coated tablet; ER cap = extended-release capsule; Oral sol = oral solution; SR tab = sustained release tablet; Tab = tablet.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed January 2023)[15] unless otherwise indicated and do not include dispensing fees. An average year is assumed to comprise 365.25 days.

[a]Source: 2012 Canadian Headache Society Guideline for Migraine Prophylaxis.[33]

[b]Source: CPhA Therapeutic Choices: Headache in Adults, Drugs Used for Migraine Prophylaxis (Accessed January 2023).[34]

[c]Saskatchewan Formulary list price (accessed January 2023).[13]

[d]Assumes 240 mg, as 320 mg is not a possible dose with SR tablets.

Appendix 2: Submission Quality

Note this appendix has not been copy-edited.

Table 12: Submission Quality

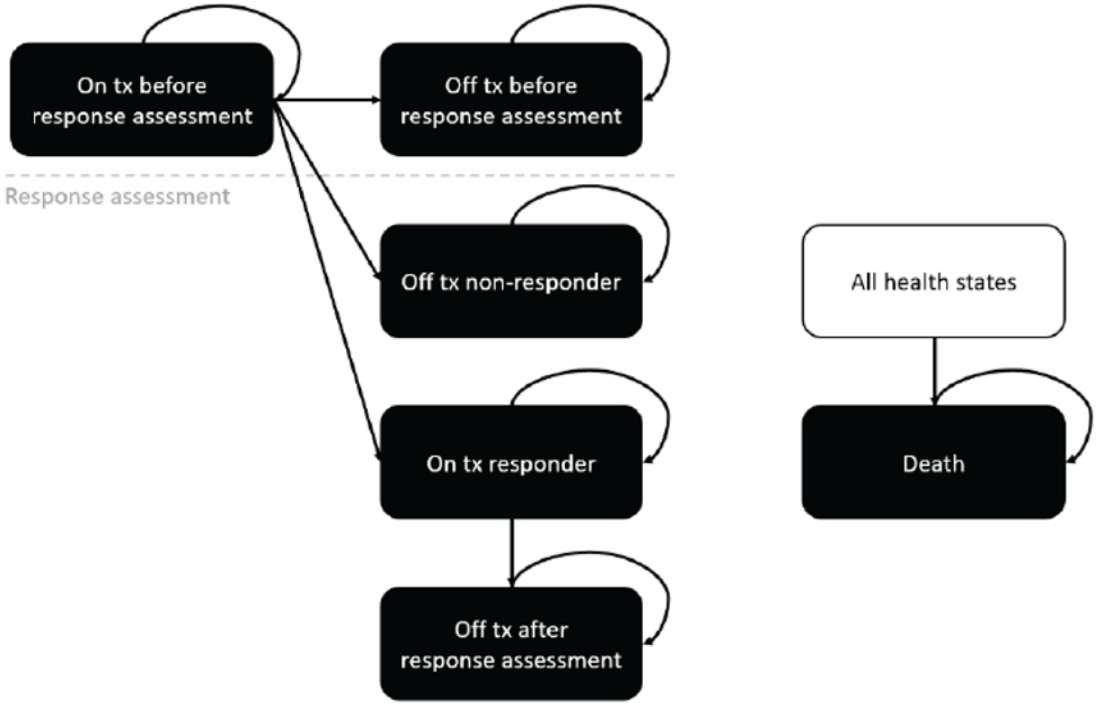
Description	Yes/no	Comments
Population is relevant, with no critical intervention missing, and no relevant outcome missing	No	The clinical evidence, and thus the modelled population, does not include patients with 1 to 3 MMDs for either the Health Canada–indicated population or the requested reimbursement population. The cost-effectiveness of atogepant in patients with 1 to 3 MMDs, and hence the full Health Canada and reimbursement request population, is unknown.
Model has been adequately programmed and has sufficient face validity	No	Due to the combination of NMA results applied to data from ADVANCE, not all inputs had face validity. The model includes numerous IFERROR statements. The systematic use of IFERROR statements makes thorough auditing of the sponsor's model impractical, as it remains unclear whether the model is running inappropriately by overriding errors.
Model structure is adequate for decision problem	Yes	No comment
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis)	Yes	No comment
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem	Yes	No comment
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details)	No	Insufficient information was provided regarding methods used to derive utility value sets. Insufficient information was provided regarding imputation methods used for comparators with missing data within the NMAs.

MMD = monthly migraine day.

Appendix 3: Additional Information on the Submitted Economic Evaluation

Note this appendix has not been copy-edited.

Figure 1: Model Structure



Tx = treatment.

Source: Sponsor's pharmacoeconomic submission.[5]

Table 13: Sponsor's Base-Case Probabilities of Response, Discontinuation, and Number of Monthly Migraine Days While Responding to Therapy

Treatment	Probability of response at 12 weeks	Probability of discontinuation before 12 weeks	Probability of discontinuation per cycle thereafter	Mean MMDs in responder state[a]
Health Canada–indicated population[b]				
BSC	32.2%	14.2%	3.70%[c]	3.668
Atogepant 10 mg	52.1%	13.4%	3.59%[c]	2.125
Atogepant 30 mg	50.9%	14.3%		2.107
Atogepant 60 mg	50.7%	10.0%		2.255
Eptinezumab 100 mg	44.2%	12.2%		2.255
Eptinezumab 300 mg	50.6%	13.0%		7.746

Treatment	Probability of response at 12 weeks	Probability of discontinuation before 12 weeks	Probability of discontinuation per cycle thereafter	Mean MMDs in responder state[a]
Fremanezumab 225 mg	54.0%	18.8%		1.304
Fremanezumab 675 mg	51.7%	16.2%		1.211
Galcanezumab 120 mg	55.2%	11.7%		0.860
Amitriptyline	51.0%	14.9%		2.000
Propranolol	61.6%	11.5%		2.727
Topiramate	58.4%	13.0%		2.521
Reimbursement population[d]				
BSC	15.8%	11.5%	3.70%[c]	7.888
Atogepant 10 mg	55.6%	10.9%	3.59%[c]	3.764
Atogepant 30 mg	44.5%	10.8%		3.620
Atogepant 60 mg	60.5%	9.6%		2.380
Eptinezumab 100 mg[e]	37.6%	9.6%		4.501
Eptinezumab 300 mg[e]	43.9%	10.4%		3.561
Fremanezumab 225 mg	55.6%	13.3%		1.925
Fremanezumab 675 mg	59.6%	11.5%		2.319
Galcanezumab 120 mg	41.0%	8.9%		1.075

BSC = best supportive care, assumed the same as placebo within the network meta-analyses; MMD = monthly migraine day.

Note: Nonresponding and discontinuing patients of all treatment groups returned to a mean baseline MMD of 8.103 for the reimbursement request population and 7.645 for the Health Canada–indicated population.

[a]Modelled patients had a probability of having a set level of MMDs within a cycle based on a Poisson distribution around the reported mean.

[b]Patients with episodic migraine (< 15 MMDs).

[c]All-cause discontinuation after response was derived from Study 302, a long-term safety and tolerability study, with the rate reported for atogepant 60 mg applied to all active comparators in the model.

[d]Patients with episodic migraine and an inadequate response, an intolerance, or a contraindication to at least 2 oral preventive migraine medications.

[e]Eptinezumab was not included in the sponsor's submitted NMAs for the reimbursement population and thus eptinezumab inputs in this analysis are based on imputed results. The method and source of this imputation was not specified in the submitted pharmacoeconomic report or model.[5]

Source: Sponsor's pharmacoeconomic submission.[5]

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

Note this appendix has not been copy-edited.

Detailed Results of CADTH Base Case

Table 14: Summary of the CADTH Base Case

Drug	Total costs ($)	Total QALYs	Sequential ICER ($/QALY)
Health Canada–indicated population[a]			
Propranolol	6,536	3.547	Reference
Amitriptyline	6,616	3.539	Dominated by propranolol
BSC	6,651	3.493	Dominated by propranolol, amitriptyline
Topiramate	6,674	3.545	Dominated by propranolol
Eptinezumab 100 mg	19,031	3.525	Dominated by propranolol, amitriptyline, topiramate
Atogepant 30 mg	**19,173**	**3.537**	**Dominated by propranolol, amitriptyline, topiramate**
Fremanezumab 225 mg	19,412	3.567	Extendedly dominated by mix of propranolol and galcanezumab
Atogepant 10 mg	**19,507**	**3.540**	**Dominated by propranolol, topiramate, topiramate, fremanezumab 225 mg**
Fremanezumab 675 mg	19,558	3.568	Extendedly dominated by mix of propranolol and galcanezumab
Atogepant 60 mg	**19,796**	**3.540**	**Dominated by propranolol, topiramate, topiramate, fremanezumab 225 mg, fremanezumab 675 mg**
Galcanezumab	21,168	3.572	577,840
Eptinezumab 300 mg	48,545	3.539	Dominated by propranolol, topiramate, fremanezumab 225 mg, atogepant 10 mg, fremanezumab 675 mg, atogepant 60 mg, galcanezumab
Reimbursement population[b]			
BSC	7,330	3.421	Reference
Eptinezumab 100 mg	18,787	3.466	Extendedly dominated by mix of BSC and fremanezumab 225 mg
Atogepant 30 mg	**18,996**	**3.484**	**Extendedly dominated by mix of BSC and fremanezumab 225 mg**
Galcanezumab	19,177	3.516	Extendedly dominated by mix of BSC and fremanezumab 225 mg
Fremanezumab 225 mg	20,166	3.530	117,395
Atogepant 10 mg	**21,083**	**3.498**	**Dominated by fremanezumab 225 mg, galcanezumab**
Fremanezumab 675 mg	21,317	3.533	398,461

Drug	Total costs ($)	Total QALYs	Sequential ICER ($/QALY)
Atogepant 60 mg	**22,208**	**3.532**	**Dominated by fremanezumab 675 mg**
Eptinezumab 300 mg	46,487	3.485	Dominated by galcanezumab, fremanezumab 225 mg, atogepant 10 mg, fremanezumab 675 mg, atogepant 60 mg

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

[a]Patients with episodic migraine (< 15 monthly migraine days).

[b]Patients with episodic migraine and an inadequate response, an intolerance, or a contraindication to at least 2 oral preventive migraine medications.

Table 15: Disaggregated Results of CADTH's Base Case for the Health Canada–Indicated Population (Patients With Episodic Migraine)

Component	Prop	Ami	BSC	Topir	Ept 100	Ato 30	Frem 225	Ato 10	Frem 675	Ato 60	Galcan	Ept 300
Discounted QALYs												
On Tx before assessment	0.190	0.190	0.190	0.190	0.190	0.190	0.190	0.190	0.190	0.190	0.190	0.190
Off Tx before assessment	0.399	0.448	0.462	0.411	0.425	0.479	0.610	0.450	0.558	0.336	0.518	0.456
Off Tx nonresponse	1.134	1.397	1.926	1.200	1.616	1.399	1.115	1.378	1.146	1.474	1.193	1.408
On Tx response	1.562	1.292	0.852	1.495	1.109	1.260	1.418	1.305	1.437	1.320	1.436	1.272
Off Tx after response	0.264	0.217	0.065	0.252	0.188	0.212	0.236	0.219	0.239	0.222	0.238	0.215
AE disutility	−0.003	−0.005	−0.003	−0.004	−0.003	−0.003	−0.003	−0.003	−0.003	−0.003	−0.003	−0.003
Total	**3.547**	**3.539**	**3.493**	**3.545**	**3.525**	**3.537**	**3.567**	**3.540**	**3.568**	**3.540**	**3.572**	**3.539**
Discounted costs ($)												
Drug acquisition	347	221	0	375	12,513	12,950	13,539	13,350	13,701	13,500	15,413	42,103
Drug administration	0	0	0	0	165	0	0	0	0	0	0	185
HCRU on Tx before assessment	245	245	245	245	245	245	245	245	245	245	245	245
HCRU off Tx before assessment	513	576	593	528	546	616	782	578	717	432	664	586
HCRU off Tx nonresponse	1,458	1,795	2,475	1,543	2,076	1,798	1,433	1,771	1,473	1,894	1,533	1,810
HCRU on Tx response	1,386	1,062	840	1,317	934	1,059	990	1,094	1,012	1,122	939	1,043
HCRU off Tx after response	336	275	83	321	235	269	293	279	297	282	295	268
Acute medications	1,990	2,041	2,175	2,022	2,065	1,978	1,883	1,931	1,869	2,065	1,808	2,068
AEs	262	401	240	324	253	259	246	259	246	257	272	239

Component	Prop	Ami	BSC	Topir	Ept 100	Ato 30	Frem 225	Ato 10	Frem 675	Ato 60	Galcan	Ept 300
Total	6,536	6,616	6,651	6,674	19,031	19,173	19,411	19,507	19,558	19,796	21,169	48,546

AE = adverse event; Amitrip = amitriptyline; Ato = atogepant; BSC = best supportive care; Ept = eptinezumab; Frem = fremanezumab; Galcan = galcanezumab; HCRU = health care resource use; Prop = propranolol; QALY = quality-adjusted life-year; Topir = topiramate; Tx = treatment.

