Single Technology Appraisal

Atogepant for preventing migraine [ID5090]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Atogepant for preventing migraine [ID5090]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

Pre-committee documents:

1. **Company submission** from AbbVie

2. **Company summary of information for patients (SIP)** from AbbVie

3. **Clarification questions and company responses:**
   a. Main response
   b. Additional responses

4. **Patient group, professional group and NHS organisation submissions** from:
   a. Migraine Trust
   b. Association of British Neurologists
   c. British Association for the Study of Headache

5. **External Assessment Report** prepared by BMJ-TAG

6. **External Assessment Report – factual accuracy check**

7. **Expert personal perspectives** from:
   a. Steph Weatherley, Information and support adviser – patient expert, nominated by The Migraine Trust
   b. Brendan Davies, Consultant Neurologist, Clinical lead, Midlands Regional Headache clinic – clinical expert, nominated by AbbVie

Post-committee documents:

8. **Company updated long-term discontinuation rate calculation**

9. **External Assessment Group response to updated long-term discontinuation rate calculation** prepared by BMJ-TAG

10. **External Assessment Group post-committee cost-effectiveness results** prepared by BMJ-TAG

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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ID5090

Document B

Company evidence submission

File name	Version	Contains confidential information	Date
Atogepant in Migraine_Document B_CON	V1	Yes	29th September 2023

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Abbreviations

Abbreviation	Definition
3+ TF	Patients in whom ≥3 prior preventive treatments have failed
A&E	Accident and emergency
AE	Adverse event
AIM-D	Activity impairment in migraine - diary
ALT	Alanine transaminase
AMO	Acute medication overuse
AST	Aspartate transaminase
ATO	Atogepant
BID	Twice daily
BMI	Body Mass Index
BNF	British National Formulary
BSC	Best supportive care
CFB	Change from baseline
CGRP	Calcitonin gene-related peptide
CI	Confidence interval
CM	Chronic migraine
CRD	Centre for Reviews and Dissemination
CSR	Clinical study report
CYP3A4	Cytochrome P450 3A4
DIC	Deviance Information Criterion
DNC	Did not converge
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	External Assessment Group
eDiary	Electronic diary
EM	Episodic migraine
EMA	European Medicines Agency
EQ-5D	European Quality of Life 5 Dimensions
EQ-5D-3L	European Quality of Life 5 Dimensions 3 Level Version
ERG	Evidence Review Group
EU	European Union
FDA	Food and Drug Administration
FE	Fixed effect
FTA	Fast track appraisal
FTE	Full-time equivalent
GP	General practitioner
HIT-6	Headache impact test-6
HR	Hazard ratio
HRQoL	Health-related quality of life

ICER	Incremental cost-effectiveness ratio
ICHD	International Classification of Headache Disorders
ICHD-3	International Classification of Headache Disorders 3rd edition
IP	Informative prior
ITT	Intent-to-treat
IWRS	Interactive Web Response System
IV	Intravenous
LS	Least squares
LSMD	Least squares mean difference
mAb	Monoclonal antibody
MAR	Missing-at-random
Max	Maximum
MD	Mean difference
MHD	Monthly headache day
MHRA	Medicines and Healthcare products Regulatory Agency
MIDAS	Migraine disability assessment
MIMS	Monthly Index of Medical Specialties
Min	Minimum
mITT	Modified intent-to-treat
MMD	Monthly migraine days
MMRM	Mixed Model for Repeated Measures
MOH	Medication overuse headache
MSQ	Migraine-specific quality-of-life questionnaire
MSQ-EF	Migraine specific quality of life emotional function
MSQ-RFP	Migraine specific quality of life role function-preventive
MSQ-RFR	Migraine specific quality of life role function-restrictive
MUD	Medication use day
N	Number of patients within a specific category
N1	Number of patients with ≥1 non-missing post-baseline value
NA	Not applicable
NHS	National Health Service
NHWS	National Health and Wellness Survey
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NSAID	Non-steroidal anti-inflammatory drug
OATP	Organic anion transporting polypeptide
OLE	Open-label extension
ONS	The Office for National Statistics
OR	Odds ratio
P-gp	P-glycoprotein
PAS	Patient access scheme
PBO	Placebo

PGI-S	Patient Global Impression of Severity scale
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcome
PSS	Personal social services
PSSRU	Personal social services research unit
PT	Preferred term
Q3	Third quarter
Q3M	Once per quarter
QALY	Quality-adjusted life year
QALE	Quality-adjusted life expectancy
QD	Once daily
QM	Once a month
RCT	Randomised controlled trial
RE	Random effect
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SNRI	Serotonin-norepinephrine reuptake inhibitor
SOC	System organ class
SSRI	Selective serotonin reuptake inhibitor
STA	Single technology appraisal
TA	Technology appraisal
TE	Treatment effect
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TF	Treatment failure
Tx	Treatment
U/L	Upper limit
UK	United Kingdom
ULN	Upper limit of normal
US	United States
USA	United States of America
V	Visit
VAT	Value-added tax
VP	Vague prior
WHO	World Health Organisation
WTP	Willingness-to-pay

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

Atogepant is an orally administered calcitonin gene-related peptide (CGRP) receptor antagonist that is licensed for prophylaxis of migraine in adults who have at least 4 migraine days per month (i.e. both episodic migraine [EM] and chronic migraine [CM]) at a dose of 60 mg once daily (QD), the dose covered by this submission.

In accordance with clinical expert feedback, atogepant is intended to be positioned for use within the National Health Service (NHS) as a preventive treatment for patients who have at least 4 migraine days per month and in whom at least 3 preventive drug treatments have failed (i.e., the fourth-line of therapy which accounts for a subgroup of the population detailed in the technology's marketing authorisation).[1] This positioning is fully aligned with the population for which injectable monoclonal antibodies (mAbs) that also block CGRP-related signalling pathways (CGRP mAbs) have received positive recommendations from the National Institute for Health and Care Excellence (NICE); galcanezumab (TA659), erenumab (TA682), and fremanezumab (TA764).[2-4]

According to UK clinical experts consulted during an advisory board and in subsequent individual consultations, atogepant is anticipated to be offered as an alternative to CGRP mAbs in the preventive treatment of migraine, with the technologies expected to have both similar efficacy and positioning.[5] Atogepant and the CGRP mAbs work in a similar way to suppress CGRP activity,[3, 4, 6, 7] are each intended for use in an identical population of patients across the full migraine continuum of patients with EM and CM,[2-4, 8] and can be self-administered by the patient at home so do not require in-clinic administration.[9]

CGRP mAbs are considered to be a key fourth-line preventive treatment across the UK. Clinical expert feedback and UK-wide market share data indicates that the majority of patients who are receiving NICE-recommended fourth-line preventive treatments for migraine are currently receiving a CGRP mAb, while new patients entering the fourth-line of therapy are typically initiated on a CGRP mAb over other NICE-recommended therapies.[5, 10, 11] CGRP mAbs were considered to be relevant comparators in the recent NICE appraisal of another CGRP inhibitor (eptinezumab [TA871; March 2023]) for the preventive treatment of patients who have at least 4 migraine days per month and in whom at least 3 preventive drug treatments have failed.[12] In agreement with this decision-making, CGRP mAbs (galcanezumab, erenumab, fremanezumab) are deemed to be appropriate comparators for the appraisal of atogepant.[2-4, 8]

While there are several other treatments that have received recommendations from NICE as preventive treatments for migraine, these do not represent relevant comparators for this appraisal.

Injectable botulinum toxin type A is recommended by NICE as a preventive treatment in a subset of adult patients which is not fully aligned to that of atogepant or the CGRP mAbs, given that it is available for those with chronic migraine only (≥15 headache days per month, of which ≥8 are with migraine [TA260]), if:[13]

- They have not responded to at least 3 prior pharmacological prophylaxis therapies
- Their condition is appropriately managed for medication overuse

Clinical experts have indicated that patients often choose to initiate on CGRP mAbs first and foremost due to extensive waiting lists for botulinum toxin type A (Section B.1.3.3) and in some cases, the need to travel to clinics capable of administering this treatment.[5, 10] Therefore, immediate access to botulinum toxin type A is restricted as a result of NHS capacity constraints, relating to an insufficient number of skilled injectors and clinics capable of administering botulinum toxin type A, as well as variations in botulinum toxin type A administration capabilities across the UK.[5] For this reason, the proportion of fourth-line patients with CM receiving botulinum toxin type A is on the decline.[10] Furthermore, clinical expert opinion is that atogepant would not be considered an alternative to botulinum toxin type A due to the requirement for dedicated in-clinic time and upfront staff investment for botulinum toxin type A administration. The exclusion of botulinum toxin type A as a relevant comparator is consistent with the recent NICE appraisal of eptinezumab (TA871), another CGRP mAb recommended for preventing migraine across both EM and CM.[12]

Eptinezumab (TA871) and rimegepant (TA906) have been recommended by NICE for the preventive treatment of migraine very recently.[12, 14] As such, eptinezumab and rimegepant are currently associated with slow uptake and very low market share, accounting for up to [redacted]% and [redacted]% of all treated migraine patients who have experienced ≥3 preventive treatment failures.[10, 11] Therefore, clinical experts have confirmed that they are not appropriate comparators as they are yet to become established care in the UK, having only received recommendations from NICE for preventing migraine on 1 March 2023 and 5 July 2023, respectively.[12, 14] Clinical expert opinion provided during the NICE evaluation of eptinezumab indicated that given its intravenous route of administration, it would be reserved for patients with severe migraine attacks or those who are unable to self-administer other CGRP mAbs subcutaneously. This also leads to an issue of inequitable access to eptinezumab due to a wide variation in in-hospital administration capabilities across the UK. On the other hand, while rimegepant could be self-administered at home, its use is restricted to a subpopulation of migraine patients (i.e., those with EM only) which is not fully aligned with atogepant.[12, 15]

As such, atogepant should be considered as an alternative to CGRP mAbs for the prophylaxis of migraine in adults who have at least 4 migraine days per month. In the context of clinical decision making, atogepant is expected to be considered interchangeable with treatments used at the same clinical position, which are galcanezumab, erenumab, and fremanezumab.

Given the disabling nature of migraine and significant impact that it can have on a patient's quality of life, there is a critical need for novel treatments. Inadequately managed patients experience debilitating symptoms which can severely impact their everyday life, mental health, and relationships. Migraine can also be associated with a substantial economic burden driven by high rates of clinician visits (Section B.1.3.2). Despite this, currently available treatment options for patients in whom three or more preventive drug treatments have failed are limited to injectable therapies only and migraine remains a leading cause of disability (Section B.1.3.3). The decision problem addressed within this submission is outlined in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with migraine who have 4 or more migraine days a month, in whom at least 3 preventive drug treatments have failed	As per the NICE final scope	The population is aligned to a subgroup of the UK marketing authorisation, the NICE-recommended population for the available CGRP mAbs, as well as the anticipated positioning of atogepant in UK clinical practice based on feedback from clinicians.[1-5] This aligns with the populations for which galcanezumab, erenumab and fremanezumab received a recommendation from NICE.[2-4] In addition, feedback from clinicians suggests that atogepant is suitable for use in patients for whom ≥3 prior preventive treatments have failed.[5]
Intervention	Atogepant	Atogepant (60mg[a]); as per the NICE final scope	NA
Comparator(s)	• Botulinum toxin type A (CM only) • Galcanezumab • Erenumab • Fremanezumab • Eptinezumab (subject to NICE evaluation) • Rimegepant (subject to NICE evaluation)	• Galcanezumab • Erenumab • Fremanezumab	CGRP mAbs (galcanezumab, erenumab, fremanezumab) are deemed to be the appropriate comparators for this appraisal; given that atogepant and the CGRP mAbs are preventive treatments that cover the same patient population which each work in a similar way to suppress CGRP activity, can be self-administered at home, and offer similar health benefits.[12] Eptinezumab (intravenous [IV] CGRP mAb) and rimegepant (oral CGRP receptor inhibitor) have both recently received recommendations from NICE (1 March 2023 and 5 July 2023, respectively).[15, 16] Due to recency of these recommendations, and wide variation in in-hospital administration capabilities for eptinezumab across the UK due to its IV route of administration, clinical experts and market share data have indicated that these drugs do not constitute established clinical practice.[10, 11] Moreover, the NICE recommendations associated with these therapies had not been published at the time of scoping. As such, neither are considered relevant comparators.

			Clinical experts noted that botulinum toxin type A is not a relevant comparator for atogepant due to the requirement for dedicated in-clinic time and upfront staff investment. It was also noted that the proportion of patients receiving botulinum toxin type A is likely to decrease for these reasons with market share forecasts indicating that the majority of patients experiencing ≥4 migraine days per month who are receiving treatment, receive CGRP mAbs as a preventive therapy.[5] Market share data further indicate that the large majority of patients across the UK are initiated on CGRP mAbs ahead of botulinum toxin type A, with clinical experts explaining that patients typically initiate on CGRP mAbs currently due to NHS capacity issues associated with botulinum-toxin type A administration and resulting waiting lists.[10, 11] As such, botulinum toxin type A is not considered by the company to be a relevant comparator.
Outcomes	The outcome measures to be considered include: • Change in frequency of migraine days per month • Change in frequency of headache days per month • Change in severity of headaches and migraines • Change in number of cumulative hours of headache or migraine on headache or migraine days • Changes in acute pharmacological medication given • AEs of treatment • HRQoL	As per the NICE final scope	NA
Economic analysis	• The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. • The reference case stipulates that the time horizon for	• A cost-effectiveness analysis has been conducted in Microsoft Excel to estimate the incremental costs of atogepant versus galcanezumab, erenumab, and fremanezumab	The economic analysis presented is aligned with the final NICE scope for this submission.