Table 16: Disaggregated Results of the CADTH Base Case for the Reimbursement Population (Episodic Migraine, ≥ 2 Previous Therapies)

Component	BSC	Ato 10	Ato 30	Ato 60	Ept 100	Ept 300	Galcan	Frem 225	Frem 675
Discounted QALYs									
On Tx before assessment	0.189	0.189	0.189	0.189	0.189	0.189	0.189	0.189	0.189
Off Tx before assessment	0.372	0.362	0.358	0.318	0.315	0.343	0.296	0.444	0.385
Off Tx nonresponse	2.419	1.312	1.603	1.190	1.820	1.616	1.739	1.247	1.158
On Tx response	0.410	1.397	1.140	1.573	0.975	1.144	1.110	1.415	1.544
Off Tx after response	0.034	0.240	0.196	0.265	0.170	0.196	0.185	0.238	0.260
AE disutility	−0.003	−0.003	−0.003	−0.003	−0.003	−0.003	−0.003	−0.003	−0.003
Total	3.421	3.498	3.484	3.532	3.466	3.485	3.516	3.530	3.533
Discounted costs ($)									
Drug acquisition	0	14,507	12,187	15,850	11,595	39,375	12,711	13,725	14,868
Drug administration	0	0	0	0	153	173	0	0	0
HCRU on Tx before assessment	250	250	250	250	250	250	250	250	250
HCRU off Tx before assessment	491	479	473	420	416	453	390	586	508
HCRU off Tx nonresponse	3,194	1,732	2,117	1,571	2,403	2,134	2,297	1,646	1,529
HCRU on Tx response	607	1,411	1,163	1,397	1,070	1,167	887	1,218	1,382
HCRU off Tx after response	45	314	257	347	221	254	237	306	335
Acute medications	2,503	2,141	2,302	2,129	2,431	2,441	2,155	2,185	2,187
AE	240	250	248	245	249	237	249	251	257
Total	7,330	21,084	18,996	22,209	18,787	46,485	19,177	20,167	21,317

AE = adverse event; Ato = atogepant; BSC = best supportive care; Ept = eptinezumab; Frem = fremanezumab; Galcan = galcanezumab; HCRU = health care resource use; QALY = quality-adjusted life-year; Tx = treatment.

Scenario Analyses

Table 17: CADTH Scenario Analyses

Scenario	CADTH base case	CADTH scenario
Scenario analyses		
1. Time horizon	5 years	10 years
2. Health state utility values	Utilities based on sponsor's EM1 regression model (based on MSQ version 2.1 data from the ADVANCE trial)	Utilities based on sponsor's EM2 regression model (based on MSQ version 2.1 data and comorbidities from the ADVANCE trial)

EM = episodic migraine; MSQ = Migraine-Specific Quality-of-Life Questionnaire.

Table 18: Summary of Scenario Analyses Conducted on CADTH Base Case for the Reimbursement Population (Episodic Migraine, ≥ 2 Previous Therapies)

Scenario analysis	Drug	Total costs ($)	Total QALYs	Sequential ICER ($/QALY)
CADTH base case	BSC	7,330	3,421	Reference
	Atogepant 30 mg	**18,996**	**3.484**	**Extendedly dominated**
	Fremanezumab 225 mg	20,166	3.530	117,395
	Atogepant 10 mg	**21,083**	**3.498**	**Dominated**
	Fremanezumab 675 mg	21,317	3.533	398,461
	Atogepant 60 mg	**22,208**	**3.532**	**Dominated**
Scenario 1: Time horizon 10 years	BSC	13,988	6.525	Reference
	Galcanezumab	31,864	6.687	110,477
	Atogepant 30 mg	**32,397**	**6.634**	**Dominated**
	Fremanezumab 225 mg	34,391	6.710	111,141
	Atogepant 10 mg	**35,928**	**6.655**	**Dominated**
	Fremanezumab 675 mg	36,161	6.714	401,095
	Atogepant 60 mg	**37,559**	**6.713**	**Dominated**
Scenario 2: Health state utility values	BSC	7,327	3.453	Reference
	Atogepant 30 mg	**18,948**	**3.479**	**Extendedly dominated**
	Galcanezumab	19,155	3.545	128,730
	Atogepant 10 mg	**20,978**	**3.484**	**Dominated**
	Atogepant 60 mg	**22,141**	**3.536**	**Dominated**

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Appendix 5: Submitted Budget Impact Analysis and CADTH Appraisal

Note this appendix has not been copy-edited.

Table 19: Summary of Key Take-Aways

Key take-aways of the budget impact analysis

• CADTH identified the following key limitations with the sponsor's analysis:
  ◦ The modelled 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 NIHB population was inappropriately calculated.
  ◦ The displacement of galcanezumab by atogepant was overestimated in year 2.
  ◦ The proportion of EM patients receiving preventive migraine therapy may have been underestimated.
• CADTH reanalyses included assuming that atogepant would capture market share from oral preventive migraine therapies and increasing the market share of atogepant in the Health Canada–indicated population, and increasing the proportion of patients prescribed a preventive 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 ≥ 2 prior therapies, where oral CGRP antagonists 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 preventive migraine therapies in the Health Canada–indicated population and the uptake of atogepant. In both populations, the estimated budget impact is highly sensitive to the price of atogepant.

MMD = monthly migraine day; NIHB = Non-Insured Health Benefits.

Summary of Sponsor's Budget Impact Analysis

In the submitted budget impact analysis (BIA), the sponsor assessed the introduction of atogepant in 2 populations: (a) among EM patients (< 15 MMDs) regardless of prior treatment received, and (b) among EM patients with 4 to 14 MMDs who previously failed at least 2 oral preventive migraine therapies. The BIA was undertaken from the perspective of a Canadian public payer over a 3-year time horizon (July 2024 to June 2027) using an epidemiological approach. The sponsor's analysis included drug acquisition costs; dispensing fees and markups were not included in the base case. Data from the model were obtained from various sources including Statistics Canada,[35] the published literature,[36-40] ODB Formulary list prices,[15] the IQVIA DeltaPA database,[12] and the sponsor's internal data.[41] The sponsor based the expected uptake of atogepant in each population on internal data. Key inputs to the BIA are documented in Table 20.

Key assumptions included:

- The proportion of patients seeking treatment for migraines and receiving preventive therapies can be represented by data from 2013.
- Non-Insured Health Benefits (NIHB) clients who reside within the borders of Quebec and the territories should be excluded.
- The same number of patients will receive atogepant, regardless of whether it is reimbursed for all adult EM patients or only those with 4 to 14 MMDs who have previously failed at least 2 oral prophylactic migraine treatments.
- Atogepant will only displace fremanezumab, galcanezumab, and eptinezumab, regardless of whether it is funded for all adult EM patients or only for EM patients with 2 or more previous therapies, based on the sponsor's expectation that the reimbursement criteria and prescribing patterns for atogepant will be similar to those of fremanezumab, galcanezumab, and eptinezumab.
- The cost of eptinezumab will be equivalent to the 100 mg dose every 12 weeks for all patients.

Table 20: Summary of Key Model Parameters

Parameter	Sponsor's estimated Health Canada–indicated population (year 1/year 2/year 3)	Sponsor's estimated reimbursement population (year 1/year 2/year 3)
Target population		
Canadian adult population (excluding Quebec, base year)	24,423,396[35]	
Prevalence of diagnosed migraine	9.55%[40]	
Patients with episodic migraine	91.2%[37]	
Patients with > 4 migraines per month	NA	49.8%[38]
Patients diagnosed and saw an HCP in the past year	51.0%[39]	
Patients prescribed preventives	36.4%[36]	
Patients failing ≥ 2 preventives	NA	45.2%[41]
Patients covered by public plan	23% to 100%, depending on jurisdiction[a]	
Annual population growth	1.05%[35]	
Number of patients eligible for drug under review	148,242 / 149,800 / 151,372	33,368 / 33,719 / 34,072
Market uptake (reference scenario, 3 years)[b]		
Atogepant	0% / 0% / 0%	0% / 0% / 0%
Eptinezumab	0.6% / 0.7% / 1.0%	2.5% / 3.0% / 4.5%
Fremanezumab	14.7% / 11.9% / 11.2%	65.4% / 52.8% / 49.75%
Galcanezumab	7.2% / 9.9% / 10.3%	32.1% / 44.2% / 45.75%
Amitriptyline	31.0% / 31.0% / 31.0%	NA
Propranolol	31.0% / 31.0% / 31.0%	NA

Parameter	Sponsor's estimated Health Canada–indicated population (year 1/year 2/year 3)	Sponsor's estimated reimbursement population (year 1/year 2/year 3)
Topiramate	15.5% / 15.5% / 15.5%	NA
Market uptake (new drug scenario, 3 years)[b]		
Atogepant[c]	2.4% / 4.9% / 6.1%	10.8% / 21.9% / 27.3%
Eptinezumab	0.5% / 0.5% / 0.7%	2.2% / 2.3% / 3.3%
Fremanezumab	12.9% / 9.9% / 8.1%	57.2% / 44.0% / 36.2%
Galcanezumab	6.7% / 7.1% / 7.5%	29.7% / 31.7% / 33.3%
Amitriptyline	31.0% / 31.0% / 31.0%	NA
Propranolol	31.0% / 31.0% / 31.0%	NA
Topiramate	15.5% / 15.5% / 15.5%	NA
Cost of treatment (per patient per year)		
Atogepant	$6,735[5]	
Eptinezumab	$7,240[14]	
Fremanezumab	$6,429	
Galcanezumab	$7,296 first year, $6,735 thereafter[12]	
Amitriptyline	$112[15]	
Propranolol	$149[15]	
Topiramate	$167[15]	

HCP = health care provider.

[a]PDCI 2021 Census of Insurer's, original data not provided.[41]

[b]Cited as based on the sponsor's internal market research using Compuscript claims data.[41]

[c]Cited as based on internal data.[41]

Summary of the Sponsor's Budget Impact Analysis Results

Results of the sponsor's analysis suggest that the reimbursement of atogepant for adults with EM and 2 or more prior therapies (reimbursement population) will be associated with an incremental cost of $340,405 in year 1, an incremental savings of $1,120,232 in year 2, and an incremental cost of $1,183,220 in year 3, for a 3-year incremental cost of $403,393. The sponsor's results for the Health Canada–indicated population (EM, regardless of prior treatment) were identical to those for the reimbursement population.

CADTH Appraisal of the Sponsor's Budget Impact Analysis

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the results of the BIA:

- **Modelled population does not reflect the reimbursement request:** The sponsor's reimbursement request is for adults with EM (< 15 MMDs) and 2 or more prior therapies; however, the sponsor restricted the modelled population to EM patients with 4 to 14 MMDs. Thus, EM patients with 2 or

more prior therapies who have 1 to 3 MMDs are not reflected in the number of eligible patients for the reimbursement population. CADTH requested that the sponsor revise their analysis to reflect the full reimbursement request; however, the sponsor declined to model the full reimbursement population (i.e., EM with 1 MMD to 14 MMDs and ≥ 2 prior therapies).[42]

    - CADTH was unable to assess the budgetary impact of reimbursing atogepant for all patients in the sponsor's reimbursement request population (i.e., including those with 1 MMD to 3 MMDs) due to a lack of information about market uptake and displacement in this group of patients. Should atogepant be used by patients with 1 MMD to 3 MMDs, this would increase the costs associated with reimbursing it.

- **Market uptake and comparator displacement do not reflect the Health Canada indication**: For the Health Canada indication, the estimated market displacement appears to reflect the expected reimbursement criteria (EM and ≥ 2 prior preventive therapies, and 4 to 14 MMDs) in terms of total displacement and comparators displaced, leading to a budget impact assessment which is identical for both modelled populations. As such, the sponsor has not modelled the budgetary impact of reimbursing atogepant for its Health Canada indication. According to clinical expert opinion solicited by CADTH for this review, if atogepant is reimbursed for the full Health Canada indication (without restriction to patients with ≥ 2 prior therapies),[1] it would displace a substantial proportion of the currently available oral preventive migraine medications and capture a larger proportion of the overall migraine prevention market than estimated by the sponsor.
    - In reanalysis, CADTH assumed that if atogepant is reimbursed for its Health Canada indication (EM patients with < 15 MMDs), half of its market share will come from displacing oral preventive migraine medications based on clinical expert opinion. CADTH also assumed that atogepant would capture a larger proportion of the overall preventive market if it were reimbursed according to its indication, capturing 5% in year 1, 10% in year 2, and 15% in year 3.
- **Displacement pattern of anti-CGRP comparators was inappropriate:** The sponsor assumed, based on internal data that was not provided, that of atogepant market shares, 75%, 40%, and 50% would come from displaced fremanezumab in year 1, year 2, and year 3, respectively, while 22%, 57%, and 46% would come from displaced galcanezumab in the same years, with the remainder displacing eptinezumab. Clinical expert opinion solicited by CADTH for this review did not find the disproportionately high displacement of galcanezumab in year 2 relative to its market share in the reference scenario to be a reasonable assumption.
    - In reanalysis, CADTH assumed that fremanezumab, galcanezumab, and eptinezumab would be displaced by atogepant proportionally to their respective market shares in the reference scenario in all 3 years of the analysis.
- **NIHB population was inappropriately calculated:** The sponsor included NIHB clients aged 18 years and older who live within the borders of 1 of the CDR-participating provinces of Canada (i.e., excluding Quebec and the 3 territories). However, as a CDR-participating jurisdiction itself, all adult clients of NIHB are relevant to the assessment of the budgetary impact of reimbursing atogepant. Additionally, NIHB clients residing within Ontario who are younger than 25 years or older than 65

years are eligible for reimbursement by ODB and thus should be counted as ODB clients rather than NIHB clients for the purposes of the modelling the budgetary impact of reimbursing atogepant. Finally, the sponsor extrapolated the population of the NIHB from March 2020 data;[43] however, more recent data from March 2021 were available.[44]

    - CADTH recalculated the eligible population of NIHB to include all clients of NIHB who are aged at least 18 years, regardless of province or territory of residence, using data derived from the NIHB 2020 to 2021 annual report. NIHB clients residing within Ontario who were aged 18 years to 24 years or at least 65 years were considered to be part of Ontario's eligible population for the purposes of the BIA.

- **Proportion of patients receiving preventive migraine therapy may be underestimated:** The sponsor estimated that, of patients with diagnosed EM who had sought assistance from their health care provider, 36.4% would be prescribed a migraine-preventive therapy, based on Canadian respondents to a 2013 survey by Blumenfeld et al.[36] Of note, in this study, Canada had the lowest reported rate of preventive migraine therapy use among included countries. Since 2013, injectable anti-CGRPs have become available in Canada, with public reimbursement that either is limited[45,46] or is expected to be limited to patients who have tried 2 or more prior preventive migraine treatments (or those with contraindications or intolerance). Clinical expert opinion solicited by CADTH for this review indicated that the proportion of patients living with migraine being treated with preventive therapies, particularly those with more than low-frequency migraines (i.e., ≥ 4 MMDs) is rising as health care providers are more likely to try oral medications sooner to enhance patients' opportunities to access injectable anti-CGRPs, should they be required. Previous CADTH reviews of anti-CGRPs for EM have assumed that for patients with at least 4 MMDs, 26.3% would be diagnosed, have sought treatment, and received a preventive therapy.[26,32]

    - To estimate the anticipated reimbursement population of patients with at least 4 MMDs and 2 or more prior therapies, CADTH assumed that 51% of patients with diagnosed migraine sought treatment, and of those, 51.6% would receive a preventive therapy. These proportions lead to a total of 26.3% of diagnosed patients seeking treatment and receiving a preventive therapy, consistent with previous reviews of the included anti-CGRP comparators.[26,32]

CADTH Reanalyses of the Budget Impact Analysis

CADTH revised the sponsor's submitted analyses by increasing the market share of atogepant and assuming atogepant would also capture market share from the oral preventive migraine therapies in the Health Canada–indicated population analysis, and increasing the proportion of patients living with migraine prescribed a preventive migraine therapy in the reimbursement population. In both populations, NIHB and ODB client eligibility was corrected, the displacement of anti-CGRP comparators was assumed to be proportional to their reference scenario market shares, and the unit price of galcanezumab was updated to reflect the publicly available list price. The changes applied to derive the CADTH base case are described in Table 21.

Table 21: CADTH Revisions to the Submitted Budget Impact Analysis

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
1. Price of galcanezumab	$561.27 per pen, as per IQVIA DeltaPA wholesale price.[12]	$560.98 per pen, as per the publicly available list price in Ontario and Saskatchewan[13,25]
Changes to derive the CADTH base case		
1. Market share and displacement of oral preventives (Health Canada–indicated population only)	Market share of atogepant (year 1/year 2/year 3): 2% / 5% / 6% Displacement of oral comparators (year 1 to year 3): 0%	Market share of atogepant (year 1/year 2/ year 3): 5% / 10% / 15% Displacement of oral comparators (year 1 to year 3):[a] Propranolol 20% Amitriptyline 20% Topiramate 10%
2. Displacement of anti-CGRP comparators	Proportion of atogepant market share coming from each comparator in year 1/ year 2/year 3: Eptinezumab: 2.5% / 3.0% / 4.5% Fremanezumab: 75.4% / 40.0% / 49.75% Galcanezumab: 22.1% / 57.0% / 45.75%	Proportion of atogepant market share coming from each comparator in year 1/year 2/year 3:[b] Eptinezumab: 2.5% / 3.0% / 4.5% Fremanezumab: 65.4% / 52.8% / 49.75% Galcanezumab: 32.1% / 44.2% / 45.75%
3. NIHB and Ontario eligibility	Adult NIHB population (base year): 569,155 Adult Ontario population (base year): 12,152,031	Adult NIHB population (base year): 683,570 Adult Ontario population (base year): 12,206,187
4. Proportion of patients prescribed preventive therapy (reimbursement population only)	36.4%	51.6%
CADTH base case	Health Canada–indicated population: Reanalysis 1 + 2 + 3 Reimbursement request population: Reanalysis 2 + 3 + 4	

NIHB = Non-Insured Health Benefits; ODB = Ontario Drug Benefit.

[a]Due to the assumption that 50% of atogepant market share was displacing oral preventives, the displacement of all anti-CGRP comparators was halved (i.e., atogepant market share coming from displacement of anti-CGRP comparators was reduced from 100% to 50%).

[b]When this reanalysis is combined with Reanalysis 1 for the Health Canada–indicated population, the proportion of atogepant market share being displaced from each anti-CGRP comparator is halved due to 50% of atogepant displacement coming from the oral preventives.

The results of the CADTH stepwise reanalysis are presented in summary format in Table 22 and a more detailed breakdown is presented in Table 23.

For the full Health Canada–indicated population (i.e., EM patients with < 15 MMDs), CADTH reanalyses suggest that reimbursement of atogepant will be associated with a 3-year budgetary incremental cost of $152,872,745.

If reimbursement of atogepant is restricted to EM patients with 4 MMDs to 14 MMDs who have previously failed at least 2 oral preventive migraine medications, CADTH reanalyses suggest an incremental cost of $1,083,612 over 3 years.

The unusual pattern of an incremental cost in year 1, a savings in year 2, and a cost in year 3 is due to the underlying expansion of galcanezumab into the market in the reference scenario, which is peaking in year 1 and year 2 (refer to Table 20). When assuming public list prices and product monograph recommended dosing, galcanezumab is more expensive than atogepant in its initiation year, and approximately the same price in subsequent years of therapy (refer to Table 10), and thus atogepant is cost saving when displacing galcanezumab in patients who would otherwise be in their first year of galcanezumab therapy.

Table 22: Summary of the CADTH Reanalyses of the Budget Impact Analysis

Stepped analysis	3-year total	
	Health Canada–indicated population[a]	Reimbursement population[b]
Sponsor's submitted base case	$403,393	$403,393
Sponsor's corrected base case	$436,599	$436,599
CADTH reanalysis 1: Atogepant market share and oral displacement (HC indication population only)	$148,995,086	NA
CADTH reanalysis 2: Anti-CGRP displacement	$785,780	$785,780
CADTH reanalysis 3: NIHB and Ontario populations corrected	$442,421	$442,421
CADTH reanalysis 4: patients prescribed preventive (anticipated reimbursement request population only)	NA	$618,538
CADTH base case	**$152,872,745**	**$1,083,612**

NA = not applicable; NIHB = Non-Insured Health Benefits; ODB = Ontario Drug Benefit.

[a]Health Canada–indicated population: Patients with episodic migraine (< 15 monthly migraine days).

[b]Sponsor's anticipated reimbursement population (patients with episodic migraine and an inadequate response, an intolerance, or a contraindication to at least 2 oral preventive migraine medications who have 4 monthly migraine days to 14 monthly migraine days). CADTH notes that this does not reflect the entire submitted reimbursement population (< 15 monthly migraine days)

CADTH conducted additional scenario analyses (Table 23) to highlight the uncertainty associated with the potential budget impact. For the Health Canada–indicated population, scenarios were conducted assuming: a higher proportion of EM patients (61%) consult a health care provider; a lower proportion of atogepant's market capture displaces oral preventives (25%); a higher proportion of atogepant's market capture displaces oral preventives; atogepant captures 2%, 5% and 6% of the preventive market share over year 1, year 2, and year 3; and a price reduction of 61% for atogepant resulting from the CADTH base-case economic evaluation for the anticipated reimbursement request population.[28]

For the reimbursement population, scenarios were conducted assuming: a higher proportion of EM patients (61%) consult a health care provider and a 61% price reduction for atogepant.