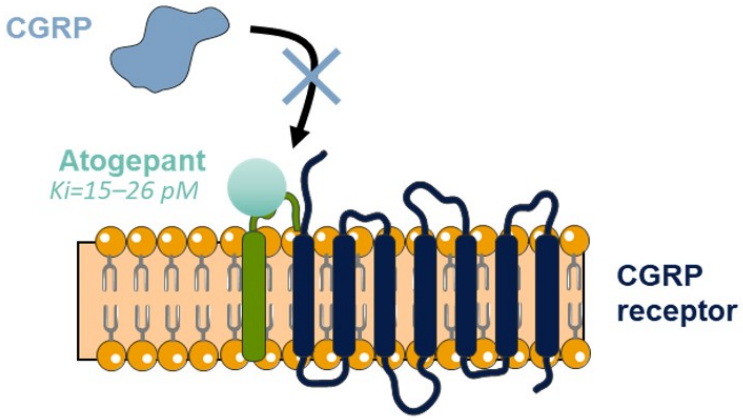
	estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. • Costs will be considered from an NHS and PSS perspective. • The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. • The availability and cost of biosimilar and generic products should be taken into account.	• A lifetime time horizon for assessing costs was used • Costs were considered from an NHS and PSS perspective • A PAS for atogepant has been included as part of the analysis	
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • Those with either EM or CM • Subgroups defined by the number of previous prophylactic treatments • Subgroups defined by the frequency of EM (in those with EM)	This submission will focus on patients with ≥3 prior preventive treatment failures in line with the NICE final scope. Subgroup analyses were conducted where applicable. Subgroups defined by the frequency of EM are not provided.	Migraine is a disease continuum in which patients can be classified as having either EM or CM based on the frequency of monthly headache days. The patient population addressed in this submission represents two subgroups of the population specified in the NICE final scope: patients with EM and CM with ≥3 prior preventive treatment failures. This appraisal did not consider subgroups defined by frequency of EM. Evidence presented in the prior appraisal of galcanezumab (TA659) suggests that patients with high frequency EM have a similar disease burden as patients with CM,[2] while published literature have demonstrated that migraines are disabling for patients with 3 or more monthly migraine days.[17] However, due to a lack of consensus on the definition of, and clinical distinctiveness of high frequency EM, NICE concluded the frequency of migraines (in those with EM) was not an appropriate subgroup for economic analysis. As such, no subgroup analysis has been explored in this submission.

Footnotes: [a]Outside of the scope of this submission, atogepant 10 mg QD is also licensed for patients who require dose modifications (concomitant use of strong CYP3A4 or OATP inhibitors), or for special populations with severe renal impairment or end-stage renal disease.
Abbreviations: AE: adverse events; CGRP: calcitonin gene-related peptide; CM: chronic migraine; CYP3A: cytochrome P450 3A4; EAG: External Assessment Group; EM: episodic migraine; mAbs: monoclonal antibodies; HRQoL: health-related quality of life; NA: not applicable; NICE: National Institute of Health and Care Excellence; NHS: National Health Service; OATP: organic anion transporting polypeptide; PAS: patient access scheme; PSS: Personal Social Services; UK: United Kingdom.

B.1.2 Description of the technology being evaluated

A summary of the mechanism of action, marketing authorisation status, costs and administration requirements associated with atogepant are presented in Table 2.

Table 2: Technology being evaluated

UK approved name and brand name	Atogepant (Aquipta™)
Mechanism of action	CGRP is a neuropeptide and potent dilator of both peripheral and cerebral blood vessels. It modulates nociceptive signalling and inflammation, and also functions as a vasodilator.[6] CGRP appears to be involved in the pathophysiology of migraine, as evidenced by increased blood levels of CGRP during migraine attacks, the induction of headaches by infusion of CGRP, and the effects of CGRP-targeted therapies in the treatment of migraine attacks and preventive treatment of migraine.[18-22] The first CGRP antagonists licensed for migraine prevention were mAbs, which require SC injection or IV administration.[18] Atogepant is a potent, selective, oral, small molecule, CGRP receptor antagonist that blocks the binding of the CGRP to its receptor and antagonises receptor function.[6] **Mechanism of action for atogepant**  **Source:** Goadsby, et al 2019.[22] **Abbreviations**: CGRP: calcitonin gene-related peptide.
Marketing authorisation/CE mark status	The marketing authorisation for atogepant was received on 30th August 2023 for the prophylaxis of migraine in adults who have at least 4 migraine days per month.[1]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Atogepant is indicated for prophylaxis of migraine in adults who have at least 4 migraine days per month.[1] This submission covers a subpopulation of this indication: adults for whom ≥3 preventive treatments have failed.
Method of administration and dosage	Atogepant 60 mg is orally administered once daily with or without food.[a,6]

Additional tests or investigations	NA
List price and average cost of a course of treatment	The list price of atogepant is £463.68 per 28-tablet pack
Patient access scheme/commercial arrangement (if applicable)	A confidential simple patient access scheme (PAS) will apply to atogepant in this indication. The with-PAS price for atogepant is [redacted] per 28-tablet pack, equating to a discount to the list price of [redacted].

Footnotes: [a] A 10mg once daily dose is also recommended in the SmPC, but is not covered by this submission; the 10 mg dose is licensed to be used in those who require dose modifications (concomitant use of strong CYP3A4 or OATP inhibitors) or special populations with severe renal impairment or end-stage renal disease.
Abbreviations: CGRP: calcitonin gene-related peptide; CYP3A: cytochrome P450 3A4; IV: intravenous; MHRA: Medicines and Healthcare products Regulatory Agency; NA: not applicable; NHS: National Health Service; OATP: organic anion transporting polypeptide; SC: subcutaneous; SmPC: Summary of Product Characteristics; Q3: third quarter; WHO: World Health Organisation.

B.1.3 Health condition and position of the technology in the treatment pathway

Summary of migraine

- Migraine is a headache disorder characterised by recurrent attacks lasting between 4–72 hours and is one of the most common neurological disorders worldwide affecting around 1 in 7 people[23-25]
- Migraine is a disease continuum; although it can be categorised as either EM or CM, but these definitions are largely considered arbitrary by clinical experts[5, 25, 26]
  - EM is defined as <15 headache days per month (affecting approximately 90% of patients)[27, 28]
  - CM is defined as ≥15 headache days per month, of which ≥8 have features of migraine, for >3 months[27, 28]
- Migraine is the third leading cause of disability in the UK, and the first among young women globally[29, 30]
- Attacks are more than a headache, they are frequently accompanied by sensitivity to light (91.1%) and sound (83.4%), difficulty concentrating (80.2%), nausea and vomiting (78.6%), fatigue (74.5%), neck pain (72.1%) as well as sensitivity to smells (63.3%)[31]
- These debilitating symptoms can severely impact the ability of people with migraine to lead a normal life, affecting their mental wellbeing, physical function, daily activities, working lives, and relationships[32]
- Furthermore, migraine is a highly comorbid disease, with common comorbidities including insomnia, depression, and anxiety.[33] These comorbidities further increase the disease burden for people with migraine, as well as the risk of progression of the disease to CM[33]

Current treatment pathway and unmet need

- Preventive treatments are key in reducing the frequency, severity, and duration of migraine attacks, in patients with ≥4 migraine days a month.[34] They also reduce the development of medication overuse headaches[34]
- Available oral prophylactic treatment options (beta-blockers, antiepileptics and antidepressants) are not migraine-specific.[35, 36] Adherence and persistence to these medications is poor among patients due to suboptimal efficacy and poor tolerability[35, 36]
- NICE recommend the CGRP monoclonal antibodies (mAbs), galcanezumab, erenumab and fremanezumab for migraine prophylaxis in EM and CM for patients for whom ≥3 preventive treatments have failed.
  - However, there are limitations associated with these treatments including slow rates of drug clearance, variable treatment effect between doses, observed rates of discontinuation and restricted access[2, 37-40]
  - Furthermore, these CGRP mAbs are only available via subcutaneous (SC) injection, which may be seen as an inconvenient, intrusive, and painful mode of administration by patients[38, 41]
- Botulinum toxin type A is approved by NICE for migraine prevention in a subset of patients with CM only, for whom ≥3 preventive treatments have failed[42]
  - There are also limitations associated with botulinum toxin type A, which are administered via up to 39 intramuscular (IM) injections.The need for specialist clinicians with the necessary training to administer this treatment can lead to capacity constraints and extensive waiting times.[5] Therefore clinicians would not consider atogepant as an alternative to botulinum toxin type A.
- Recently, a further two therapies have been recommended by NICE in the same indication, eptinezumab (1 March 2023) and rimegepant (5 July 2023).[15, 16] However, neither eptinezumab nor rimegepant are considered established clinical practice[15, 16]
- In line with the anticipated place in the treatment pathway, galcanezumab, erenumab and fremanezumab represent relevant comparators to atogepant in this submission.[42]

Position of atogepant in the treatment pathway

- Atogepant is a migraine-specific, small molecule, CGRP receptor inhibitor that will be positioned as an option alongside the specified CGRP mAbs in patients for whom ≥3 preventive treatments have failed
- Atogepant 60 mg is orally administered once daily (QD) and has shown efficacy, safety, and tolerability in prophylactic treatment of migraine[6]
- Atogepant has a short half-life which facilitates flexibility of prescribing in patients who need to discontinue treatment due to unplanned pregnancy or in patients trying to conceive, and also in the management of adverse events[6]
- Atogepant would offer an alternative to the subcutaneously injected CGRP mAbs, addressing the unmet need for the first oral treatment option for the preventive treatment of both EM and CM in patients for whom ≥3 preventive treatments have failed, with minimal budget impact.

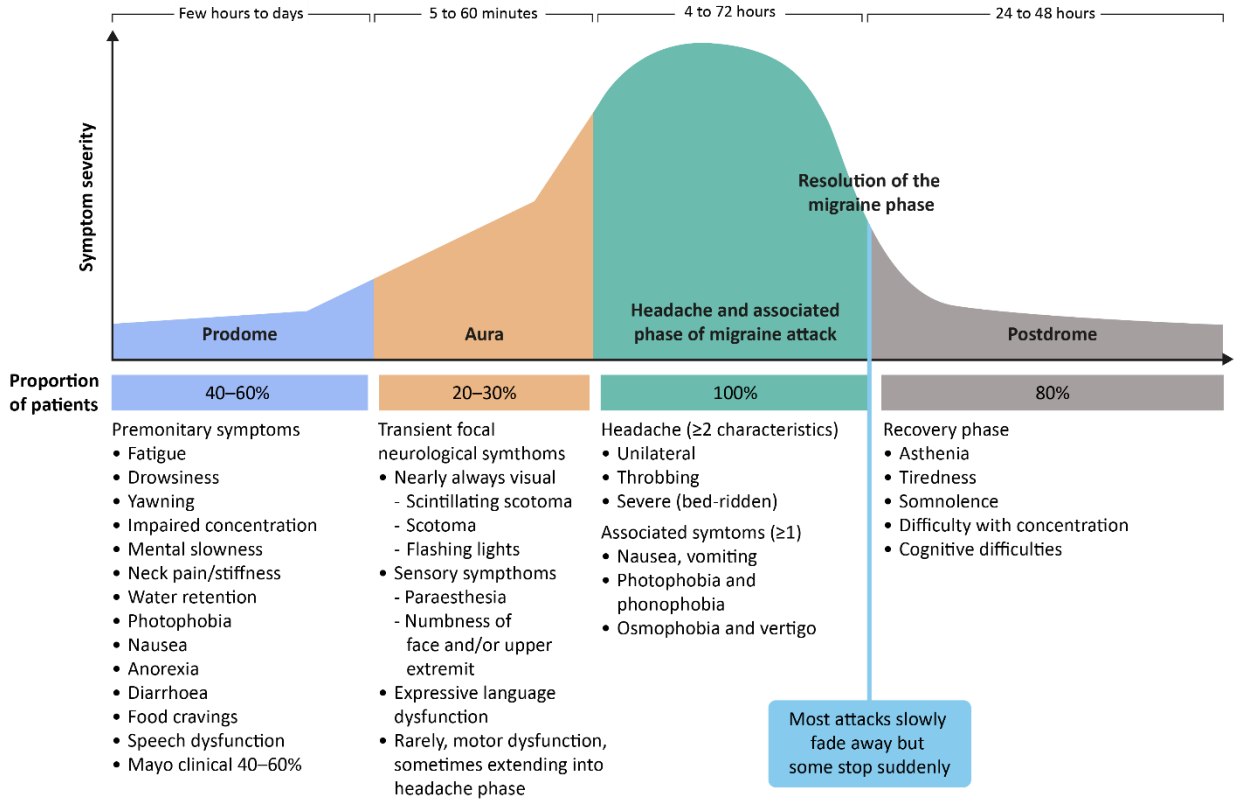
B.1.3.1 Health condition

Disease overview

Migraine is a neurological disease characterised by recurrent, debilitating headaches of moderate to severe intensity which may last 4–72 hours; it is the second leading cause of disability worldwide (third in the UK).[25, 27, 29, 30] Migraine attacks may also be accompanied by other symptoms which negatively impact patient quality of life, which are experienced either before or after the headache itself.[25]

Migraine is characterised by a multiphasic process which includes a prodrome phase, an aura phase, the migraine pain phase, the resolution of the migraine and the postdromal phase (Figure 1). This process consists of various signs and symptoms, thus highlighting the complexity of migraine and the involvement of numerous neural networks and brain regions throughout an attack.[43] Migraine attacks can therefore fluctuate in frequency and severity and are often unpredictable.[44, 45]

Figure 1: Phases of migraine



Source: Adapted from Ferrari et al 2022;[32] Karsan and Goadsby 2018;[46, 47] Mayo Clinic: Migraine Aura.[48]