Table 23: Detailed Breakdown of the CADTH Reanalyses of the Budget Impact Analysis

Stepped analysis	Scenario	Year 0 (current situation)	Year 1	Year 2	Year 3	3-year total
Health Canada–indicated population[a]						
Sponsor's submitted base case	Reference	$235,414,096	$236,482,920	$241,010,394	$242,125,894	$719,619,208
	New drug	$235,414,096	$236,823,326	$239,890,161	$243,309,114	$720,022,601
	Budget impact	**$0**	**$340,405**	**−$1,120,232**	**$1,183,220**	**$403,393**
Sponsor's corrected base case	Reference	$235,385,245	$236,445,124	$240,957,793	$242,071,940	$719,474,857
	New drug	$235,385,245	$236,788,517	$239,853,078	$243,269,861	$719,911,455
	Budget impact	**$0**	**$343,393**	**−$1,104,716**	**$1,197,921**	**$436,599**
CADTH base case	Reference	$238,513,679	$239,587,580	$244,160,317	$245,289,207	$729,037,104
	New drug	$238,513,679	$264,707,312	$294,756,150	$322,446,386	$881,909,849
	Budget impact	**$0**	**$25,119,733**	**$50,595,833**	**$77,157,179**	**$152,872,745**
CADTH scenario 1: 61% consult an HCP	Reference	$285,281,067	$286,565,536	$292,034,889	$293,385,131	$871,985,556
	New drug	$285,281,067	$316,610,707	$352,551,474	$385,671,168	$1,054,833,348
	Budget impact	**$0**	**$30,045,170**	**$60,516,585**	**$92,286,038**	**$182,847,793**
CADTH scenario 3: 25% of atogepant capture displaces orals	Reference	$238,513,679	$239,587,580	$244,160,317	$245,289,207	$729,037,104
	New drug	$238,513,679	$252,509,702	$270,019,207	$285,379,013	$807,907,923
	Budget impact	**$0**	**$12,922,123**	**$25,858,891**	**$40,089,806**	**$78,870,819**
CADTH scenario 4: 75% of atogepant capture displaces orals	Reference	$238,513,679	$239,587,580	$244,160,317	$245,289,207	$729,037,104
	New drug	$238,513,679	$276,904,922	$319,493,093	$359,513,760	$955,911,774
	Budget impact	**$0**	**$37,317,342**	**$75,332,776**	**$114,224,552**	**$226,874,671**
CADTH scenario 5: lower atogepant capture	Reference	$238,513,679	$239,587,580	$244,160,317	$245,289,207	$729,037,104
	New drug	$238,513,679	$251,645,051	$268,947,351	$276,435,801	$797,028,204

Stepped analysis	Scenario	Year 0 (current situation)	Year 1	Year 2	Year 3	3-year total
	Budget impact	**$0**	**$12,057,472**	**$24,787,035**	**$31,146,594**	**$67,991,100**
CADTH scenario 6: 61% PR for atogepant	Reference	$238,513,679	$239,587,580	$244,160,317	$245,289,207	$729,037,104
	New drug	$238,513,679	$233,848,628	$232,390,749	$227,916,030	$694,155,407
	Budget impact	**$0**	**−$5,738,952**	**−$11,769,568**	**−$17,373,178**	**−$34,881,697**
Reimbursement population[b]						
Submitted base case	Reference	$219,248,369	$220,146,893	$224,503,655	$225,445,269	$670,095,817
	New drug	$219,248,369	$220,487,298	$223,383,423	$226,628,489	$670,499,210
	Budget impact	**$0**	**$340,405**	**−$1,120,232**	**$1,183,220**	**$403,393**
Sponsor's corrected base case	Reference	$219,219,507	$220,109,081	$224,451,034	$225,391,293	$669,951,408
	New drug	$219,219,507	$220,452,474	$223,346,318	$226,589,214	$670,388,006
	Budget impact	**$0**	**$343,393**	**−$1,104,716**	**$1,197,921**	**$436,599**
CADTH base case	Reference	$337,934,967	$339,469,166	$345,968,446	$347,569,647	$1,033,007,259
	New drug	$337,934,967	$339,509,805	$345,828,189	$348,752,877	$1,034,090,872
	Budget impact	**$0**	**$40,639**	**−$140,257**	**$1,183,230**	**$1,083,612**
CADTH scenario 1: 61% consult an HCP	Reference	$404,196,725	$406,031,748	$413,805,396	$415,720,558	$1,235,557,702
	New drug	$404,196,725	$406,080,355	$413,637,638	$417,135,795	$1,236,853,787
	Budget impact	**$0**	**$48,607**	**−$167,758**	**$1,415,236**	**$1,296,085**
CADTH scenario analysis 2: 61% PR for atogepant	Reference	$337,934,967	$339,469,166	$345,968,446	$347,569,647	$1,033,007,259
	New drug	$337,934,967	$318,210,877	$302,232,188	$293,865,535	$914,308,600
	Budget impact	**$0**	**−$21,258,290**	**−$43,736,258**	**−$53,704,112**	**−$118,698,659**

EM = episodic migraine; HCP = health care provider; MMD = monthly migraine day; PR = price reduction.

[a]Health Canada–indicated population: patients with episodic migraine (< 15 MMDs).

[b]Sponsor's anticipated reimbursement population (patients with episodic migraine and an inadequate response, an intolerance, or a contraindication to at least 2 oral preventive migraine medications who have 4 MMDs to 14 MMDs). CADTH notes that this does not reflect the entire submitted reimbursement request (< 15 MMDs).

Stakeholder Input

List of Tables

List of Figures

Patient Input

Migraine Canada and Migraine Quebec

About Migraine Canada and Migraine Quebec

Migraine Canada is a national federally registered charity, founded in late fall of 2018, with a mission to provide support and education as well as raise awareness about the impact of migraines. We advocate for optimal care for those living with migraines and support research to find a cure. With the help of dedicated physicians and contributors, Migraine Canada delivers evidence based, up-to-date disease and treatment information to Canadian living with migraine, including patients and caregivers, as well as healthcare professionals. We educate patients, caregivers, and healthcare professionals by researching, developing, and sharing electronic and print materials containing the most current migraine information. We drive awareness and education through our website, social media channels and forums. We have a growing community of over 2,000 individuals subscribing to our email list. We provide patient support through participation in regional on-line support groups, with more than 3,000 members on our Facebook page.

Migraine Quebec is a provincial non-profit patient organization founded in 2014 whose mission is to provide support and information to people with the disease, as well as to educate the public about the repercussions of migraine. We advocate for optimal care for migraine sufferers and support research to find cures to improve the quality of life of patients with this chronic disease. We educate patients, caregivers and healthcare professionals by researching, developing and sharing electronic and print documents containing the most recent data on migraine. We promote awareness and education through our website, social media, workshops and forums. We help patients by offering regional on-line support groups, with more than 5,000 members on our Facebook page) for the province of Quebec).

Both organizations have a broader reach by interacting with several other on-line Canadian and International groups and leverage traditional and social media channels to empower patients to share stories and experiences to advocate for the supports needed to live full and active lives while coping with migraines.

Website (English): www.migrainecanada.org

Website (French): www.migrainequebec.com

Information Gathering

The information provided in this submission was collected through a Quality-of-Life online survey that was launched by Migraine Canada in late fall of 2021. It was promoted across Canada in both French and English through Migraine Canada's digital and social media channels with promotion support by Migraine Quebec. In total, 1,165 Canadian adults with migraine and their caregivers responded to the online survey. Of our total respondents, 19% live with low frequency migraine, 28% live with 8-14 days / month with migraine and 52% live with chronic migraine 15 or more days. The spectrum of representation was national with the majority (68%) participating between the age of 30-59.

Migraine Canada launched a second national online survey in mid-January 2022 to gather additional insights to support our submission and seek input from patients with experience on atogepant. It was promoted across Canada through Migraine Canada's digital and social media channels with promotion support by Migraine Quebec. In total, 300 Canadian with migraine responded to the survey. Of our total respondents, 15% live with low frequency migraine, 26% live with 8-14 days / month with migraine and 59% live with chronic migraine 15 or more days. The spectrum of representation was national with the majority (74%) participating between the age of 30-59

Migraine Canada also received direct input from 8 patients (2 Canadian / 6 American) who have experience taking atogepant that has been integrated into the submission.

Disease Experience

Migraines are not just headaches but a neurological disease. Migraine impacts 1 billion people worldwide, or about 1 in 7 people. Migraine is most common between the ages of 25 and 55 but it can impact people of all ages including children (10%) but it affects three-times as many women as men (8%).

Migraines are classified according to their monthly frequency. Episodic Migraine is defined as impacting less than 15 days per month and 12% of adults living with migraine fall into this group; Chronic Migraine impacts more than 15 days per month and 2% of the adult migraine populations. Migraines often present with severe, throbbing, recurring pain, usually on one side of the head (or both sides or no pain at all). Nausea, vomiting, dizziness, extreme sensitivity to sound, light, touch, and smell, and tingling or numbness in the extremities or face are also common symptoms. About 25% of migraine sufferers also have a visual disturbance called an aura, which usually lasts less than an hour. Attacks usually last between 4 and 72 hours.

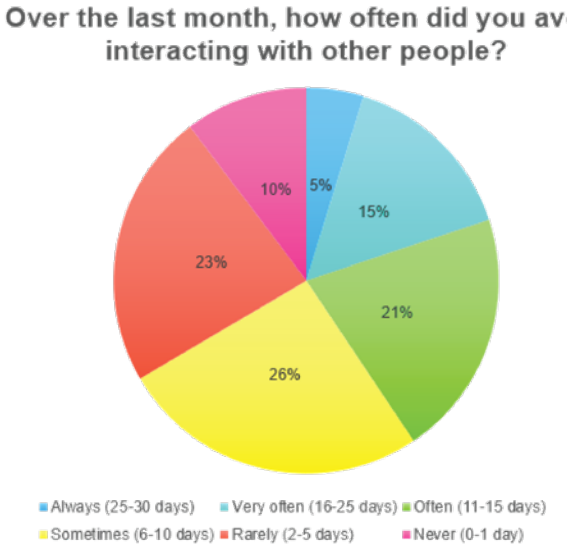
Migraine is usually categorized according to accompanying symptoms (aura, vestibular, hemiplegic) but also according to monthly frequency of attacks. Episodic migraine refers to attacks occurring 14 days or less and is now further separated in low-frequency (1-6 days) and high frequency (7-14 days). Chronic migraine is diagnosed when patients have 15 or more headache days per month. Chronic migraine is associated with increased disability and co-morbidities. It is also associated with medication overuse headache (MOH), a complication of frequent use of acute treatments that induce even more frequent and intractable headaches. The estimated prevalence of MOH varies according to countries but is usually between 0.5% and 2% of the global population (GBD 2015). Medication overuse feeds the headache cycle and patients are trapped in a vicious cycle, unable to get adequate pain relief.

There are two main states of life for a migraine patient: the active attack (ictal state) and in-between attacks (interictal state). During the attack itself, symptoms may prevent the person's ability to accomplish their tasks, work and interact with others. The pain is at least moderate and often severe, throbbing, and diffuse. The nausea and vomiting are obviously disruptive and may prevent oral medications efficiency. The sensory hypersensitivity forces many patients to isolate themselves in a dark room and stop all activities. Auras are neurological deficits that can accompany migraines (including loss of vision, speech, and sensation, even muscle strength) which can last for hours. Some migraines are also accompanied with dizziness, vertigo, and loss of balance. People generally experience reduced cognition during a migraine, with slowed thinking,

lack of focus, and difficulty reading and speaking. This typically disrupts most activities involving a computer or interacting with other people. A controlled migraine attack managed with effective treatment can be brief, but uncontrolled attacks may last multiple days in a row.

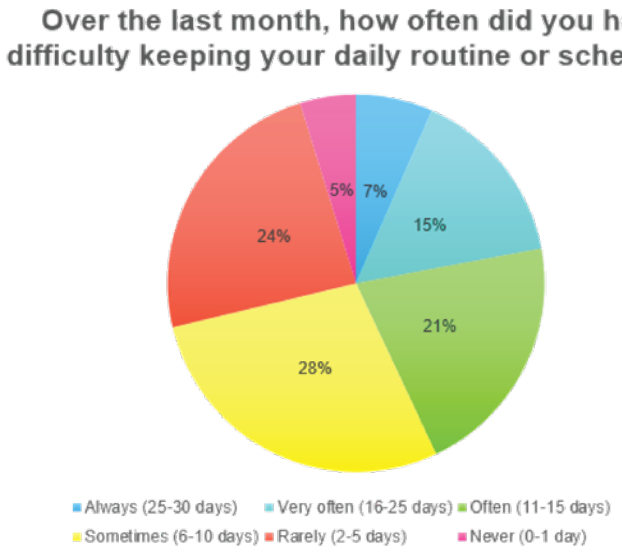
Migraine patients' quality of life is considerably negatively impacted. Participants in the quality-of-life survey indicated all aspects of their life is impacted and range from regularly needing to change or cancel plans or avoid interacting with people altogether (67%).

Figure 1: Percentage Avoiding Interactions With People



When asked, over the last month, how often was it difficult to keep a daily routine or schedule, over 52% had difficulty. 39% of patients were unable to do usual household chores. Many people reported that although their migraine was excruciating, they learn to push through it because they have no other choice.

Figure 2: Percentage Having Difficulty With Daily Routine or Schedule

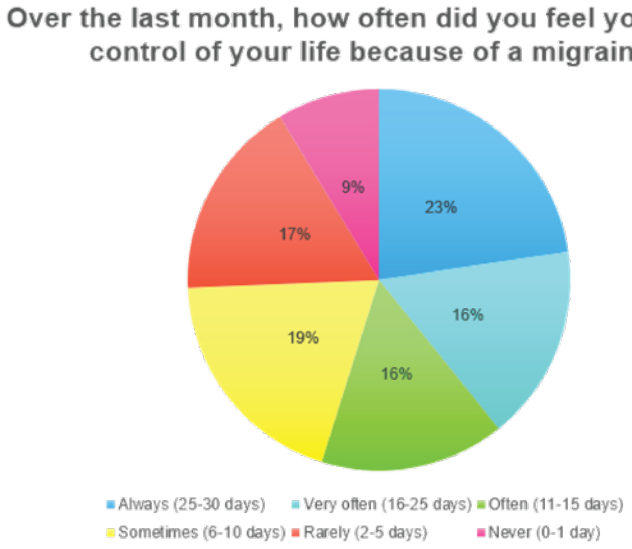


Approximately 30% did not have concentration affected while 29% noted they sometimes had trouble (6-10 days) and 68% were regularly unable to do activities that required concentration.

The majority (73%) of survey respondents indicated they live in fear of the next attack and have difficulty planning ahead. Only 9% they didn't worry about their next attack.

A significant number of people (55%) experience feeling lack control of their life because of migraine ranging from always (25-30 days/month) to often (11-15 days/month).

Figure 3: Percentage Feeling Lack of Control

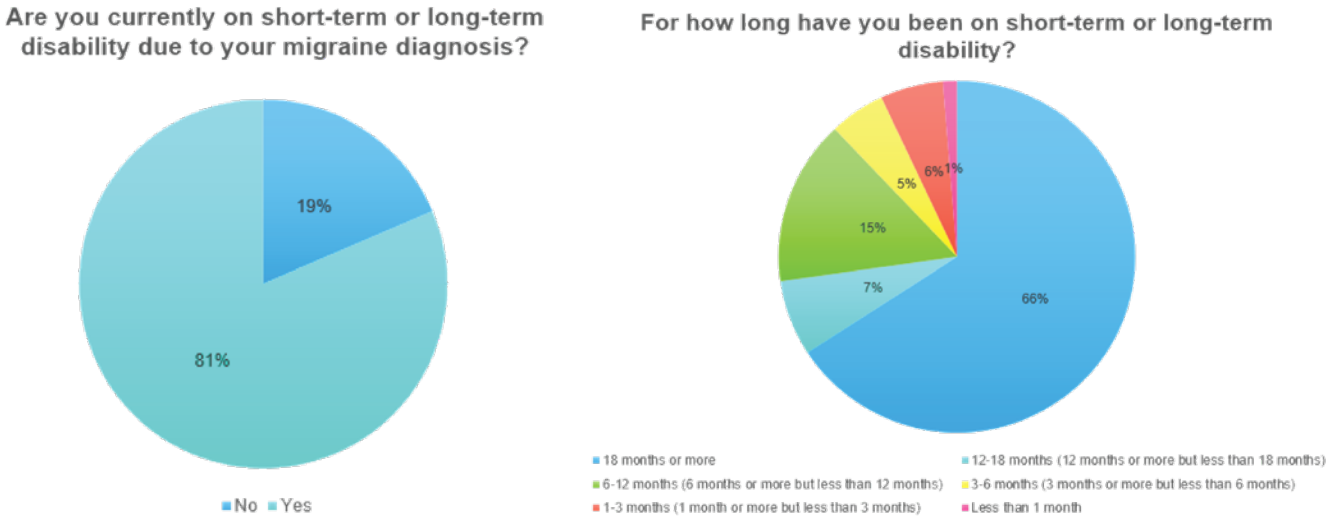


Employment

Only 46% of patients reported to work full time and 11% are able to work part-time. For many who indicated they work part time, they are also on CPP disability. Over 20% are on short- or long-term disability or retired early due to their condition (migraine). There were many people (3%) who shared they were unemployed and not able to have any support through disability programs.

For the patients who are on short-term or long-term disability, 81% reported it was due to their migraines and 66% have been on disability more than 18 months.

Figure 4: Percentage on Disability

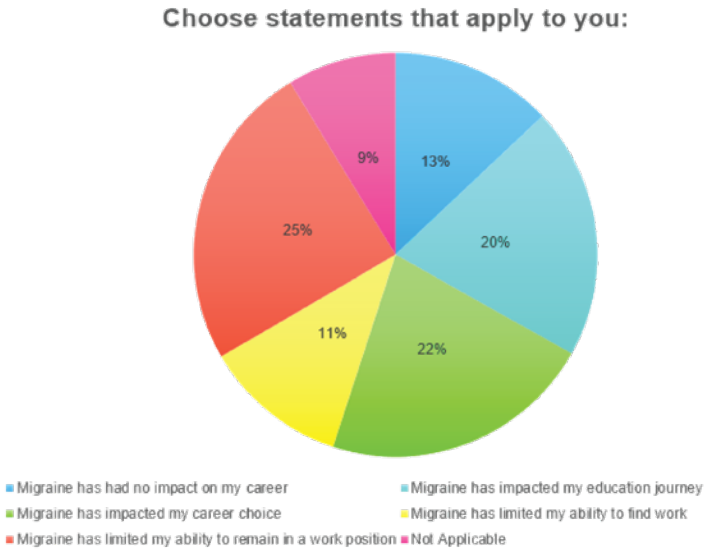


The graph below illustrates the impact migraine has on people's work / career.

- 13% reported migraine has had no impact on career
- 20% reported migraine has impacted education journey
- 22% reported migraine has impacted career choice
- 11% reported migraine has limited ability to find work
- 25% reported migraine has limited ability to remain in a work position.

Impact on Work

Figure 5: Impact of Migraine on Career



Patient Testimonials

> "It sucks. I'm in too much pain and missed so much work that I lost my job of 25 years. But not disabled enough for LTD or disability pension. Since I was the primary income earner it was a HUGE impact on our family-not just paycheques but also medical, dental, pension-all those sorts of things that all come with a long-term job. And the impact it has on my sense of self and self-worth."
>
> "My colleagues don't understand. When I have a migraine, I suffer in silence and can't wait for the day to be done."
>
> "I feel guilty when I call in sick and then show up a couple days later looking fine. People don't understand what a migraine is."
>
> "I've asked for accommodations and been denied. I had to get a doctor's note to be somewhat believed."

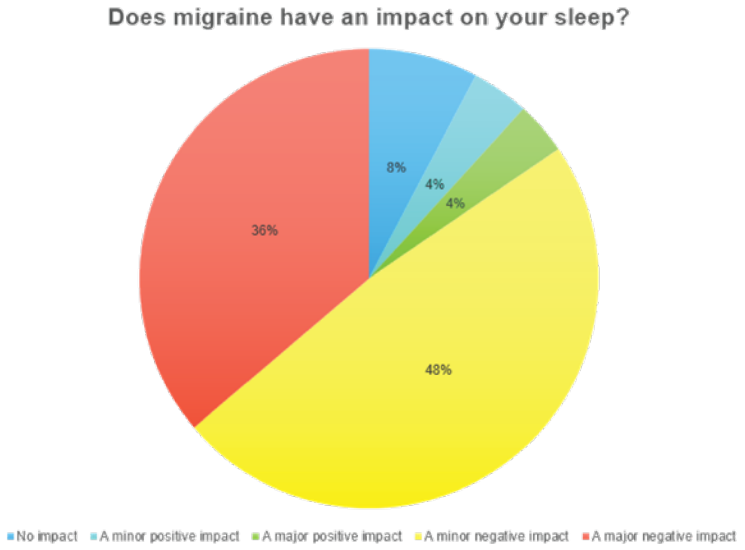
Impact on Sleep

Issues with sleep is significant ranging from 7% having no issues with sleep to 38% always or regularly have sleep disrupted due to their migraine.

Sleep disruption reported by patients caused by migraine over the past month was significant for respondents. Close to 20% reported 16-30 days as always or very often disrupted, followed by 19% who reported 11-15 days of disrupted sleep.

Patients rated their quality of sleep as very poor (17%), often disrupted (37%) and sometimes disrupted (30%). Only 16% rated their sleep as "good". When as specifically if migraine impacts sleep, 84% of patients attribute their migraine as having a negative impact.

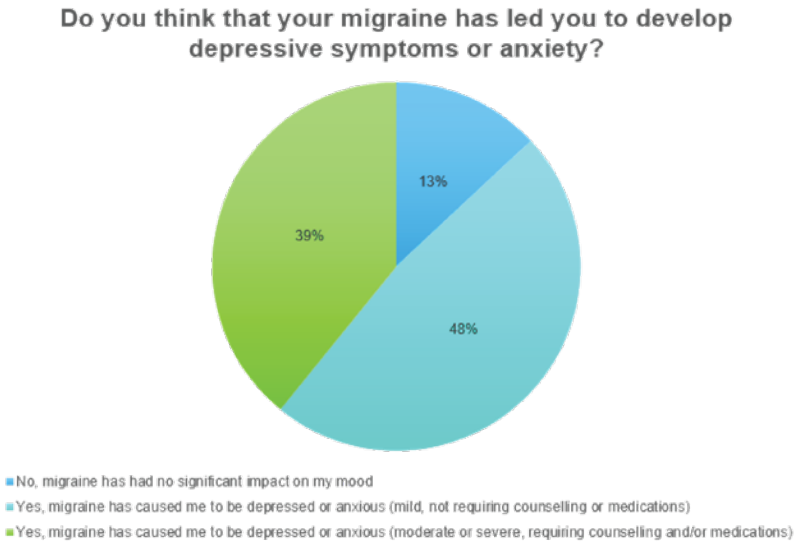
Figure 6: Impact of Migraine on Sleep



Mental Health

When asked if migraine has led to the development of depression and anxiety, 39% reported that migraine has caused the individual to be depressed and/or anxious (moderate to severe) requiring counselling and/or medication. Approximately 48% said migraine has caused them to become depressed and/or anxious but not to the point counselling or medication was required. Only 13% reported migraine has had no significant impact.

Figure 7: Impact of Migraine on Mental Health

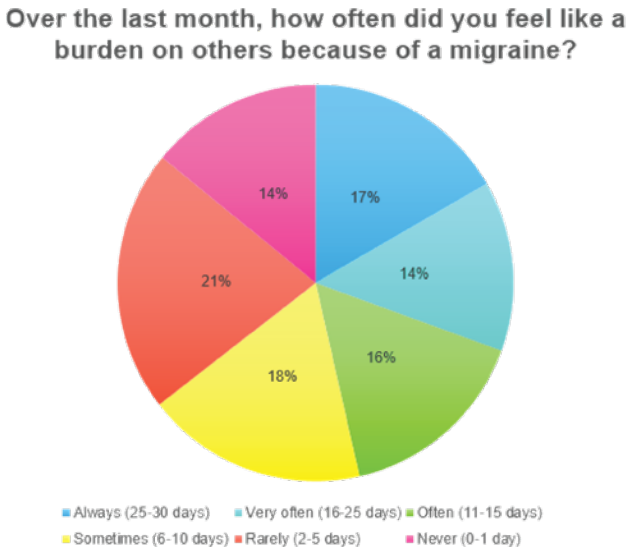


The secondary survey had similar responses. For 88%, their migraine led to depression and anxiety. About 45% reported that migraine has caused the individual to be depressed and/or anxious (moderate to severe) requiring counselling and/or medication and 43% said migraine has caused them to become depressed and/or anxious but not to the point counselling or medication was required. Only 4% reported migraine has had no significant impact mental health.

Burden on Family

When asked how often individuals felt they were a burden on others, only 14% responded with never and 21% rarely (2-5 days). The majority felt they were a burden (31% 16-30 days/month) and 35% between 6-15 days/month.

Figure 8: Migraine and Burden on Others



Respondents reported (39%) that they always or very often feel a lack of control over their life because of migraine. Only 9% did not feel migraine impacts control over their life.

When asked, over the last month, how often did the participants partner have to take over the parenting activities, only 30% had no impact. 60% had some degree of impact (10% noted their partner had to take over between 12-30 days/month.