Classifications of migraine

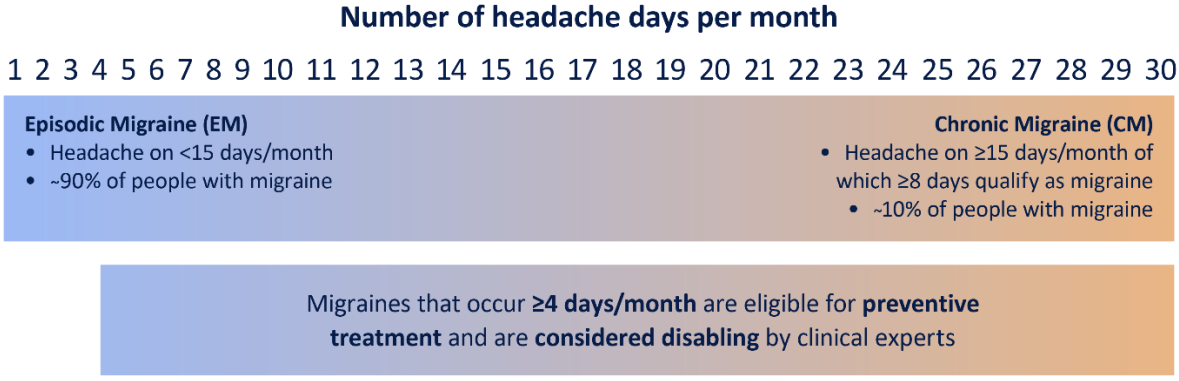
Migraine is a disease continuum, with migraines causing disability in patients with three or more monthly migraine days (MMDs).[17] In particular, headache severity is highly correlated with disability and productivity.[49, 50] However, the International Headache Society defines migraine in terms of two classifications: EM (<15 headache days per month) which accounts for approximately 90% of patients with migraine, and CM (≥15 headache days per month of which ≥8 days qualify as migraine) which accounts for approximately 10% of patients with migraine.[25, 27, 28]

Whilst there are important differences between the two ends of the spectrum in terms of disease severity, advisory board feedback from clinical experts experienced in the treatment of migraine suggests that the relationship between headache days per month and disability is not linear, and EM and CM represent artificial classifications.[5, 51] The clinical experts agreed that migraine should be considered a single disease, as the distinction between EM and CM was seen to be an artificial boundary which is both simplistic and not clinically meaningful. They noted that there were no specific biomarkers to distinguish between the two subgroups and highlighted that the distinction between EM and CM is an artefact of methodological trial design and regulatory processes.[13] This distinction was carried forward to guide NICE's decision-making in migraine appraisals following the recommendation of botulinum toxin type A specifically in the CM population, in line with its licence.[13] Published literature have demonstrated that migraines are disabling with at least 3 MMDs,[17] with no correlation between headache frequency and either disability or productivity loss.[49, 50] Instead, higher headache intensities are associated with greater headache-related disability,[49] and productivity is highly correlated with headache pain intensity.[50]

In addition to limitations in the clinical relevance of EM and CM subgroups; patients with migraine are likely to fluctuate between EM and CM over time and progression from EM to CM occurs at a rate of 2.5% per year.[52, 53] Transition from CM to EM is also possible, particularly with effective prophylactic treatment, highlighting the high level of short-term variability between the classifications.[5] The Chronic Migraine Epidemiology and Outcomes Study, using data from 5,464 repondents with EM and 526 respondents with CM, found that nearly three quarters of people with CM at baseline transition from CM to EM at least once over the course of a year.[54] Similarly, the American Migraine Prevalence and Prevention study found that 26% of people with CM experienced remission over a 2-year period.[55]

A summary of migraine as a disease continuum is presented in Figure 2.

Figure 2: Classifications of migraine



Source: International Classification of Headache Disorders, 3rd edition;[25] AbbVie, Atogepant in Migraine UK Advisory Board Meeting Report, 2022.[5]

Aetiology

Although the aetiology of migraine is not fully understood, it has been linked to genetic factors, environmental factors, certain comorbid conditions and stress.[34, 56] Environmental factors that can potentially evoke an attack include hormonal fluctuations, comorbid diseases, sensory stimuli, fatigue, food and changes in the environment or habits.[52] Comorbid conditions associated with an increased migraine risk include allergies, respiratory illnesses, cardiovascular

disorders, psychiatric disorders, arthritis, obesity, non-cephalic pain and ulcers.[52] Comorbid conditions are more common in patients with more severe disease.[52]

Epidemiology

Migraine is one of the most common neurological disorders worldwide affecting around 1 in 7 people.[23, 24] Limited data on the incidence of migraine are available. However, the annual incidence of migraine in the general population from prospective cohort studies ranges from <1% to 2% or approximately 8 to 14 per 1,000 person-years.[57-59] In the UK, it is estimated that over 10 million people experience the disease.[60] It is expected that, each year, there are approximately 14,500 patients in England (as calculated in the buget impact analysis) with ≥4 migraines per month who have experienced ≥3 prior preventive treatment failures, and therefore would be eligible for treatment with atogepant.

B.1.3.2 Disease burden

Clinical burden

Patients with migraine frequently experience debilitating symptoms that can have a severe negative impact on their mental wellbeing, physical function, daily activities, and ability to lead a normal life, and as a result, migraine represents the third leading cause of disability in the UK.[23, 29, 30, 52, 61, 62] The Global Burden of Disease 2016 study further reported that migraine was the leading cause of years lived with disability worldwide in both males and females for the age group 15–49 years.[63]

Migraine symptoms are severe and incapacitating.[64] During a migraine attack, patients can experience various neurological symptoms, namely sensitivity to light (91.1%) and sound (83.4%), difficulty concentrating (80.2%), nausea and vomiting (78.6%), fatigue (74.5%), neck pain (72.1%) as well as sensitivity to smells (63.3%).[31] Over 70% of patients experience cutaneous allodynia, the perception of pain when non-painful stimuli are applied to the painful skin area.[43] Migraines typically last between 4 and 72 hours[25] but can have a much longer duration; in a global study of people with migraine, 44% of people with ≥4 monthly headache days (MHDs) reported migraine attacks lasting 1 to 2 days or more and 19% reported attacks lasting longer than 3 days.[65]

Furthermore, as shown in Figure 1, the impact of migraine is not limited to the attack itself. For 40–60% of patients, attacks can begin with prodromes such as fatigue, excessive yawning, cravings for particular foods, and mood changes, which can last from a few hours to days.[25, 47, 48] Aura, a short-term sensory disturbance, can precede or sometimes accompany the attack and affects approximately 20% patients with migraine.[25, 40, 48] Types of aura include visual, sensory, speech and/or language, motor, brainstem, and retinal disturbances.[25] Following the migraine attack, some patients can experience a migraine hangover (or postdrome) and have similar symptoms to the prodrome phase such as fatigue, inability to concentrate, and mood changes.[32]

Despite these debilitating symptoms, the burden of migraine is often underestimated and there is a misconception of migraine being limited to headaches only. In reality, migraines have been shown to be significantly more painful than tension-type headaches.[66] In a study including 244 women diagnosed with migraine who had experienced childbirth (on a rating scale from 0–10), the pain of a typical migraine was rated as 7.1, childbirth as 7.3, and the worst migraine pain was given a rating of 8.6.[67] The symptoms associated with migraine can also be underdiagnosed. A survey conducted by the Migraine Trust found that 52% of people who had experienced a migraine attack in the past had not been diagnosed with migraine. Of those who had been

diagnosed, 51% had waited more than a year for their diagnosis. Furthermore, only around one third of people with migraine were diagnosed on their first visit to a health-care professional, and 29% had returned five or more times before they received a correct diagnosis.[68]

Patients suffer from migraine symptoms on a recurring and sometimes frequent basis. This high symptom severity and pain can also result in patients overusing acute migraine medication which can lead to disease progression along the migraine spectrum due to medication overuse headaches (MOH).[69-71]

In addition to the considerable symptom burden, migraine is associated with psychological comorbidities, including comorbid anxiety and comorbid depression.[33] In fact, depression affects almost 80% of people with migraine at one time or another, and patients with migraine are 2–4 times more likely to experience depression than patients who do not have migraine.[33, 72, 73] Furthermore, those with migraine are three times more likely to experience anxiety; as between migraines, patients may worry in anticipation of the next painful attack and face anxiety over hindrance to future plans or activities.[33, 74] Migraine is also associated with cardiovascular disorders, neurologic diseases, sleep conditions, inflammatory conditions, and chronic pain conditions.[33] People with migraine are reported to be three times more likely to experience anxiety, insomnia, or gastric ulcers than those without migraine.[33] These comorbidities further increase the disease burden for people with migraine, as well as the risk of progression of the disease.[33] These comorbid conditions can also complicate the diagnosis and treatment options for patients with migraine, making the management of the disease more difficult.[33]

Migraine disproportionately affects women, as it is approximately two to three times more common in women than men.[17, 27, 64, 75, 76] In women, migraine attacks tend to be longer in duration, with a pattern of increased risk of headache recurrence, greater disability and a longer period of time needed to recover.[77] This disparity may be due to the influence of hormones, genetic factors and exposure to environmental stressors.[52] On the other hand, as migraine is less prevalent in men it can be under-recognised, under-reported and under-treated in men.[52]

Humanistic burden

Migraine attacks have a profound impact on all aspects of individuals' lives. A survey of people with migraine with ≥4 MMDs across 16 countries in Europe, South America, Asia and Australia found that migraine affected overall health and wellbeing (69%), social life (60%), work/career (56%), or relationship with family (39%).[78] It is estimated that over three-quarters of people with migraine have reduced ability to function normally during an attack and over half report severe impairment or the need for bed rest.[17, 79] In a global study of people with migraine, 74% reported spending time in darkness or isolation due to migraine (for an average of 19 hours per month). Sleeping difficulties were reported in 83%, fear of the next attack in 55%, and 49% reported feeling limited in daily activities throughout all migraine phases.[65] People with migraine also report reduced participation in family activities, a perception that their partners/spouses underestimate the severity of their disease, and concerns over their long-term financial security.[80] Furthermore, half of people with migraine report missing important events, avoiding making commitments, a negative impact on their sex life and 44% report feeling guilty about the impact of migraine on their family.[65, 81]

As migraine impacts people throughout their prime working years, it can result in significant reductions in work performance, with 5% of people with migraine reporting that they are unable to work and more than 20% worrying about job loss.[81] More than half of those with migraine (57%) miss at least 5 days of work over 3 months (equating to 20 or more sick days per year)

and roughly one-third worry about their finances, such as covering household expenses and long-term financial security.[81, 82]

The high symptom burden and associated impact on daily life result in significant reductions in health-related quality of life (HRQoL) for people with migraine, with a utility value of 0.68 reported for people experiencing ≥4 MHDs reporting compared with 0.81 for matched controls.[83-86] This impacts people with migraine across many important aspects of life (relationships, career/financial outcomes, overall health and functioning). Whilst headache intensity is correlated to levels of disability, the proportion of patients experiencing severe disability is comparable across patients with EM and CM.[87]

Economic burden

Migraine is associated with high levels of healthcare resource utilisation due to its relatively high prevalence compared to other diseases, and imposes a heavy economic burden.[88-90] In total, the NHS spends around £150 million per year on treating migraines.[91] In the UK, migraine is the most common neurological reason for consulting a general practitioner (GP), accounting for 2.5 million appointments or ~4.4% of all consultations in primary care every year.[68] In 2021–2022, there were 33,562 hospital admissions due to migraine.[92] Accident and Emergency (A&E) attendance for headache and migraine attacks has also increased by 14% over the last five years.[68] Accordingly, 1 in 20 migraine patients nationally are being diagnosed in A&E, making headache the most common neurological reason for A&E attendance.[68] According to NHS England, nearly 16,500 emergency admissions for headaches and migraine attacks could be avoided by optimising care pathways, and £11.5 million could be saved on non-elective admissions.[68]

Healthcare resource utilisation costs tend to increase with increasing migraine frequency,[93-97] and with successive preventive treatments failures which can result in patients cycling through multiple preventive drug classes.[98, 99] The economic burden of migraine for patients who receive inadequate preventive care is significantly higher compared with those who receive effective and tolerable preventive care and are persistent with treatment.[100-103]

There are also considerable indirect costs associated with migraines. Migraine impacts people throughout their prime working years, leading to significant reductions in performance at work.[61, 89, 93] Moreover, each year an average of 11.4 equivalent workdays are lost per person with migraine, with the associated absenteeism alone costing £2.25 billion per year in the UK.[104, 105] This can lead to people with migraine being forced to take up to 43 million days off work due to migraine each year.[68]

B.1.3.3 Clinical pathway of care and proposed positioning of atogepant

Diagnosis

Clinical history, examination and evidence from migraine diaries form the basis of diagnosis. However, there is no specific test to diagnose migraine. As a result, migraine often remains undiagnosed, with a 2021 survey by the Migraine Trust reporting that up to 52% of people who had experienced a migraine attack had not received a diagnosis (see Section B.1.3.2). Patients may be referred to specialists to further assess their disease and to discuss treatment options, particularly if patients cannot be adequately managed on acute treatment.[106]