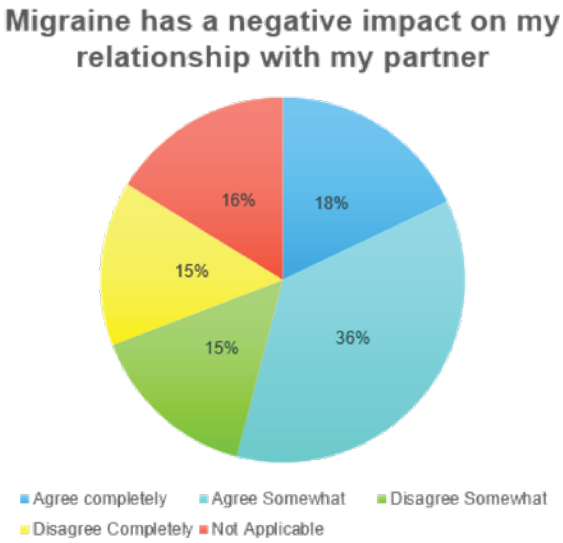
Over the last month, although the patients reported to rarely or never (56%) miss a family activity, 23% missed activities 6-10 days/month and 14% between 11-15 days/month.

Approximately 37% of respondents agreed they would be a better parent if they didn't have migraine and only 7% feel their migraine has no influence on parenting.

Because of their migraine 50% worry about their family's financial stability.

The majority of people (54%) indicated migraine has a negative impact on their relationship with their partners. Only 15% disagreed with the statement.

Figure 9: Impact of Migraine on Partner



Patient Testimonials

"I've had chronic migraine for about 10 years. It has impacted every aspect of my life. I'm not able to earn a consistent income, I'm not able to look after my kids or my home in any regular way and more often than not, I have to cancel plans with my spouse, family and friends because of my migraines. It's very isolating and discouraging, and there have been times when I've felt like it's just not worth living like this."

"I'm not a mother or a wife anymore. I am a shell. I take up space in my home but don't contribute. This is not a life."

"My children see a much more angry, frustrated mom because of migraine. They also experience more anxiety and fear not knowing if I will be able to do things with them or seeing me violently throwing up or going to emerge. The on my kids is huge."

"I cannot be there for my family because I'm not physically or emotional available for them, even if I try my hardest. I know my family loves me but just being unavailable to do my job as a mom and wife. I also become a huge burden as they to adapt their needs to accommodate mine, not to mention the INCREDIBLY big expense just to have me able a little bit more functional. I feel I'm watching life go by without being able to participate in it. Like a by-stander. This is no way to live, specifically if we are not supported or recognized as disable, or even worse, dismissed."

"My ex-husband was not able to understand the level of pain that I had and was not able to understand the limitations that it gave me some days. It put a huge strain on our relationship and it probably was a part of the demise of the marriage along with other issues."

> "With how bad my migraines have become, I am not the partner or parent that I once was. A lot of my day is spent in the bedroom. My husband must pick up the slack on my bad days after he has worked really hard all day. It is hard to explain to my family that even with meds and some treatments, none of it is a long-term fix. I try to push thru a lot but feel like I am letting them down a lot. I feel like emotionally I am wrecked. I am so tired of pain."

Experiences With Currently Treatments Available

When asked, at this point in time, if the care patients have received so far has led to an improvement in quality of life, 25% report no improvement and 49% has a mild improvement. Only 24% has experienced a marked improvement.

We also learned that in the past 6 months 57% of people did not fill their prescription due to cost and lack of coverage.

Over 78% of respondents have taken a prescriptions medication to prevent migraines. Close to 53% reported they were not satisfied with the current preventative medication treatment available that they have access to.

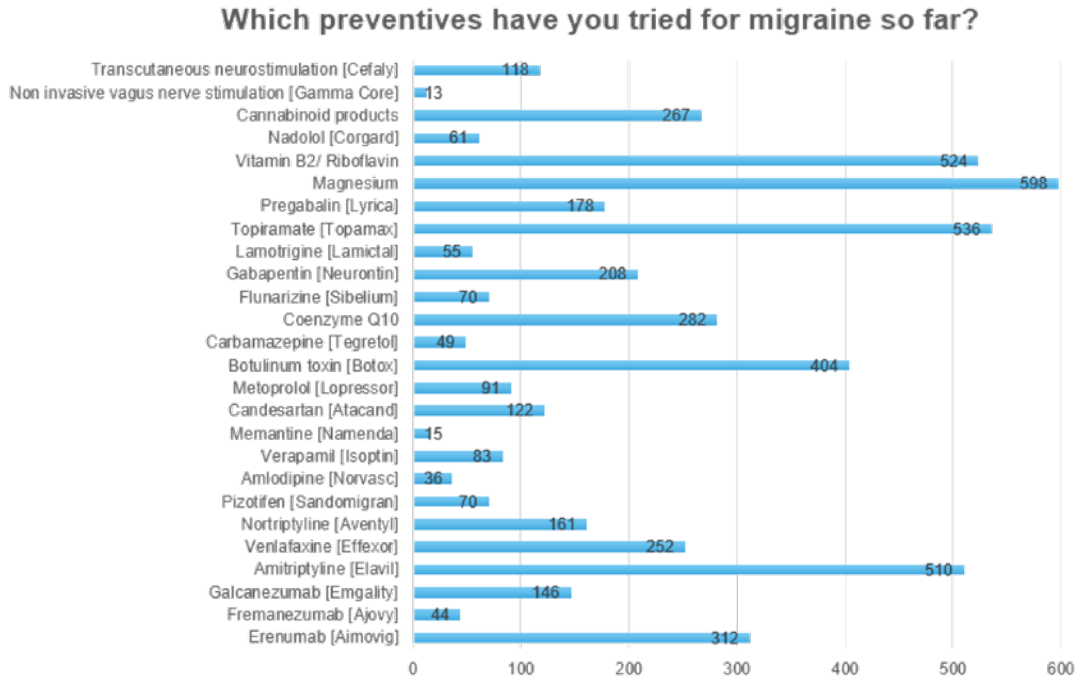
Close to 45% of people have not found an effective and tolerated way to control the majority of their migraine attacks. When asked how satisfied patients are with the current preventative prescriptions that are available in Canada, 53% are not satisfied. Only 21% reported they were satisfied with the options available.

Patient Testimonials on Satisfaction of Current Medications

> "Helps reduce frequency but has side effects."
>
> "I have only tried one CGRP. It worked better in the beginning; it seems to be growing less effective. I am also disturbed that what I have tried to report as side effects are discounted by my neurologist. And although I answered "yes" to the previous question (have you found an effective and tolerated way to control the majority of your migraines - the answer is not really. I used to get more than 20 per month, now I usually get about half that BUT - they seem to be increasing in frequency."
>
> "I have a prescription that helps prevent one type of migraine symptoms…. haven't found anything that prevents the migraines which feel like an axe is in my head."
>
> "CGRP has reduced me from 19.6/month on average to 10-12."
>
> "I'm not completely dissatisfied. The med I'm on lowers the severity but I'm still living with daily constant headaches/migraine".
>
> "I still have migraine symptoms daily but the intensity of the symptoms are markedly less severe than without my medication protocol".
>
> "I've tried everything. Nothing has worked for me. I feel at times its hopeful and this is my death sentence and punishment. I would like to try some of the newer products".

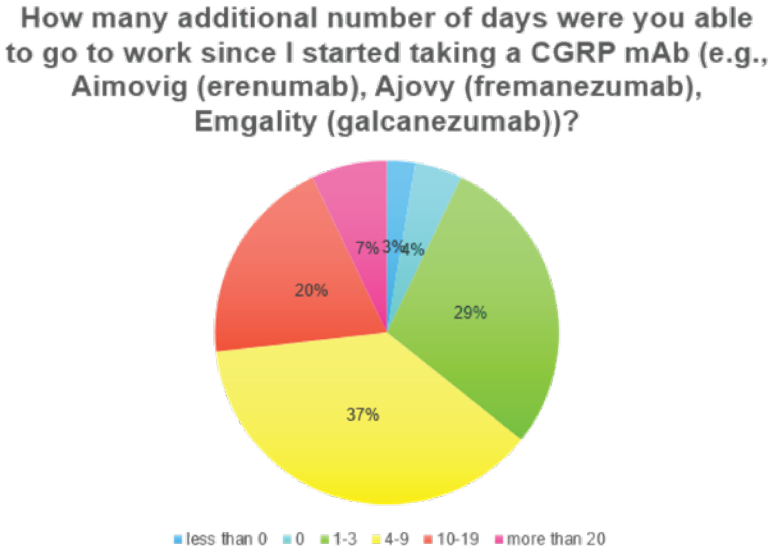
Overall, the patients who responded indicated they have tried the following treatments, when given the option to choose all that apply.

Figure 10: Preventives to Relieve Migraines



For respondents who have had experience on new treatments (CGRP's) many have had notable improvements in ability to work. Close to 10% were able to work 20 or more days per month and 20% were able to work 10-19 more days per month.

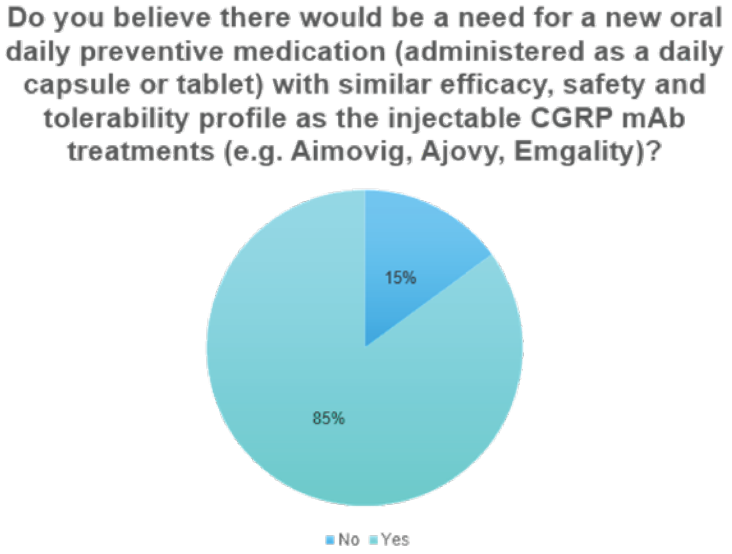
Figure 11: Additional Number of Working Days After Taking CGRP mAb



Need for More Medication Options in Canada

Over 85% of respondents believe there would be a need for a new oral daily preventative medication.

Figure 12: Need for New Oral Daily Preventive Medication



In the secondary survey, close to 62% of patients have tried 5 or more preventative treatments, followed by 21% who have tied 3 or 4.

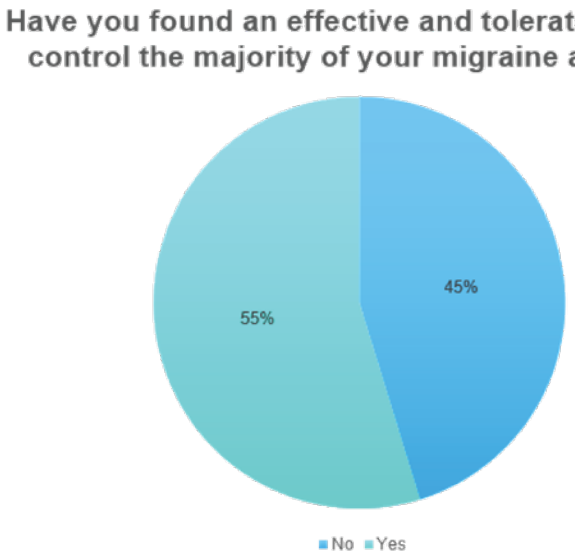
When asked if patients had found an effective and tolerated way to control their migraines, 45% they have not.

Most respondents (73%) believe there is a need for additional new treatment options in Canada. And 19% were unsure. For those who answered, “it depends”, there were several comments specific to side effects and efficacy.

Patient Testimonials Who Answered “It depends”

> “There is always need for new medications and more medications. They wear off and people need to know there are more to try.”
>
> “I have tried almost everything. My doctor doesn’t know what else do to. Yes, more medication is needed if they have less side effects and work.”
>
> “We need more medication. We also need to be able to get them. The new ones are expensive, and I can’t afford to pay, and I don’t have private insurance. I hear from many people they work really well.”
>
> “Only if they are safe and have fewer side effects.”
>
> “I agree Canadians need to have more options but with less side effects.”

Figure 13: Percent With Effective Ways to Control Migraine Attacks



When asked if people have found a preventative providing >50% improvement in frequency and/or intensity of migraines with NO significant side effects, close to 30% have found a treatment.

Patient Testimonials on Currently Available Treatments

> "The side effects are horrible."
>
> "They made symptoms more manageable, but I still struggle with side effects."
>
> "CGRP's have changed my life for the better."
>
> "CGRP has reduced my migraine from 20 times/month to 8 times/month."
>
> "It has recently stopped working and I've tried all the others, but I don't have private insurance and can't access new medications."
>
> "I have been on three and after 11-14 months, they all stop working. So far, the one I am now on is starting to work. I pray it continues."

When asked about side effects experienced from the current preventative medication for migraine, 66% responded side effects lead to discontinuation of the prescribed medication and close to 25% had side effects but tolerated them.

Improved Outcomes

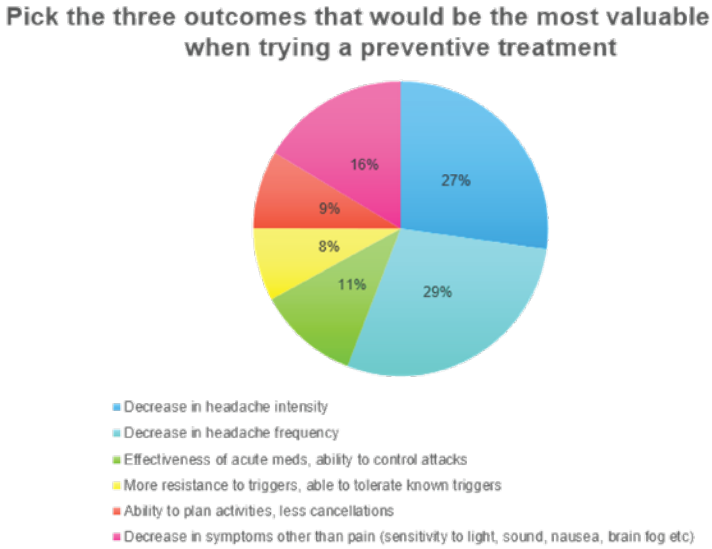
Canadians diagnosed with migraine expect to have access to new innovative medicines that address gaps in the current treatment options, names medications that will address their condition and improve quality of life. Many of the therapies currently available are not effective and have intolerable side effects.

In both surveys, the three outcomes that would be most valuable to patients when trying a preventative were:

- Decrease in headache intensity

- Decrease in headache frequency
- Decrease in symptoms other than pain (sensitivity to light, sound, nausea, brain fog, etc.)

Figure 14: Most Valuable Preventive Treatment Outcomes



Patient Testimonials from patients who answered the questions asking how daily and quality of life for patients, caregivers and families be different if the new treatment provide desired improvements.

> "Being able to live life again…being able to care for yourself without help…being able to care for others in your instead of the one being cared for."
>
> "It would allow patients to have better quality of life. It wouldn't come down to whether or not the patient has a specialist, or even a doctor (in BC especially). It would help people riddled with pain to return to work and family life without feeling stressed if they could afford treatment or not."
>
> "Decrease symptoms and increase quality of life for patients which will create less demand on caregivers."
>
> "Having a normal life with normal activities would make a huge different. Not just on pain but also on social and intimate relationships. And more efficiency at work."
>
> "No more 4-hour car to go to Botox every 10 weeks that cause big migraine and family dispute."
>
> "It would be a major life change in every way."
>
> "I'd be able to take part in my life again and be with those I love."
>
> "I would feel like a good mom, a good spouse and feel less depressed because I can't take it anymore."

"For me, being able to get back to work would be a great outcome. Migraine has made me leave a job I loved and created financial strain on our family."

"If my migraines were reduced in frequency and / or severity, I would be able to engage in social and physical activities. I would also be able to drive again (due to my migraines, I have not driven in a few years)."

"I would be able to work and contribute financially to the family. I would also be able to take part in more of family life. Years have passed without me able to do so."

"To be able to access, easily access, treatments that can rapidly help reduce migraine can open up while new worlds for migraine patients. There's nothing more dehumanizing than waiting in an ER room waiting for someone to believe you are in as much pain as you are, and to have to literally beg for relief through the tears."

"People could live without life-altering pain. They and their family members could live life regularly like regular people, making plans and enjoying their days without the threat of a migraine looking over them. They could be more productive in terms of work and social contributions."

When asked about what trade-offs are considered when choosing a therapy, people responded with:

"Tolerable side effects for reduction in frequency and pain would be more than welcome."

"Some side effects that aren't harmful but are better than the migraine."

"I'm desperate for anything to work."

"I would pay anything and give nearly anything to have them stop or be reduced more."

"Cost and effectiveness."

"Lower intensity migraines, taking meds every day."

"I will take some mild side effects as long as the intense pain from my migraine is gone."

"Benefits need to outweigh the negatives – I'm using Botox. I don't like the aesthetics or costs (I'm broke) but I'm not vomiting daily at work."

"If it improves pain management, length of time between migraines etc. it's worth it even if minor side effects of it allows more normal levels of activity in daily life."

"Convenience (how many pills/injections) side effects (short term vs long term)."

"Everything."

"I'm willing to accept non-life-threatening side effects as long as they do not impair my ability to physically and mentally function more than migraines currently do."

"Honestly, I've tried all the preventatives out there except Botox because I can't afford it. None of them work. I will take ANYTHING to make the pain stop…I don't care what the tradeoffs are."

"Anything at this point."

> "At this time in my life, I don't really have any, I just keep trying different treatments and pray one will work real soon."
>
> "I am willing to try ANYTHING if there's a real chance that the number and intensity of my migraine is lessened. But I can't stay on a therapy when it makes my non-migraine life intolerable."

Experience With Drug Under Review

There was a total of 8 people who have had experience on atogepant. Two were Canadian and 6 were from the US.

Overall, the majority (6 of 8) experienced improvement in the frequency and/or intensity of their migraine.

There were only three comments about the benefits and disadvantages:

> "I had my first 6-day migraine streak for the first time in years in December."
>
> "Helped by slightly reducing frequency and severity."
>
> "Even though the benefits are constant right now (not improving more after 4 months of use), the overall improvement has been significant, going from 17 migraines per month to around 4-5."

When asked about side effects, 66% report they did experience some side effect which were either slight and/or improved/stopped after some time.

Because there have not been new medications to treat migraine in decades, with the exception of Botox, new and innovative treatments like atogepant are welcome to the patient and clinician community. New options that are safe, tolerable and effective bring hope to Canadians and their loved ones living with this disease.

Companion Diagnostic Test

Not applicable.

Anything Else?

Migraine affects children, women, and men worldwide. It is a life altering and debilitating condition characterized by severe, often "pounding", head pain, nausea and/or vomiting and sensory hypersensitivity. In the case of aura, neurological deficits occur. Dizziness, vertigo and cognitive difficulties and neck pain are frequently associated with migraine attacks. Migraine significantly impacts quality of life, mental health, relationships, social interactions, and workplace productivity.

For some Canadian patients' current therapies are sufficient in managing their condition, however for many others, current therapies are ineffective or poorly tolerated leaving patients suffering and without hope. Struggling with 8, 14, or even 28 days of migraine per month is not living and significantly impacts quality of life. Although people will not die from migraine, it steals life away, one day in the dark room at a time. The stigma associated with migraine (it's all in your head) makes this suffering worse. People with migraine need access to effective treatments to get back to living life and be productive.

There is currently no cure for migraine, but years of research have led to the development of the CGRP antibody and Gepant classes, specific migraine preventatives. For the first time, preventative treatments based on the biological understanding of migraine mechanisms are now available. For many Canadians living with chronic migraine, new innovative medications like atogepant have been life changing, giving back days of normal function. Atogepant is the first Gepant to receive an NOC in Canada; making it the first Gepant option for patients and clinicians.

It is important Canadians and clinicians have options. Canadians living with migraine are desperate to find a treatment that may improve their quality of life. Until a cure is found, patients are looking for improved outcomes. Many are desperate to have any degree of normalcy returned to their lives. New treatment options may allow patients the ability to return to work, interact with their family and friends and feel like they are contributing to society.

Patient Testimonials

When asked about the need for new medications in Canada, shared the following comments:

> “Migraine is very debilitating and it is being a big limitation in my life (sometimes I am afraid I will not be bel to finish my Ph.D studies. I would request please to make novel and medications for migraine available with public coverage and promote they are covered by all insurers.”
>
> “Need more availability of choices in Canada without have to wait years for approval.”
>
> “It is completely cruel and unacceptable that some of the leading treatment for migraine disease like Botox and CGRP’s are NOT covered on provincial programs. Migraine disease is debilitating and yet there’s potential new medications could work but they are only available to the privileged.”
>
> “This is an incredibly misunderstood, stigmatized disability. I feel like I spend just as much energy defending and 'proving' the fact that I'm truly ill as I do cope with the symptoms. It impacts my every single day. My career, family, finances, (lifespan I'm sure), and quality of life have all been drastically affected. I have spent tens of thousands of dollars out of pocket on medications and treatments when I've been between drug plans DUE TO migraine affecting my ability to work, or limits and maximums on drug and benefits plans. My passion head given me a lot of patience and compassion for others, but you don't see a lot of that back, even from medical professionals unfortunately. I hate feeling like a criminal who has to answer 20 questions correctly every time I pick up a T3 prescription (to manage pain for the really bad ones) - I know pharmacists have to be careful but my doctor and I have a good relationship and she would not prescribe them otherwise. I have no idea what 'normal' life would be like.”
>
> “It is VERY difficult to access critical mental health care services. Near impossible to receive government disability payments. No idea where to go to get advice on managing work. I was forced out because I didn't know my rights or what to ask for in order to get the short-term

disability that I deserved. Access to new medications is awful. be it waiting on Health Canada approvals, or negotiations for provincial formularies or insurance."

"It's heartbreaking to see the lack of knowledge and compassion that we encounter, we have to beg and push for more treatments and medication to helps us, we are continuously being looked at like attention seeking, depressive/anxious patients, drug seeking addicts. We are not taken seriously, and it takes many months or years for a diagnosis, acute treatment at home or preventatives. We are not recognized as people who are suffering from a complex and debilitation condition, but instead we get the acknowledgment of suffering migraines/chronic migraines but not the compassion and support we need. It's hard to find a specialist and they are spread so thin that it's really hard if not impossible to make an appointment between follow ups and the latter ones are a few minutes long if you consider that it's at the same time as your being injected with Botox that happens every 3 or more months. Not being able to work and not have any help to offset the amount of money that goes out of the family budget to pay out of pocket needed for accommodations, treatment and prevention of migraines is very high, not only for meds but also for accommodations needed (noise canceling earphones, special glasses that tend to be many) lifestyle changes, multidisciplinary approach (physio, ENT, Ophthalmologist, personal trainer for exercising with this disability, psychologist, massage therapist, diet, etc.)."

"Migraines have huge impacts in our lives, as I mentioned above, but also it impedes our cognitive function, emotion and physical, plus impacts everyone's mental and physical health around us."

"I constantly worry about how I'm going to get through this and how will we get through without bringing in an income and hemorrhaging money because right my big disability that is not recognized as such. I'm treated like a healthy person when I most certainly am not."

"I feel I have reached a plateau as does my healthcare team, my insurance and work. They have deemed me fully disabled, and I am resigned to that outcome after almost 2 plus years of continuous 5-7 pain. I have a high pain tolerance and that is only thing I think that allows me to function."

"I am learning new ways of living after being active, outgoing, and going to the gym 5-6 days a week 2-3 hours a day. Life is going to be what I make it and I am not saying it's rosy, but I will try my best to NOT sink into my manic depression disorder."