Treatment

Clinical management of migraine in the UK is informed by clinical guidelines published by NICE (CG150; 2021) and the British Association for the Study of Headache (2019).[42, 107] Patients with migraine may receive acute treatment either alone, or in conjunction with a prophylactic, preventive treatment if they experience ≥4 migraine days per month.[42] Acute migraine treatment aims to stop the attack, or reduce the severity of the headache and other associated symptoms. Preventive treatment aims to reduce the frequency, severity, and duration of migraine attacks and development of medication overuse headaches.[108] However, there is currently no cure for migraine.[109] In patients for whom ≥3 preventive treatments have failed, some may continue to receive BSC only for the acute management of migraine (not the prevention of migraine). BSC consists of treatments such as simple analgesics (i.e., ibuprofen, aspirin or paracetamol), a triptan (with or without paracetamol or an non-steroidal anti-inflammatory drug [NSAID]), or antiemetics (e.g., metoclopramide or prochlorperazine).[42, 110]

As a general principle, migraine prevention should be considered when attacks affect quality of life and is indicated in roughly one third of migraine patients.[42, 110-112] Treatment plans are developed based on several factors: patient preference; status with respect to pregnancy, lactation, or plans to conceive; the frequency and severity of attacks; the presence, type, and severity of associated symptoms; attack-related disability; prior treatment response; the presence of comorbid and coexistenting illness; contraindications (e.g., cardiovascular disease); factors such as body habitus and physiological measures (e.g., blood pressure, heart rate); and the use of concomitant medications.[40] Consistency in use of preventive medications can reduce migraine frequency, reduce migraine severity, improve HRQoL, reduce health care resource use, and limit costs.[113-115] Furthermore, preventive medication use is associated with less work impairment and lower direct costs.[100, 102] Therefore, early diagnosis combined with effective and well-tolerated preventive treatments are key to reducing disease morbidity for patients with migraine.[34]

NICE guidance recommends assessment of the effectiveness of preventive treatment based on reduction in migraine frequency.[2-4] However, this does not capture improvements in the severity and duration of migraine attacks. International guidelines also recommend that improvements in HRQoL measures such as the Migraine Disability Assessment (MIDAS) score and Headache Impact Test-6 (HIT-6) should be considered when assessing response to preventive treatments, which represent migraine severity as well as the level of patient disability, unlike migraine frequency-related endpoints.[40, 112, 116-118] Clinical experts agreed that improvements in these HRQoL measures are representative of changes in migraine severity and are important in assessing the impact of migraine on patients.[5]

Preventive treatments: first-, second-, and third-line

For migraine prophylaxis, three classes of oral generic treatments are recommended by NICE CG150 2021: antidepressants, antiepileptics, and beta-blockers.[42] Propranolol (a beta-blocker) is recommended as first-line preventive treatment in patients, with other beta-blockers available if propranolol is unsuitable (e.g., metoprolol, atenolol, nadolol). Bisoprolol may also be considered, particularly if patients are already taking the treatment due to cardiac issues. Should a beta-blocker be unsuitable, topiramate (antiepileptic) is recommended, followed by amitriptyline (antidepressant).[42, 119]

Preventive treatments: fourth-line and beyond

For patients with ≥3 prior preventive treatment failures, SC CGRP mAbs (galcanezumab [TA659], erenumab [TA682] and fremanezumab [TA764]) are recommended by NICE as treatment options for migraine prophylaxis in both patients with EM and CM who have ≥4 migraine days per month.[2-4] NICE also recommend botulinum toxin type A for patients with ≥3 prior preventive treatment failures, but in line with its licence, it is only recommended in patients with ≥15 headache days per month (of which ≥8 days are with migraine), otherwise defined as CM (TA260).[13] More recently, NICE recommended an intravenous (IV) CGRP mAb, eptinezumab, for the same indication as SC CGRP mAbs (TA871; 1 March 2023).[16] An oral CGRP inhibitor, rimegepant, was also recently recommended as an option for preventing EM in adults who have at least 4 and fewer than 15 migraine attacks per month, only if at least 3 preventative treatments have not worked (TA906; 5 July 2023).[15]

Galcanezumab and erenumab are administered as a SC injection once per month with a dose of 120 mg and 140 mg, respectively.[2, 3, 120, 121] Fremanezumab is available as a SC injection, either as a 225 mg dose every month or 675 mg dose every three months.[4, 122] The recommended dose of botulinum toxin type A is 155–195 units, administered intramuscularly as 0.1 ml (5 units) injections to between 31 and 39 sites around the head and back of the neck every 12 weeks.[13] Eptinezumab is administered as an IV infusion every three months with a dose of 100 mg.[12] Rimegepant is available as an oral medication that can be self-administered by the patient as a 75 mg dose every other day.[15]

Beyond CGRP mAbs or botulinum toxin type A, the only remaining treatment option currently available on the NHS is BSC, which is limited to treatments for the acute management of migraine that aim to alleviate symptoms within ~2 hours of a migraine attack.[13]

Unmet need

Despite available treatments, migraine remains a leading cause of years lived with disability and the adverse effects of migraine continue to pose a major economic burden on healthcare systems.[30]

First- to third-line oral generic prophylactic treatments of migraine (beta-blockers, anti-depressants, and anti-epileptics) were not specifically designed to prevent migraine. They are associated with high discontinuation rates, with only 14% of patients reported to persist on treatment at 12 months.[35] Among people with migraine who discontinued oral generic preventive treatments in the International Burden of Migraine Study-II in Australia, Canada, France, Germany, the UK and the US, 35–48% did so due to poor efficacy and 34–53% discontinued due to poor tolerability.[123, 124] High levels of discontinuation in oral generic prophylactic treatment can result in acute medication overuse (AMO) due, in part, to the sustained use of BSC therapies, and patients cycling through prophylactic treatments without adequate reduction in migraine frequency or severity.[35] For example, in the MAST study which included 13,649 respondents,

15% of people with migraine were shown to have AMO, and it was associated with increased symptom severity, pain intensity, and rates of cutaneous allodynia.[69]

Access to oral generics is also limited by a series of contraindications. Beta-blockers are contraindicated in patients with asthma, cardiac failure, insulin-dependent diabetes, and Raynaud's disease.[125] In addition, the anti-epileptic, topiramate, is contraindicated in pregnancy and in women of childbearing potential due to the increased risk of congenital malformations and effects on foetal growth if used during pregnancy (subject to ongoing MHRA safety review initiated in July 2022).[126] Given the limitations of oral generic prophylactic treatments in first- to third-line, there is a clear need for effective treatment options in patients for whom ≥3 prior preventive treatments have failed.

Among people with migraine for whom ≥3 oral generic preventive treatments have failed; SC CGRP mAbs provide effective treatment options, with average reductions in MMDs across SC CGRP mAbs versus placebo in EM and CM reported to be 1.9 and 2.2 days, respectively.[127] However, these too are associated with limitations, including administration by injection or infusion, a "wear-off effect" of effectiveness between treatment cycles,[39, 128] slow rates of clearance (half-lives of 27–30 days), restricted access, resource burden associated with in-clinic treatment administration among a subset of patients, and clerical activities associated with homecare dispensing.[129-131] These limitations may be particularly challenging for pregnant women and women trying to conceive. CGRP mAbs are not recommended for pregnant women and due to their long half-life, a washout period of 6 months prior to conception is recommended.[132] This lack of flexibility is an important consideration given that migraine commonly affects women of child-bearing age.

CGRP mAbs currently recommended in patients with EM and CM are only available via SC injection or infusion, which may be seen as an inconvenient, intrusive, and painful mode of administration, in addition to having cold storage requirements.[41, 120-122] There are also capacity issues associated with the SC CGRP mAbs, with an average waiting time for treatment across the UK between 3–5 months.[68] Whilst SC treatments can be self-administered, they can impose a high administrative burden due to their delivery via homecare providers, which was considered the key limiting factor for CGRP mAb prescribing by clinical experts.[5] In addition, some patients with migraine are unable to self-administer or are needle-phobic, which potentially limits access to treatment if assistance is not available.[2] Clinical experts consulted during the galcanezumab NICE appraisal suggested that 10% of patients may not be able to self-administer.[2] Approximately 10% of people with migraine are needle-phobic and would therefore require assistance with SC administration or avoid injectables or infusions altogether.[2, 133]

According to a study that included [redacted] outpatients with migraine to determine patients' preferences for acute and preventive headache treatment, the large majority of patients ([redacted]) preferred oral administration over other administration routes.[38] For preventive pharmaceutical treatment, most patients preferred to take a pill once per day ([redacted]) compared to an injection SC or IV each month ([redacted] and [redacted], respectively), or three months ([redacted] and [redacted], respectively), assuming all treatments have a comparable efficacy and safety profile.[38] A discrete choice experiment that surveyed [redacted] patients with EM further demonstrated that an oral once daily tablet was associated with [redacted] than self-injection under skin every 1 and 3 months, as well as IV infusion every 3 months. In addition, [redacted] of patients preferred a treatment of atogepant's profile to SC CGRP mAbs, when comparing an oral once daily treatment to an injectable once monthly treatment with similar efficacy and safety.[134] Moreover, a UK-based vignette study (N = 400; 2019) demonstrated that injectable treatments (CGRP mAbs and

botulinum toxin type A) are associated with small utility decrements relative to oral treatments due to route of administration, which have been validated by consulted UK clinical experts who believed that the reported disutilities are both realistic and appropriate given that patients receiving injectable therapies may be subject to pain, discomfort, anxiety, and/or the need to attend a clinic for an invasive procedure.[135] As a result, there is an unmet need for treatments that are both effective and have convenient, oral modes of administration, which can be easily administered at home, preventing delays and reducing the burden on overstretched infusion clinics.

Botulinum toxin type A also represents an effective treatment option for patients with CM who have experienced ≥3 prior preventive treatment failures. However, botulinum toxin type A is administered in-clinic as IM injections to between 31 and 39 sites in the head and the back of the neck every 12 weeks, and can only be administered by skilled injectors.[13] Botulinum toxin type A is largely administered by headache specialists, with few general neurologists and general practitioners with special interest able to administer the treatment.[5] A survey conducted by the Migraine Trust found that only 20% of NHS Trusts reported having a specialist headache clinic, and reported only 1.1 full-time equivalent (FTE) neurologists per 100,000 population.[68] There were also significant geographic differences in staff dedicated to headache and migraine care, ranging from 0 to 4 FTE headache specialist doctors.[68] This has led to geographic inequities, with some patients unable to travel large distances to centres with the necessary expertise to administer botulinum toxin type A, as well as lengthy waiting lists of up to 12 to 18 months that restrict immediate access.[5] Generally, clinical experts agreed that availability and capacity restrictions were the primary limiting factors for access to botulinum toxin type A.[5]

Overall, established treatment options currently available on the NHS to patients for whom ≥3 preventive treatments have failed are limited to injectable therapies in the form of SC CGRP mAbs and botulinum toxin type A, and there are no preventive oral therapies recommended for patients with CM. SC CGRP mAbs require training to self-inject, or recurring clinical visits to receive the injection by a trained professional.[2-4] Botulinum toxin type A requires recurring visits to clinic for a more invasive procedure of up to 39 injections by a trained professional, which can result in access issues due to limited capacity.[13] People with migraine who have needle-phobia may face discomfort receiving currently available injectable treatments or avoid treatment altogether. Furthermore, a lack of flexibility exists for women of childbearing age treated with currently available CGRP mAbs, which presents challenges for those trying to conceive and/or those who become pregnant on these treatments. There is a clear unmet need for an oral form of preventive treatment for both people with EM and people with CM with a short half-life, which could provide an alternative, more convenient treatment option.

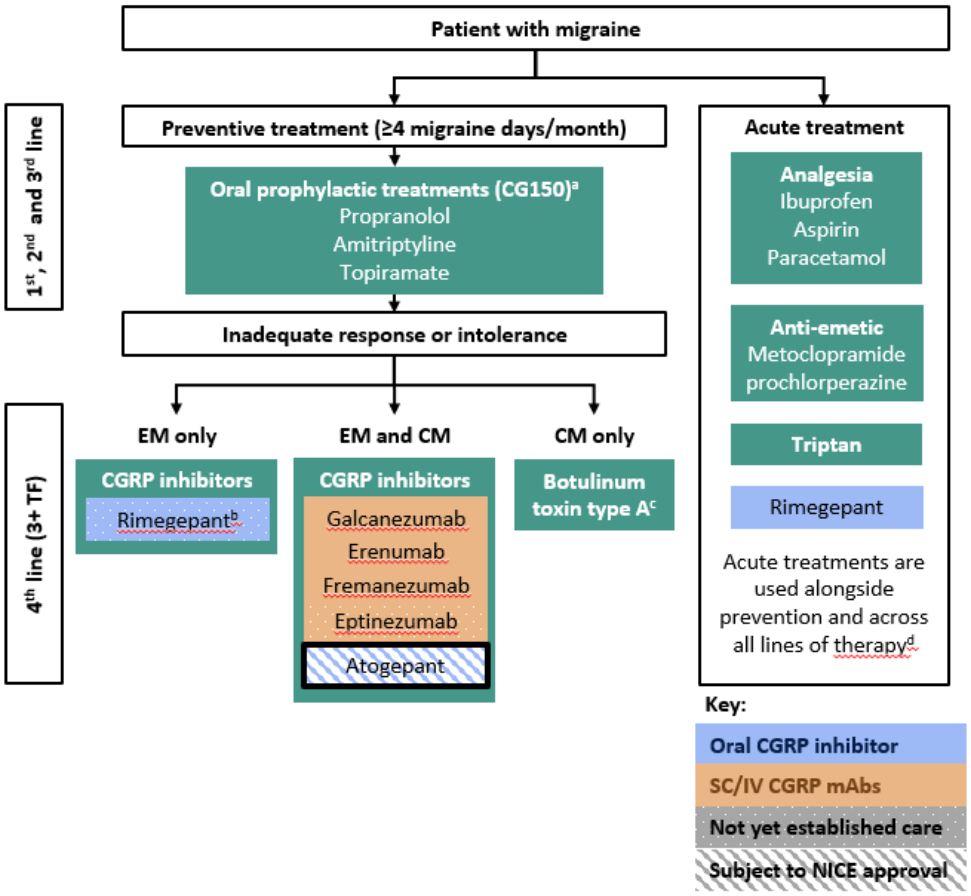
Anticipated positioning of atogepant in UK clinical practice

In accordance with clinical expert feedback, atogepant is intended to be positioned for use within the NHS as a preventive treatment for patients with migraine in whom at least 3 preventive drug treatments have failed (i.e., a subgroup of the technology's marketing authorisation).[1] This positioning is fully aligned with the population for which SC CGRP mAbs have received positive recommendations from NICE for the prophylaxis of migraine in adults with ≥4 monthly migraine days per month and for whom ≥3 prior preventive treatments have failed (Figure 3).[2-4] Therefore, SC CGRP mAbs (galcanezumab, erenumab, fremanezumab) are deemed to be appropriate comparators for this appraisal; given that atogepant and the SC CGRP mAbs are preventive treatments that cover the same patient population which each work in a similar way to suppress CGRP activity, can be self-administered at home, and offer similar health benefits. UK clinical

experts at an advisory board considered atogepant to be an alternative to SC CGRP mAbs and anticipated that the technologies would have similar efficacy and positioning.[5]

Atogepant is a migraine-specific, fast-acting CGRP inhibitor with proven efficacy, safety, and tolerability in prophylactic migraine treatment.[136-138] Atogepant would offer an alternative to SC CGRP mAbs, addressing the unmet need for an oral treatment option for patients with ≥3 prior preventive treatment failures, with reduced or minimal budget impact.