"Anything you can do to help us or anyone else coming home who has migraines would be amazing. It is an utterly lonely, debilitating and soul sucking disease. It takes away everything and is extremely hard to navigate and make people understand. It is not just a headache and if I just had a headache, I'd be happy with that."

To learn more about migraine, please refer to our Quality-of-Life survey report that will be posted in April on our website (www.migrainecanada.org)

Conflict of Interest Declaration — Migraine Canada & Migraine Quebec

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.

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

This submission was summarized and written solely by the staff at Migraine Canada and reviewed by Migraine Quebec, free from consultation, advice, influence or financial support from any outside individual, group, or company.

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.

Migraine Canada worked with a third party to create the on-line Quality of Life survey. Analysis was completed internally.

Migraine Canada independently developed and analyzed the second survey circulated for feedback on atogepant.

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.

Table 1: Financial Disclosures for Migraine Canada

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Abbvie Canada	–	–	–	X
Novartis Canada	–	–	–	X
Lundbeck Canada	–	–	–	X
Teva Canada	–	–	–	X
Eli Lilly Canad	–	–	X	–
Miravo Canad	–	–	X	–

Table 2: Financial Disclosures for Migraine Quebec

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Novartis Pharma Canada	–	–	–	X
Eli Lilly Canada	–	–	X	–
Aralez/Novo/Miravo	–	–	X	–
Teva Canada Innovation	–	–	–	X
Upjohn	X	–	–	–

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Allergan/Abbvie	–	–	X	–
Viatris (Upjohn/Pfizer)	–	X	–	–
Lundbeck	–	–	X	–

Women's Health Coalition of Alberta Society

Email from Women's Health Coalition of Alberta Society to Migraine Canada

The Women's Health Coalition of Alberta Society (WHC) is committed to creating a movement that empowers people to speak openly, learn and engage with purpose to address barriers, gaps, policies, and unconscious bias, that impact women's menstrual, reproductive, and sexual health. We are enabling advocacy, awareness, and education in gynecological, uro-gynecological, menstrual, uterine, and reproductive health, through all the ages and stages of a woman's life.

The WHC is pleased to support Migraine Canada's recommendations for access and reimbursement of atogepant as a therapeutic option for preventive treatment of episodic migraine.

The WHC is highly committed to ensuring that women have access to the right treatment and support at the right time, for improved health outcomes. An oral calcitonin gene-related peptide (CGRP) option for the treatment of episodic migraine offers significant treatment plan advantages that will be better tolerated and easier to adhere to.

Women's health matters and migraines affect women more often than men (80%). Severe and debilitating migraines are often associated with hormonal imbalances, perimenopause, and menopause – affecting as many as 25% of women. WHC members and stakeholders have reported that episodic menstrual and hormonal migraine attacks can be severe, causing pain, nausea, anxiety, and depression, and prompt absences from work, and opting out of family activities.

Women in their 40's, dealing with perimenopause, may be at increased risk of disease progression, more frequent attacks, and progression to chronic migraines. Conditions are complicated further by increased family and professional demands. Enhanced options for preventive treatment of migraines is significant to managing health and quality of life for women of all ages.

Recommendation of atogepant will not only improve treatment options, choice, and access for women dealing with hormonal migraine symptoms, it may raise clinician awareness of the importance of treating menstrual, perimenopause and menopausal conditions.

Thank you for taking the lead on advancing options for treatment and choice in the treatment of migraines. If you would like to address this further, please contact me at CarmenWHC@gmail.com.

Sincerely,

Carmen Wyton, Chair/President

March 10, 2023

Conflict of Interest Declaration — The Women's Health Coalition of Alberta Society
The Women's Health Coalition of Alberta has not received any assistance in preparing this letter of support and has not collected or analyzed data using sources outside of the organization.

Table 3: Financial Disclosures for The Women's Health Coalition of Alberta Society

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
AbbVie	–	X	–	–
Hologic	–	X	–	–
Allergan	–	X	–	–

Clinician Input

Canadian Headache Society

About the Canadian Headache Society
The Canadian Headache Society (CHS) is a scientific society of health care 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/

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

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 vague nerve simulator
- **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-pockets, 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, neuroleptics

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 is still present 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 2023. Options for migraine prevention available in 2022 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) and 2020 (fremanezumab). Eptinezumab has been approved in 2021 but is not yet marketed. The concept of CGRP blockade for migraine treatment is supported by a robust corpus of evidence, and these treatments are considered specific to migraine.

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 publicly in Alberta, Saskatchewan and Quebec. Erenumab did not reach an agreement with PcPA and therefore is not likely to be covered publicly. Galcanezumab and eptinezumab are under assessment. 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 is also the first oral drug to be exclusively developed for the preventive treatment of episodic migraine. 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). 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

Treatment Goals

The treatment goals of atogepant 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).

Treatment Gaps (Unmet Needs)

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 in an unpredictable manner)
- 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

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
- Patients who do not have coverage for certain treatments, particularly onabotulinumtoxinA and CGRP antibodies.

Place in Therapy

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 (oral preventives, onabotulinumtoxinA) thoug 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 could be an option, as both target different sensory fibers. OnabotulinumToxinA also has an effect on other peptides released from sensory fibers that could be complementary to CGRP blockade.
- Primary care providers 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 would be a great option to be prescribed 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 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 from a medical perspective.

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.

From a purely medical perspective, looking at studies of similar methodology and also acknowledging the lack of head-to-head trials, atogepant could be a 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 scientifically demonstrated pathophysiology, is also a strong element for patients who want to treat the cause of their disease. The opinion of neurologists specialized in headache medicine is quite clear on this.

Unfortunately, access to treatments is also 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 probably 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?

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

Would there be harm to patients submitted to drugs with a higher risk of side effects? Weight gain is harmful to health and is commonly seen with tricyclic. It is not easily reversible. 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 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. And older options such as valproate, flunarizine and pizotifen carry even higher risks of adverse events such as 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.

Therefore, awaiting the systematic literature review of our society, atogepant could be seen as a first line treatment from a medical perspective. Only financial arguments would justify a second-line place and the requirement of other oral preventives.

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

At present time, there is no scientifically supported way to predict the response to a treatment in a migraine patient, and this applies both to acute and preventive medications. Therefore, the choice of preventives is usually 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.

Therefore, a lot depends on the proposed cost for atogepant.

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 at present time in practice.

If it leads to the requirement of previous failures, then it could be used only after 2 or 3 other preventives. Evidence and experience suggest that some patients may respond to CGRP blockade with antibodies event 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.

It seems very unlikely that atogepant will be priced higher than CGRP antibodies. Therefore, if it comes after cheaper oral preventives, it could probably be used prior to CGRP antibodies, once again for financial reasons. From a medical perspective, effectiveness and tolerability are similar across RCTS for episodic migraine for CGRP antibodies and atogepant.

Since onabotulinumtoxinA is only approved for chronic migraine and atogepant for episodic migraine (for now, as future RCTs may change this), the algorithm for atogepant would be separate from the one for chronic migraine.

As a separate note, the dichotomial approach between episodic and chronic migraine is also under scrutiny as it does not represent the continuum of attack frequency in migraine. The future may allow a more precise approach with two arbitrarily defined categories.

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

Currently, there is no specific markers to suggest patients would respond to the medication under review.

The need for treatment increases with the attack frequency and severity (see the list of goals for migraine prevention). Still, the need for prevention and the importance of the migraine burden are underestimated by health care 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.

Still, the burden of episodic migraine is also worth 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 lowering expectations due to ineffective or poorly tolerated

treatments. Expectations for migraine treatment are now revisited in the light of specific therapies and it is quite interesting to observe this shift in paradigm where the term «migraine freedom» is starting to be used.

What is an «acceptable» migraine state is therefore under discussion and research is now demonstrating the burden associated with «high frequency episodic migraine» usually defined as 8 or more days of migraine per month. From a cost-effectiveness perspective, we must remind that 80% of people with migraine have less than 6 migraine days per month. Of course, the frequency is not the only parameter to take into account, 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 /month bar. Intervention before chronification is a therapeutic goal. Factors for chronification have been described. A high baseline frequency is a key factor for chronification. Even if there are no studies to demonstrate in long term cohorts that a successful preventive therapy can prevent chronification, it would be scientifically rational to think so. Experience in the clinic 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. Any physician treating migraine patient's wishes to prevent this painful scenario.

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.

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.

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.

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.

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 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.

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 (not

- 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.

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.

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 underline that a therapeutic success (for example a decrease in migraine frequency) should not be seen as a reason to discontinue treatment. This quite absurd reasoning has been seen with other therapies for migraine. We always wondered if any doctor would stop an anti-epileptic if seizures are controlled, or an anti-hypertensive if blood pressure is now within normal limits. A patient who responds to atogepant should be allowed to stay on treatment.

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

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

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.

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.

Conflict of Interest Declarations — Canadian Headache Society

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 refer to the Procedures for CADTH Drug Reimbursement Reviews (section 6.3) for further details.

Did you receive help from outside your clinician group to complete this submission?

No.

Did you receive help from outside your clinician group to collect or analyze any information used in this submission?

No.

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: Tasjeel Ansari, MD, FRCPC, DABPN

Position: Headache Neurologist

Date: 09/03/2022

Table 4: COI Declaration for Canadian Headache Society — Clinician 1

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
AbbVie (Honoraria)	X	—	—	—
Lundbeck (Honoraria)	X	—	—	—
Eli Lilly (Honoraria)	X	—	—	—

Declaration for Clinician 2

Name: Lik Hang Tommy Chan, MBBS, FRCPC, DABPN

Position: Headache Neurologist

Date: 12/03/2022

Table 5: COI Declaration for Canadian Headache Society — Clinician 2

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Teva (Educational Grant)	X	—	—	—
Lundbeck (Honoraria)	—	X	—	—
Eli Lilly (Honoraria)	—	X	—	—
Novartis (Honoraria)	—	X	—	—
Miravo (Honoraria)	—	X	—	—
AbbVie (Honoraria)	—	X	—	—

Note: No direct or indirect compensation received for the purpose of this submission or related to this product.

Declaration for Clinician 3

Name: Danny Adel Monsour, MD, FRCPC

Position: Headache Neurologist

Date: 14/03/2022

Table 6: COI Declaration for Canadian Headache Society — Clinician 3

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	—	—	—

Declaration for Clinician 4

Name: Elizabeth Leroux, MD, FRCPC

Position: Headache Neurologist, President - Canadian Headache Society

Date: 16/03/2022

Table 7: COI Declaration for Canadian Headache Society — Clinician 4

Company	$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	–
Lundbeck	–	–	X	–
McKesson	–	X	–	–
Miravo	–	X	–	–
Novartis	–	–	X	–
Teva	–	–	X	–

Declaration for Clinician 5

Name: William Kingston, MD, FRCPC, FAHS

Position: Headache Neurologist, Board member – Canadian Headache Society

Date: 16-03-2022

Table 8: COI Declaration for Canadian Headache Society — Clinician 5

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	–	–

ISSN: 2563-6596

Redactions: Confidential information in this document may be redacted at the request of the sponsor in accordance with the CADTH Drug Reimbursement Review Confidentiality Guidelines

Stakeholder Input: The views expressed in each submission are those of the submitting organization or individual; not necessarily the views of CADTH or of other organizations. As such, they are independent of CADTH and do not necessarily represent or reflect the view of CADTH. No endorsement by CADTH is intended or should be inferred. By filing with CADTH, the submitting organization or individual agrees to the full disclosure of the information. CADTH does not edit the content of the submissions.

CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no identifying personal information or personal health information is included in the submission. The name of the submitting organization or individual and all conflict of interest information are included in the submission; however, the name of the author, including the name of an individual patient or caregiver submitting the patient input, are not posted.

Accessibility: CADTH is committed to treating people with disabilities in a way that respects their dignity and independence, supports them in accessing material in a timely manner, and provides a robust feedback process to support continuous improvement. All materials prepared by CADTH are available in an accessible format. Where materials provided to CADTH by a submitting organization or individual are not available in an accessible format, CADTH will provide a summary document upon request. More details on CADTH's accessibility policies can be found here.

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

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