Figure 3: Anticipated clinical pathway of care for migraine patients



Source: NICE. Headaches in over 12s: diagnosis and management [CG150];[42] NICE. Fremanezumab for preventing migraine [TA764];[4] NICE. Erenumab for preventing migraine [TA682];[3] NICE. Galcanezumab for preventing migraine [TA659];[2] NICE. Eptinezumab for preventing migraine [TA871];[16] NICE. Rimegepant for preventing migraine [TA906];[15] NICE. Atogepant for preventing migraine [ID5090];[139] AbbVie Data on File, Atogepant in Migraine UK Advisory Board Meeting Report, 2022.[5]
Footnotes: [a]The treatments listed are not exhaustive. Propranolol, amitriptyline and topiramate are the most widely used agents in first- to third-line, but other anti-convulsants, beta-blockers, antihistamines, candesartan and flunarizine are also available; [b]Rimegepant is licensed and recommended for the preventive treatment of EM only; [c]Botulinum toxin type A is only licensed and recommended for the preventive treatment of CM; [d]Non-pharmacological pathways, such as behavioural interventions, acupuncture (10 sessions over 5–8 weeks), riboflavin or transcutaneous electrical stimulation, can be initiated at any point of the treatment pathway for cases when there is low tolerance to medical strategies, when medication is not indicated, or in conjunction with classic pharmacological therapies.[140]
Abbreviations: CGRP: calcitonin gene-related peptide; IV: intravenous; CM: chronic migraine; EM: episodic migraine; mAb: monoclonal antibody; NICE: National Institute for Health and Care Excellence; SC: subcutaneous; 3+ TF: ≥3 prior preventive treatment failures.

Clinical expert feedback has also been consistent in indicating that atogepant will enable the NHS to realise additional efficiencies within the migraine clinical care pathway. As a well-

tolerated, effective, oral treatment; clinicians anticipate that atogepant will be much more likely than CGRP mAbs to be used among secondary care general neurologists and primary care general practitioners (GPs), which will ultimately relieve pressure on headache specialist clinics and reduce specialist waiting lists.

The UK migraine referral pathway has been mapped using two web-assisted telephone interview-based studies with UK HCPs (including GPs, general neurologists, and headache specialists; 2022), and then subsequently validated by three headache specialists during the development of this company submission.[141, 142] In current practice, patients who have experienced 3 or more prior preventive treatment failures in primary care are often subjected to an extensive referrals pathway; whereby a GP refers a patient to a general neurologist, who may then either initiate a fourth preventive treatment (such as a CGRP mAb) or refer on to a headache specialist for treatment.[141, 142]

Headache specialists indicated that general neurologists typically refer patients to headache specialist for treatment with CGRP mAbs; with general neurology barriers including the lack of access to supporting specialist nurse facilities, the requirement to monitor patients receiving injectable treatments, and the heavy clerical administrative burden associated with CGRP mAbs. However, atogepant is an effective, well tolerated orally administered CGRP inhibitor that is not subject to the same homecare-related administrative burden as CGRP mAbs, and is therefore expected to facilitate wide use among general neurologists in the secondary care setting. In doing so, the NHS are likely to benefit from cost-savings associated with avoided headache specialist visits at initiation, and lower costs on a per-visit basis for general neurology visits relative to headache specialist visits. Market research and clinical expert opinion indicates that headache specialist consultations are generally longer than general neurologist visits; with consulted headache specialists estimating an average visit time of 60 minutes for headache specialists at initiation versus 30 minutes for general neurologists.[142]

B.1.3.4 Equality considerations

Migraine is considered a disability under the Equality Act 2010 when it leads to physical and mental impairment, and has a substantial and long-term adverse effect on the ability to perform normal day-to-day activities. Therefore, it is particularly important to ensure that patients with migraine have access to effective treatments to support them in their day-to-day life.[143] It is not anticipated that the provision (or non-provision) of atogepant would exclude from consideration any people protected by equality legislation, lead to a recommendation that has a different impact on people protected by equality legislation than on the wider population, or lead to recommendations that have an adverse impact on people with a particular disability or disabilities. Moreover, there may be geographical inequity in access to current treatments, given that CGRP mAbs are only available in SC or IV formulations, which may require hospital visits. Introduction of atogepant, which is administered orally, may help reduce inequity in access.[5]

B.2 Clinical effectiveness

Clinical evidence

- The efficacy and safety of atogepant for migraine prophylaxis has been demonstrated in one Phase 2b/3 and three Phase 3 trials: CGP-MD-01 (EM), ADVANCE (EM), ELEVATE (EM), and PROGRESS (CM), which are multicentre, randomised, double-blind, placebo-controlled, parallel group clinical trials. In the case of this submission, ELEVATE and PROGRESS are the most robust and relevant sources for evidence across EM and CM, respectively:
  - ELEVATE (Phase 3) evaluated the efficacy, safety, and tolerability of atogepant for the prophylaxis of migraine in adults with EM who have previously failed 2 to 4 classes of oral preventive treatments; a pre-specified subgroup of this trial provides information on the efficacy of atogepant in patients with ≥3 prior preventive treatment failures (3+ TF modified intent-to-treat [mITT])
  - PROGRESS (Phase 3) evaluated efficacy and safety of atogepant for the prevention of migraine in adults with CM. This trial did not include a pre-specified 3+TF mITT subgroup, nor was it powered to assess the efficacy of atogepant in patients with ≥3 prior preventive treatment failures

Efficacy

- The pre-specified 3+ TF mITT subgroup within the ELEVATE trial was appropriately powered and stratified; as such, this study is considered the primary source of evidence for EM patients in this appraisal. However, as noted above, the PROGRESS trial was not powered to assess efficacy for the limited number of included CM 3+ TF mITT patients, nor did this patient subgroup feature in the stratification of randomised patients by classes of failed prior preventive treatments, leading to imbalances in key baseline characteristics between treatment arms. On review of the PROGRESS 3+ TF mITT data, UK clinical experts have noted artefactually high placebo response rates, which may be a consequence of the limited sample size and/or that 3+ TF was not a stratification factor for randomisation in PROGRESS. Thus, these data cannot be used to draw reliable conclusions regarding the efficacy of atogepant in this patient subpopulation. An appropriately powered analysis of the overall mITT population, inclusive of 3+ TF mITT patients is therefore used for the CM population. Use of overall mITT data has been accepted as the preferred approach by the NICE committee in the recent appraisal of rimegepant, another oral CGRP inhibitor recommended for the prevention of EM (TA906).[15]
- ELEVATE met its primary endpoint, change from baseline (CFB) in monthly migraine days (MMDs). Atogepant demonstrated a statistically significant improvement over placebo across a 12-week treatment period for all secondary endpoints including ≥50% reduction in mean MMDs, CFB in mean MHDs, CFB in mean monthly acute medication use days (MUDs) and health-related quality of life (HRQoL)
- In the 3+ TF mITT subgroup from the ELEVATE study, patients on atogepant achieved a statistically significantly greater reduction in least squares (LS) mean MMDs from baseline across the 12-week treatment period, compared with patients on placebo ([redacted] vs [redacted], p=0.0002)
- Like the ELEVATE study, PROGRESS met its primary endpoint, CFB in MMDs. Atogepant also demonstrated a statistically significant improvement over placebo across a 12-week treatment period for all secondary endpoints, as in the ELEVATE study
- The rapid efficacy of atogepant is further demonstrated in both trials, whereby the atogepant group had a significantly lower proportion of patients with a migraine day than the placebo group from 1 day after the initial dose
- Atogepant was associated with significantly greater improvements in patient reported HRQoL outcomes across both ELEVATE and PROGRESS

Indirect and mixed treatment comparisons

- In the absence of head-to-head RCTs, NMAs were developed to compare the efficacy, safety and impact on HRQoL outcomes of atogepant relative to existing treatments.
- Evidence from RCTs was identified in the clinical SLR presented in Section B.2.1: 16 studies

considered for inclusion in the EM NMAs for either the overall mITT population (inclusive of treatment failure studies) or 3+ TF mITT subgroup, and 10 were considered for inclusion in the CM NMAs (overall mITT only, inclusive of treatment failure studies)
- NMAs were conducted for efficacy and safety endpoints including CFB in MMDs, ≥50% and ≥30% (CM only) reduction in MMDs, CFB in monthly acute MUDs, TEAEs, all-cause discontinuation, and HRQoL outcomes including CFB in MSQ v2.1 and HIT-6 scores
- NMA results demonstrate that atogepant has similar efficacy to SC CGRP mAbs (galcanezumab, erenumab, fremanezumab), with no statistically significant differences identified across all efficacy endpoints, and safety endpoints observed between atogepant and all relevant active comparators in both EM and CM. Additionally, in EM, atogepant demonstrated statistically significantly superior HRQoL versus all three CGRP mAbs in at least one HRQoL measure

Adverse reactions

- Atogepant demonstrated an acceptable safety and tolerability profile in patients with EM and CM. The most common adverse events (AEs) were consistent with the known safety profile of other CGRP inhibitors. No new safety signals were identified
- On review of the atogepant safety data, clinical experts indicated that atogepant has improved safety and tolerability benefits compared to oral generic treatments used between first and third lines of therapy. They further noted a similar safety profile to existing CGRP-mAbs, with the additional advantage of being an orally administered therapy[5]

B.2.1 Identification and selection of relevant studies

Two clinical systematic literature reviews (SLRs), one each in EM and CM, were conducted in May 2020 and updated in September 2022 to identify relevant clinical evidence on the efficacy and safety of atogepant and other preventive treatments in patients with migraine, in order to facilitate an indirect comparison via NMA and to support an initial company submission in February 2023. Given the scope of this submission was finalised at a similar time and the relevant comparators detailed, the use of these SLRs is considered appropriate and in line with the scope.

A total of 563 publications reporting on 187 unique studies were identified in the EM SLR and 597 publications reporting on 32 unique studies were identified in the CM SLR. Of those, three Phase 3 studies with atogepant as the primary intervention were retrospectively included on the basis of available clinical study reports: ADVANCE, ELEVATE, and PROGRESS;[137, 138, 144] while a Phase 2b/3 study was also identified: CGP-MD-01.[22] An overview of the SLR methodology, including search strategy, study selection process, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram, list of included/excluded studies at full text review, and results can be found in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

Four separate randomised controlled trials (RCTs) provide evidence for the efficacy and safety of atogepant in patients with migraine:

- The CGP-MD-01 study (NCT02848326) was a Phase 2b/3, randomised, double-blind placebo-controlled trial evaluating the efficacy and safety of atogepant for the prevention of migraine in adults with EM.[22]
- The ADVANCE study (NCT03777059) was a Phase 3, randomised, double-blind placebo-controlled trial evaluating the efficacy and safety of atogepant for the prevention of migraine in adults with EM. As a Phase 3 study that investigated atogepant, data from ADVANCE are provided in the CSR located in the reference pack accompanying this submission for

completeness.[144] ADVANCE has since been followed, and thereby superseded by a study dedicated to assessing atogepant in an EM treatment failure-specific population (ELEVATE).

- The ELEVATE study (NCT04740827) was a Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group trial evaluating the efficacy, safety, and tolerability of atogepant for the prophylaxis of migraine in patients with EM in whom 2 to 4 classes of oral preventive treatments have previously failed; a pre-specified subgroup of this trial (patients in whom ≥3 prior preventive treatments have failed [hereafter referred to as patients with 3+ TF]) is in line with the target population for this submission[138] Randomisation conducted in the ELEVATE trial stratified patients according to failed prior preventive treatment classes, meaning that pre-specified subgroup analyses of key endpoints in the 3+ TF modified intent-to-treat (mITT) population specifically were sufficiently statistically powered. Data have also been presented from the overall mITT population of the ELEVATE trial, providing supportive evidence with a larger sample size for the efficacy of atogepant, with generally consistent clinical results observed. This is in line with NICE TA659, which presented clinical outcomes in an overall mITT population in addition to a 3+ TF mITT population to support clinical efficacy in patients with ≥3 prior preventive treatment failures.[2]
- The PROGRESS study (NCT03855137) was a Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group trial, which is the sole study evaluating the efficacy and safety of atogepant for the prevention of migraine in adults with CM. This trial did not include a pre-specified 3+TF subgroup, nor was it powered to assess the efficacy of atogepant in these patients. While the overall mITT population of this study did include a small number of patients with 3+ TF (atogepant 60 mg QD [n=[redacted]]; placebo [n=[redacted]]); PROGRESS was not powered to assess efficacy in these patients, nor did this patient subgroup feature in the stratification of randomised patients by classes of failed prior preventive treatments, leading to imbalances in key baseline characteristics between treatment arms. On review of the PROGRESS 3+ TF mITT data, UK clinical experts have noted artefactually high placebo response rates, which may be a consequence of the limited sample size and/or that 3+ TFs was not a stratification factor for randomisation in PROGRESS.[5] Thus, no robust subgroup analyses could be provided for the 3+ TF mITT population, as these data cannot be used to draw reliable conclusions regarding atogepant's efficacy in this patient subpopulation. As the source of evidence for atogepant in patients with CM, data from the overall mITT population of the PROGRESS trial have been presented in this submission. The use of clinical efficacy data from the overall mITT population is also in line with the recent decision taken by NICE for another oral CGRP inhibitor, rimegepant, whereby the committee agreed and preferred to use the overall mITT data collected in a Phase 3 study that excluded patients "with no response to at least 2 preventative treatments" for decision-making.[15] Whereas, the PROGRESS overall mITT population is inclusive of the 3+ TF mITT subgroup target population, and does not exclude patients with ≥2 preventive treatment failures.[136] Data from the overall mITT population is therefore used for the CM population, with its larger sample size and where randomisation is retained. Data from the PROGRESS trial have been published by Pozo-Rosich *et al.* (2023).[145]

In accordance with the above reasoning, the ELEVATE and PROGRESS studies are the primary sources of evidence supporting the efficacy and safety of atogepant in this submission. Importantly, ELEVATE is statistically powered to assess the efficacy of atogepant in patients with EM who have experienced multiple treatment failures (2–4), thereby superseding CGP-MD-01 and ADVANCE as the most robust, relevant source of evidence in the EM patient population.

On the other hand, PROGRESS is the sole study in which atogepant has been assessed in patients with CM. For this reason, CGP-MD-01 and ADVANCE are not presented further in this

submission. In line with the UK license for atogepant, results for atogepant 60 mg QD (once daily) dose are presented in Section B.2.

Table 3: Clinical effectiveness evidence

Study	CGP-MD-01	ADVANCE	ELEVATE[a]	PROGRESS[a]
Study design	Phase 2b/3 multicentre, randomised, double-blind, placebo-controlled, parallel-group trial	Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group trial	Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group trial	Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group trial
Population	Adult (18–75 years) patients with EM. Patients were excluded if they had a history of inadequate response to ≥3 prior preventive migraine treatments	Adult (18–80 years) patients with EM	Adult (18–80 years) participants with EM in whom 2 to 4 classes of oral preventive treatments have failed	Adult (18–80 years) participants with CM
Number of participants	ITT population: 834 overall mITT population: 795	ITT population: 910 overall mITT population:[b] 873	ITT population: [redacted] overall mITT population:[b] [redacted]	ITT population: 778 overall mITT population:[b] 755
Intervention(s)	Atogepant 10 mg QD, 30 mg (QD or BD), or 60 mg (QD or BD)	Atogepant 10 mg, 30 mg, or 60 mg QD	Atogepant 60 mg QD	Atogepant 30 mg BID Atogepant 60 mg QD
Comparator(s)	Placebo	Placebo	Placebo	Placebo
Indicate if study supports application for marketing authorisation (yes/no)	Yes	Yes	Yes	Yes
Reported outcomes specified in the decision problem	NA – not considered a primary source of evidence for atogepant in the submission, and is superceded by ELEVATE which is powered for the target patient population in EM	NA – not considered a primary source of evidence for atogepant in the submission, and is superceded by ELEVATE which is powered for the target patient population in EM	• Change in frequency of migraine days per month o CFB in the mean number of MMDs o Reduction from baseline of ≥30%, ≥50% and ≥75% in mean MMDs[c] • Change in frequency of headache days per month o CFB in the mean number of MHDs • Changes in acute pharmacological medication given o CFB in mean monthly acute MUDs	

			• CFB in weekly migraine days during the first month of treatment • Proportion of participants with a migraine day during the first week of treatment • CFB in PGI-S score • HRQoL o CFB in HIT-6 total score o CFB in MSQ v2.1 Role Function-Restrictive domain score o CFB in MSQ v2.1 Role Function-Preventive domain score o CFB in MSQ v2.1 Emotional Function domain score o CFB in MIDAS total score • AEs of treatment
All other reported outcomes	NA	NA	NA

Source: AbbVie Data on File. ELEVATE CSR, 2022,[138] AbbVie Data on File. PROGRESS CSR 2022,[137] AbbVie Data on File. ADVANCE CSR 2020.[144] and Goadsby 2020.[22]
Footnotes: [a]Patients reported on their migraine frequency and severity, including migraine and headache days, pain intensity and intake of medication; [b]The overall mITT population includes all randomised patients who received at least one dose of study intervention, had an evaluable baseline period of eDiary data and had at least one evaluable post-baseline four-week period of eDiary data during the double-blind treatment period (Section B.2.3.1); [c]Results for the reduction from baseline of ≥25% and 100% are available in the ELEVATE and PROGRESS CSRs.[137, 138]
Abbreviations: AEs: adverse events; BID: twice daily; CFB: change from baseline; CM: chronic migraine; CSR: clinical study report; eDiary: electronic diary; EM: episodic migraine; HIT-6: Headache Impact Test-6; HRQoL: health-related quality of life; ITT: intent-to-treat; MHDs: monthly headache days; MIDAS: Migraine Disability Assessment; mITT: modified intent-to-treat; MMDs: monthly migraine days; MSQ v2.1: Migraine-Specific Quality of Life questionnaire, Version 2.1; MUDs: medication use days; NA: not applicable; PGI-S: patient global impression of severity scale; QD: once daily; UK: United Kingdom.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Trial design and methodology

ELEVATE

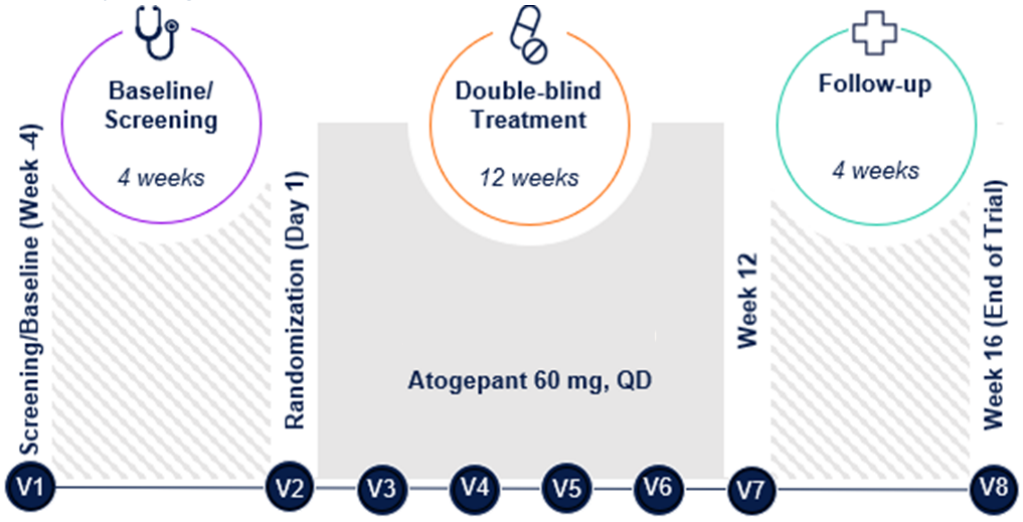
ELEVATE is a Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group trial evaluating the efficacy, safety, and tolerability of atogepant for the prophylaxis of migraine in patients with EM in whom two to four classes of oral preventive treatments have failed.

The trial screened a total [redacted] patients for eligibility. Among these, [redacted] patients were randomised (ITT population) and [redacted] patients were treated (safety population). The overall mITT population (patients who received ≥1 dose of study intervention and had evaluable data; see Section B.2.4) was used for the efficacy analyses and comprised [redacted] patients who were stratified based on region (North America, Europe, and East Asia), number of migraine days during the screening/baseline period (4 to <8 and ≥8) and number of classes of failed prior preventive treatments (2 and >2). Full patient disposition is presented in Section B.3.3.1.

The trial consisted of three phases for a total duration of 20 weeks: a four-week screening and baseline period, a 12-week double-blind treatment period, and a four-week follow-up period (Figure 4). After the screening and baseline period, patients who met all study inclusion criteria at Visit 2 were randomised in a 1:1 ratio into the following treatment groups: placebo or atogepant 60 mg once daily (QD). The study intervention was administered orally for 12 weeks in the treatment period and the patients were followed for four weeks following study completion or discontinuation of study intervention.

The primary endpoint was the CFB in mean MMDs across the 12-week treatment period, calculated as the change in MMDs from baseline to each post-baseline month averaged over the three study months. The secondary endpoints included reductions in MHDs and acute MUDs, and percentage of patients with ≥50% reduction in three-month average of MMDs. Additional efficacy endpoints included ≥30% and ≥75% reduction in three-month average of MMDs, CFB in monthly cumulative headache hours, CFB in monthly moderate/severe headache days and CFB in weekly migraine days during the first month of treatment. The impact of atogepant on patient reported outcomes (PROs) including daily functioning and health-related quality of life (HRQoL) (HIT-6, MSQ v2.1 and MIDAS) were also assessed. In line with the decision problem, pre-specified subgroup analyses were conducted for the primary efficacy endpoint (CFB in MMDs) in patients for whom three or more prior oral preventive treatments had failed.

Figure 4: Study design of ELEVATE trial



Source: AbbVie Data on File. ELEVATE protocol [Figure 1-1].[138]
Abbreviations: QD: once daily; V: visit.

PROGRESS

PROGRESS is a Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group trial evaluating the efficacy and safety of atogepant for the prevention of migraine in adults with CM.

The trial screened a total of 1,489 patients for eligibility. Among these, 778 patients underwent randomisation (ITT population) and 773 patients received treatment (safety population). The overall mITT population (patients who received ≥1 dose of study intervention and had evaluable data; see Section B.2.4) comprised 755 patients who were stratified by use of acute headache medication during the baseline period, migraine prevention medication exposure with proven efficacy (current use, past use, or never used), and region (North America, Europe, and East Asia). Patients with current or past use were further stratified based on the number of medications failed with unique mechanisms of action (0 medications or ≥1 medication(s) with the same mechanism of action, and 2–4 medications with different mechanisms of action). Full patient disposition is presented in Section B.2.3.3.

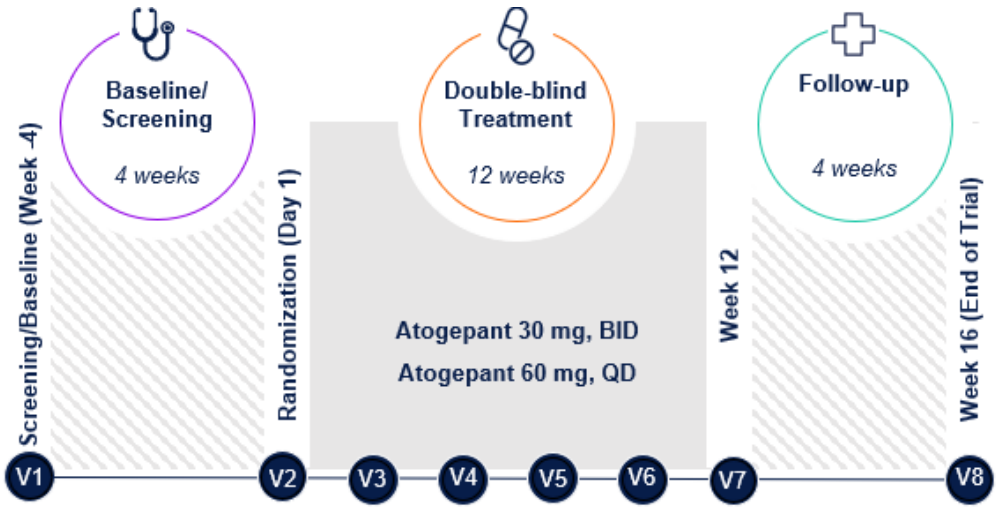
The trial consisted of three phases for a total duration of 20 weeks: a four-week screening and baseline period, a 12-week double-blind treatment period, and a four-week follow-up period (Figure 5). After the screening and baseline period, patients who met all study inclusion criteria at Visit 2 were randomised in a 1:1:1 ratio into the following treatment groups: placebo, atogepant 30 mg twice daily (BID), or atogepant 60 mg QD. The study intervention was administered orally for 12 weeks in the treatment period and then patients were followed for four weeks following study completion or discontinuation of study intervention.

The primary endpoint was the CFB in mean MMDs across the 12-week treatment period, calculated as the change in MMDs from baseline to each post-baseline month averaged over the three study months. The secondary endpoints included reductions in MHDs and acute monthly medication use, percentage of patients with ≥50% reduction in three-month average of MMDs. Additional efficacy endpoints included ≥30% and ≥75% reduction in three-month average of MMDs, CFB in weekly migraine days during the first month of treatment, assessment of the impact of atogepant on patient reported outcomes including daily functioning and HRQoL (HIT-6, MSQ v2.1, and MIDAS). As stated previously, the overall mITT population of this study included

a subgroup of patients with 3+ TF (atogepant 60 mg QD [n=[redacted]]; placebo [n=[redacted]]) but the study was not powered to assess efficacy in this subgroup. As the source of evidence for atogepant in patients with CM, only data from the overall mITT population of the PROGRESS trial have been presented in this submission.[137]

Table 4 summarises the methodology of the ELEVATE and PROGRESS trials.

Figure 5: Study design of PROGRESS trial



Source: AbbVie Data on File. Study 303 PROGRESS CSR [Figure 1].[137]
Abbreviations: BID: twice daily; QD: once daily; V: visit.

Table 4: Summary of the methodology

Trial name	ELEVATE	PROGRESS
Location	Australia, Canada, Czechia, Germany, Denmark, Spain, France, Hungary, Italy, Netherlands, Poland, Russian Federation, Sweden, **United Kingdom**, United States	Australia, Canada, China, Czechia, Germany, Denmark, Spain, France, Italy, Japan, Republic of Korea, Poland, Russian Federation, Sweden, Taiwan, **United Kingdom**, United States
Trial design	Phase 3, multicentre, randomised, double blind, placebo-controlled, parallel group	
Eligibility criteria for participants	**Inclusion criteria** • ≥1-year history of EM with a diagnosis according to the ICHD-3, 2018 • 4–14 MMDs on average in the three months prior to Visit 1 and in the 28-day baseline period per eDiary • Age at migraine onset <50 years • Males or females 18 to 80 years, inclusive • Completed ≥20 out of 28 days in the eDiary during baseline period • Failed 2–4 classes of oral migraine prophylaxis medications[a] • AND failed ≥1 of the following treatments: o Propranolol OR metoprolol o Topiramate o Flunarizine o Amitriptyline **Exclusion criteria** • Usage of barbiturate-containing or opioid-containing analgesics >2 days/month, triptans or ergots ≥10 days/month, or simple analgesics (e.g., aspirin, NSAIDs, acetaminophen) ≥15 days/month in the three months prior to Visit 1 • Clinically significant cardiovascular, cerebrovascular, hematologic, endocrine, pulmonary, hepatic, gastrointestinal, or neurologic disease, laboratory values, or psychiatric conditions, dementia, epilepsy, or significant risk of harm to self or others	**Inclusion criteria** • ≥1-year history of CM with a diagnosis according to the ICHD-3, 2018 • ≥15 MHDs on average in the three months prior to Visit 1 and during the four-week baseline period per eDiary, and ≥8 MMDs during four-week baseline per eDiary • Age at migraine onset <50 years • Males or females 18 to 80 years, inclusive • Completed ≥20 out of 28 days in the eDiary during baseline period **Exclusion criteria** • Inadequate response to >4 preventive medications • Taking >1 preventive medication or, if one medication used, dose not stable and/or well-tolerated for ≥12 weeks prior to Visit 1, or unwilling or unable to maintain stable dose/regimen during trial • Usage of opioids and/or barbiturates >4 days/month in the three months prior to Visit 1 • Clinically significant cardiovascular, cerebrovascular, hematologic, endocrine, pulmonary, renal, hepatic, gastrointestinal, or neurologic disease, laboratory values, or psychiatric conditions, dementia, epilepsy, or significant risk of harm to self or others • Concurrent pain condition • Difficulty distinguishing migraine headaches from other types

Trial name	ELEVATE	PROGRESS
	• Concurrent pain condition • Difficulty distinguishing migraine headaches from other types	
Intervention	Atogepant 60 mg QD[b]	Atogepant 30 mg BID or atogepant 60 mg QD[b]
Method of study drug administration	Oral administration	
Permitted and disallowed concomitant medication	**Permitted concomitant medications** • Aspirin up to 325 mg/day for cardiac prophylaxis • SSRIs or SNRIs if treatment is stable,[c] continues without change in dose throughout the study and is not indicated for treatment of migraines or headaches • Rescue medications for acute treatment of migraine: o Any triptan o Any ergot derivative o Any other form of analgesic (including acetaminophen, metamizole) o Any NSAID agent o Any antiemetic agent **Disallowed concomitant medications** • Strong and moderate CYP3A4 inhibitors and inducers • Strong P-gp inhibitors • Strong OATP1B1/OATP1B3 inhibitors • Drugs with narrow therapeutic margins with theoretical potential for CYP drug interactions • Medications with demonstrated efficacy for the prophylaxis of migraine, regardless of indication • Cannabidiol oil, cannabis • Injectable monoclonal antibodies blocking the CGRP	**Permitted concomitant medications** • Aspirin up to 325 mg/day for cardiac prophylaxis • SSRIs or SNRIs if treatment is stable,[c] continues without change in dose throughout the study • Medications for acute treatment of migraine: o Any triptan o Any ergot derivative o Any opioid o Any other form of analgesic (including acetaminophen) o Any NSAID agent o Any antiemetic agent **Disallowed concomitant medications** • Strong and moderate CYP3A4 inhibitors and inducers • Strong OATP1B1 inhibitors • Drugs with narrow therapeutic margins with theoretical potential for CYP drug interactions • Medications with demonstrated efficacy for the prevention of migraine are prohibited when used for any indication other than migraine prevention • Cannabidiol oil, cannabis • Injectable monoclonal antibodies blocking the CGRP pathway[d] • Therapeutic or cosmetic botulinum toxin injections into areas of the head, face, or neck[d]

Trial name	ELEVATE	PROGRESS
	pathway[d] • Ubrogepant and rimegepant is prohibited[e] • Therapeutic or cosmetic botulinum toxin injections into areas of the head, face, or neck[d] • Cranial traction, nociceptive trigeminal inhibition, occipital nerve block treatments, or dental splints for headache[f] • Use of acupuncture, non-invasive neuromodulation devices for the prophylaxis of migraine[f] • Any opioid-containing medication is prohibited[e]	• Cranial traction, nociceptive trigeminal inhibition, occipital nerve block treatments, or dental splints for headache[f] • Use of acupuncture, non-invasive neuromodulation devices for the prophylaxis of migraine[f] • For China, South Korea, Japan, and Taiwan, herbal and traditional medicine is prohibited[e]
Primary outcome(s)	CFB in mean MMDs across the 12-week treatment period	
Secondary endpoints	• CFB in mean MHDs across the 12-week treatment period • CFB in mean monthly acute medication use days across the 12-week treatment period • Percentage of patients with ≥50% reduction in mean MMDs across the 12-week treatment period • CFB in MSQ v2.1 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 (all regions except Europe and Canada) • CFB in mean monthly Physical Impairment domain score of the AIM-D across the 12-week treatment period (all regions except Europe and Canada) • CFB in HIT-6 total score at Week 12 (Europe and Canada only)	
Exploratory endpoints (relevant to the submission)	• Percentage of patients with ≥30% and ≥75% reduction in mean MMDs • CFB in weekly migraine days during the first month of treatment • CFB in PGI-S score at Week 12 • CFB in MSQ v2.1 Role Function-Preventive domain score at Week 12 • CFB in MSQ v2.1 Emotional Function domain score at Week 12 • CFB in the MIDAS total score at Week 12	
Pre-planned subgroup analyses	Subgroup factor and categories (for primary efficacy endpoint): • Region: North America, Europe, Asia/Pacific • Baseline migraine days: 4 to <8; ≥8	Subgroup factor and categories: • Region: North America, Europe, and East Asia • Age group: <40 years; 40 to <65 years; ≥65 years • Sex: Male; Female

Trial name	ELEVATE	PROGRESS
	• Prior oral preventive treatment failure: o 2 classes of treatments o ≥3 classes of treatments o 3 classes of treatments	• Race: White; Asian; All other races • BMI: Underweight or normal (<25); Overweight (≥25–<30); Obese (30) • Baseline monthly migraine days: <18 days; ≥18 days • Acute medication overuse: Yes; No • Prevention medication current use: Yes; No • Prior exposure to a migraine prevention medication with proven efficacy: Yes; No • Migraine prevention medication use and number of failures: o Current use o Past Use only and "failed 0 medications or failed 1 or more medication(s) with the same mechanism of action" o Past Use only and "failed 2 or more medications with different mechanisms of action o Never used • Number of migraine prevention medication failures: o Current use or past use and "failed 0 medication" o Current use or past use and "failed 1 or more medication(s) with the same mechanism of action"
Duration of study and follow-up	The total study duration was 20 weeks, including a 4-week screening and baseline period, 12-week treatment with 4-week follow-up	

Source: AbbVie Data on File. PROGRESS CSR [Sections 9.0, 10.0], Protocol [Sections 3.1, 4.2, 4.3, 4.4, 7.2.1, 7.2.2], Statistical Analysis Plan [Section 12.2];[137] AbbVie Data on File. ELEVATE protocol [Sections 3, 4.1, 5.1, 5.2, 6.5], Statistical Analysis Plan [Section 9.6].[146]
Footnotes: [a]Oral migraine prophylaxis medications include propranolol, metoprolol, atenolol, bisoprolol, timolol, or nadolol; topiramate; flunarizine; sodium valproate or divalproex; amitriptyline or nortriptyline; venlafaxine or desvenlafaxine; lisinopril; candesartan; locally approved products (e.g., oxeterone or pizotifen); [b]60 mg QD is the principal licensed dose of atogepant in the UK marketing authorisation; [c]Stable for ≥60 days prior to screening (Visit 1); [d]Within six months prior to Visit 1 and through the study period; [e]From Visit 1 and throughout the study period; [f]Within four weeks prior to Visit 1 or at any time during the study.
Abbreviations: AIM-D: Activity Impairment in Migraine - Diary; BID: twice daily; BMI: body mass index; CFB: change from baseline; CGRP: calcitonin gene-related peptide; CM: chronic migraine; CYP3A: cytochrome P450 3A4; eDiary: electronic diary; EM: episodic migraine; HIT-6: Headache Impact Test; HIV: human immunodeficiency virus; ICHD-3: International Classification of Headache Disorders 3rd edition; MHDs: monthly headache days; MIDAS: Migraine Disability Assessment; MMD: monthly migraine days; MSQ: Migraine Specific Quality of Life Questionnaire; NA: not applicable; NSAID: non-steroidal anti-inflammatory drug; OLE: open label extension; PGI-S: patient global impression of severity scale; P-gp: p-glycoprotein; PBO: placebo; QD: once daily; SNRIs: serotonin–norepinephrine reuptake inhibitor; SSRIs: selective serotonin reuptake inhibitor.

Definition of outcome measures

The definitions of the efficacy outcomes used in ELEVATE and PROGRESS are presented in Table 5. The HIT-6, MSQ v2.1 and MIDAS questionnaires are typically used in the UK to assess HRQoL.

Table 5: Outcome definitions used in ELEVATE and PROGRESS

Outcome measure	Definition
Migraine day	A migraine day is defined as any calendar day on which a headache occurs which meets criteria A, B, and C **OR** meets criteria D and E, as listed below, as per participant eDiary. A. Headache has at least two of the following four characteristics: i. Unilateral location ii. Pulsating quality iii. Moderate or severe pain intensity iv. Aggravated by or causing avoidance of routine physical activity (e.g., walking or climbing stairs) B. At least one of the following: i. Nausea and/or vomiting ii. Photophobia and phonophobia iii. Typical aura (i.e., visual, sensory, or speech/language) accompanying or within 60 minutes before headache begins C. Duration of headache lasting two 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 will be specified. **OR** D. Any headache which fulfills one criterion from (1) and at least one criterion from (2) OR fulfills at least two criteria from (1) and no criteria from (2). 1) Headache characteristics: i. Unilateral location ii. Pulsating quality iii. Moderate or severe pain intensity iv. Aggravated by or causing avoidance of routine physical activity (e.g., walking or climbing stairs) 2) Symptoms: i. Nausea and/or vomiting ii. Photophobia and phonophobia iii. Typical aura (i.e., visual, sensory, or speech/language) accompanying or within 60 minutes before headache begins E. Duration of headache lasting two 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 will be specified.
Headache day	A headache day is defined as any calendar day on which headache pain lasting two hours or longer occurs unless an acute headache medication (e.g., ibuprofen, triptan) was used after the start of the headache, in which case no minimum duration will be specified, as per participant eDiary. Note that antiemetics are not counted as an acute headache medication for headache day identification.

Moderate/severe headache day	Moderate/severe headache day is defined as a headache day during which the maximum pain severity is either moderate or severe.
Acute MUD	An acute medication use day is defined as any day on which a patient reports, per eDiary, the intake of allowed medication(s) to treat an acute migraine. The allowed medications include the following categories of drugs: triptans, ergots, opioids, analgesics (including acetaminophen), NSAIDs (including aspirin), and antiemetics.
PGI-S	A single item used to measure the patient's overall impression of severity in relation to migraine symptoms at the time of administration of the measure. The measure uses a 5-point rating scale with responses ranging from "none" to "very severe". PGI-S was administered in the eTablet at the clinic visits.
MSQ v2.1	A 14-item questionnaire designed to measure health-related quality-of-life impairments attributed to migraine in the past four weeks. It is divided into three domains: 1. Role Function-Restrictive (MSQ-RFR) assesses how migraines limit one's daily social and work-related activities 2. Role Function-Preventive (MSQ-RFP) assesses how migraines prevent these activities 3. Emotional Function (MSQ-EF) domain assesses the emotions associated with migraines. Patients respond to items using a six-point scale. 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. MSQ v2.1 was administered in the eTablet at clinic visits.
HIT-6	A six-question assessment used to measure the impact that headaches have on a patient's ability to function. Responses are based on frequency using a five-point scale and the HIT-6 total score, which ranges from 36 to 78, is the sum of the responses. HIT-6 was administered in the eTablet at clinic visits.
MIDAS	The MIDAS is a seven-item questionnaire designed to quantify headache-related disability over a three-month period. The MIDAS score is the sum of missed work or school days, days at work or school where productivity was reduced by half or more, missed household workdays, days of household work where productivity was reduced by half or more, and missed non-work activity days due to headaches in the last three months. MIDAS was administered in the eTablet at clinic visits.

Source: AbbVie Data on File. PROGRESS CSR, Statistical Analysis Plan [Section 10.1.1];[137] AbbVie Data on File. ELEVATE Protocol [Sections 8.1, 8.9] .[147]
Abbreviations: eDiary: electronic diary; HIT-6: Headache Impact Test-6; MIDAS: Migraine Disability Assessment; MUD: medication use day; MSQ v2.1: Migraine Specific Quality of Life Questionnaire, Version 2.1; MSQ-EF: Migraine Specific Quality of Life Emotional Function; MSQ-RFP: Migraine Specific Quality of Life Role Function-Preventive; MSQ-RFR: Migraine Specific Quality of Life Role Function-Restrictive; NSAIDs: non-steroidal anti-inflammatory drugs; PGI-S: patient global impression of severity scale.

B.2.3.2 Baseline characteristics

ELEVATE

The baseline characteristics of patients included in the ELEVATE trial for the overall mITT population are presented in Table 6. These baseline characteristics were validated by clinical experts to be generalisable to patients who are anticipated to be treated with atogepant in the UK clinical practice.[5] In the overall mITT population, the majority of patients were female (atogepant 60 mg QD: [redacted]; placebo: [redacted]) and white (atogepant 60 mg QD: [redacted]; placebo: [redacted]), with a mean age of [redacted] years and [redacted] years in the atogepant 60 mg QD and placebo groups, respectively. Clinical characteristics were very similar across treatment groups in terms of MMDs (atogepant 60 mg QD: [redacted]; placebo: [redacted]) and MHDs (atogepant 60 mg QD: [redacted]; placebo: [redacted]).

Baseline characteristics of patients in the 3+ TF mITT subgroup of the overall mITT population are presented in Table 6. Similarly, the majority of the patients were female (atogepant 60 mg QD: [redacted]; placebo: [redacted]) and white (atogepant 60 mg QD: [redacted]; placebo: [redacted]), and the mean age of patients was [redacted] years and [redacted] years in the atogepant 60 mg QD and placebo groups, respectively. The baseline characteristics of the overall mITT population and 3+ TF mITT subgroup were comparable.

Table 6: Baseline characteristics of patients included in the ELEVATE trial

Demographics (overall mITT population)	**ATO 60 mg QD (N=[redacted])**	**Placebo (N=[redacted])**
Age, years, mean (SD)	[redacted]	[redacted]
Female, %	[redacted]	[redacted]
BMI, kg/m^2, mean (SD)	[redacted]	[redacted]
Race group, %		
White	[redacted]	[redacted]
All other races	[redacted]	[redacted]
Region, %		
North America	[redacted]	[redacted]
Europe[a]	[redacted]	[redacted]
Migraine History (overall mITT population)	**ATO 60 mg QD (N=[redacted])**	**Placebo (N=[redacted])**
MMDs, mean (SD)	[redacted]	[redacted]
MHDs, mean (SD)	[redacted]	[redacted]
Monthly acute MUDs, mean (SD)	[redacted]	[redacted]
MSQ-RFR, mean (SD)	[redacted]	[redacted]
Migraine History (safety population)	**ATO 60 mg QD (N=[redacted])**	**Placebo (N=[redacted])**
Migraine disorder duration (years), mean (SD)	[redacted]	[redacted]

Source: AbbVie Data on File. ELEVATE CSR [Tables Table 14.1-1.1.B, 14.1-3.1.2, 14.1-3.1.5, 14.1-3.2.2, 14.1-4.1.A, 14.2-4.6.A, 14.2-4.11.A, 14.2-4.14.A, 14.2-5.1.A; 14.2-5.11.A, 14.2-5.14.A].[138]
Footnotes: [a]The ELEVATE study included 3 patients in the UK.
Abbreviations: ATO: atogepant; BMI: body mass index; MHDs: monthly headache days; mITT: modified intent-to-treat; MMDs: monthly migraine days; MSQ-RFR: Migraine-Specific Quality of Life Role Function – Restrictive domain score; QD: once daily; SD: standard deviation; UK: United Kingdom.

Table 7: Baseline characteristics of patients included in the ELEVATE trial (3+ TF mITT subgroup)

Demographics (3+ TF mITT population)	**ATO 60 mg QD (N=[redacted])**	**Placebo (N=[redacted])**
Age, years, mean (SD)	[redacted]	[redacted]
Female, %	[redacted]	[redacted]
BMI, kg/m^2, mean (SD)	[redacted]	[redacted]
Race group, %		
White	[redacted]	[redacted]
All other races	[redacted]	[redacted]
Region, %		

North America	[redacted]	[redacted]
Europe	[redacted]	[redacted]
Migraine history (safety population)	**ATO 60 mg QD (N=[redacted])**	**Placebo (N=[redacted])**
Migraine disorder duration (years), mean (SD)	[redacted]	[redacted]
Migraine history (3+ TF mITT population)	**ATO 60 mg QD (N=[redacted])**	**Placebo (N=[redacted])**
MMDs, mean (SD)	[redacted]	[redacted]
MHDs, mean (SD)	[redacted]	[redacted]
Monthly acute MUDs, mean (SD)	[redacted]	[redacted]
MSQ-RFR, mean (SD)	[redacted]	[redacted]

Source: AbbVie Data on File. Atogepant Migraine MAAP 304 study_combined priority 1 2 3 analysis.[148]
Abbreviations: ATO: atogepant; BMI: body mass index; MHDs: monthly headache days; MIDAS: Migraine Disability Assessment; mITT: modified intent-to-treat; MMDs: monthly migraine days; MSQ-RFR: Migraine-Specific Quality of Life Role Function – Restrictive domain score; MUDs: medication use days; PGI-S: patient global impression of severity scale; QD: once daily; SD: standard deviation.

PROGRESS

The baseline characteristics of patients included in the PROGRESS trial are presented in Table 8. These baseline characteristics have been validated by clinical experts at a UK advisory board as generalisable to patients in UK clinical practice who are anticipated to receive atogepant.[5]

The majority of patients were female (atogepant 60 mg QD: 86.3%; placebo: 88.2%) and white (atogepant 60 mg QD: 59.8%; placebo: 57.7%), with a mean age of 41.5 years and 42.2 years in the atogepant 60 mg QD and placebo groups, respectively. A large majority of patients in both groups had ≥1 prior treatment failure, and the proportion of patients who had experienced prior treatment failures was similar across both groups. Clinical characteristics were generally comparable across treatment groups in terms of MMDs, MHDs, monthly acute MUDs, MSQ v2.1 and HIT-6 scores.

Table 8: Baseline characteristics of patients included in the PROGRESS trial[a]

Demographics (overall mITT population)	**ATO 60 mg QD (N=256)**	**Placebo (N=246)**
Age, years, mean (SD)	41.5 (12.3)	42.2 (12.4)
Female, %	86.3	88.2
BMI, kg/m^2, mean (SD)	25.0 (5.5)	25.5 (6.0)
Race group, %		
White	59.8	57.7
Asian	35.9	38.2
All other races	4.3	4.1
Region, %		
North America	29.3	27.6
Europe[b]	35.2	35.4
East Asia	35.5	37.0
Migraine history (safety population)	**ATO 60 mg QD (N=[redacted])**	**Placebo (N=[redacted])**
Migraine disorder duration (years), mean (SD)	[redacted]	[redacted]

Migraine History (overall mITT Population)	ATO 60 mg QD (N=[redacted])	Placebo (N=[redacted])
MMDs, mean (SD)	[redacted]	[redacted]
MHDs, mean (SD)	[redacted]	[redacted]
Monthly acute MUDs, mean (SD)	[redacted]	[redacted]
Weekly migraine days during the first month of treatment, mean (SD)	[redacted]	[redacted]
MSQ-RFR domain score, mean (SD)	[redacted]	[redacted]
Prior Preventive Medication Use (ITT Population), %	**ATO 60 mg QD (N=[redacted])**	**Placebo (N=[redacted])**
Current	[redacted]	[redacted]
Prior	[redacted]	[redacted]
Never	[redacted]	[redacted]
Prior preventive treatment failures (overall mITT population), %	**ATO 60 mg QD (N=[redacted])**	**Placebo (N=[redacted])**
≥1 class	[redacted]	[redacted]
≥2 classes	[redacted]	[redacted]
≥3 classes	[redacted]	[redacted]

Source: AbbVie Data on File. PROGRESS CSR [Tables 14.1-1.1, 14.1-3.1.2, 14.1-4.1.2, 14.1-4.2.1, 14.2-4.22.A.1, 14.2-4.5.B.1, 14.2-4.8.B.1, 14.2-4.10.1; Table 14.1-1.3.2, 14.2-4.23.1].[137]
Footnotes: [a]Baseline characteristics for the atogepant 30 mg BID group are available in the CSR; [b]The PROGRESS study included 1 patient in the UK.
Abbreviations: ATO: atogepant; BID: twice daily; BMI: body mass index; ITT: intent-to-treat; MHDs: monthly headache days; mITT: modified intent-to-treat; MMDs: monthly migraine days; MSQ-RFR: Migraine-Specific Quality of Life Role Function – Restrictive domain score; MUDs: medication use days; QD: once daily; SD: standard deviation.

B.2.3.3 Participant flow

ELEVATE

A total of [redacted] patients were screened for eligibility at [redacted] sites, of which [redacted] patients underwent randomisation and composed the ITT population. Of these, [redacted] patients received ≥1 dose of the study intervention, which formed the safety population, and [redacted] patients met the criteria for the overall mITT population (Table 9). The majority of the patients ([redacted]) in the ITT population completed the double-blind treatment period, and the main reasons for study discontinuation ([redacted]) included protocol deviation, AEs, and withdrawal by patient.

Further details on the patient disposition are presented in Appendix D.

PROGRESS

Among the 1,489 patients screened for eligibility at 142 sites, 711 patients discontinued from the study prior to randomisation. The remaining 778 patients, who underwent randomisation, composed the ITT population. Of these, 773 patients received ≥1 dose of the study intervention, which formed the safety population, and 755 patients met the criteria for the overall mITT population (Table 9). The majority of the patients (89.2%) in the overall mITT population completed the double-blind treatment period, and the main reasons for study discontinuation (10.8%) included AEs and withdrawal by the patient. Similarly, the majority of randomised patients ([redacted]) who entered the safety follow-up period completed the safety follow-up, with the main reason for discontinuation ([redacted]) being AEs.

Further details on the patient disposition are presented in Appendix D.

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

The definitions used for the study populations in the trials are presented in Table 9. In line with the prior appraisal of galcanezumab (TA659),[2] a population of patients who received at least one dose of study intervention and had an evaluable baseline and post-baseline period per eDiary is appropriate to accurately assess efficacy across treatment arms. The overall mITT population was used for all efficacy and baseline analyses, including the indirect comparisons presented in Section B.2.8. Patients were included in the analysis according to the treatment groups to which they were randomised. A summary of the statistical analysis methods used in the trials are presented in Table 10.

Table 9: Trial populations used for the analysis of outcomes in PROGRESS and ELEVATE

Analysis Set	Definition
Intent-to-treat (ITT) population	Includes all randomised patients
Safety population	All patients who received ≥1 dose of study intervention. All safety analyses were performed using the Safety Population and based on the treatment actually received, regardless of assigned treatment according to the planned randomisation. Patients were summarised according to the study treatment received for the majority of treatment period.
Modified intent-to-treat (overall mITT) population	All randomised patients who received ≥1 dose of study intervention, had an evaluable baseline period of eDiary data, and had ≥1 evaluable post-baseline four-week period (Weeks 1 to 4, 5 to 8, and 9 to 12) of eDiary data during the double-blind treatment period. This population was used for the efficacy analyses.
Off-Treatment Hypothetical Estimand Population	Includes all randomised patients who received at least one dose of study treatment, had an evaluable baseline period of eDiary data and had at least one evaluable post-baseline four-week period (Weeks 1 to 4, 5 to 8, 9 to 12) of eDiary data during the double-blind treatment period and follow-up period, regardless of whether on study treatment or off study treatment. This population was required by the EMA to inform the efficacy analysis in support of regulatory filings in Europe but has not been considered further in this submission, with all efficacy analyses reported for the overall mITT population that informs subsequent indirect comparisons presented in B.2.8.[a]

Source: AbbVie Data on File. PROGRESS CSR [Section 10.3];[137] AbbVie Data on File. ELEVATE Protocol [Section 9.3].[146]
Footnotes: [a] This population was an EMA requirement and differences between the Off-Treatment Hypothetical Estimand and mITT populations are minimal.
Abbreviations: eDiary: electronic diary; EMA: European Medicines Agency; ITT: intent-to-treat; mITT: modified intent-to-treat.

Table 10: Statistical methods for the primary analysis

Trial	ELEVATE	PROGRESS
Hypothetical objective	The primary efficacy endpoint is the CFB in mean MMDs across the 12-week treatment period: • Null: ATO 60 mg QD is equally effective to placebo in decreasing from baseline in mean MMDs across the 12-week treatment period • Alternative: ATO 60 mg QD is superior to placebo in decreasing from baseline in mean MMDs across the 12-week treatment period	The primary efficacy endpoint is the CFB in mean MMDs across the 12-week treatment period: • Null: ATO 30 mg BID and 60 mg once daily are each equally effective as placebo in mean CFB in mean MMDs across the 12-week treatment period • Alternative: ≥1 of the 2 doses of atogepant has a greater effect than placebo
Statistical analysis	• Baseline was defined as the number of migraine days during the last 28 days prior to the randomisation date • The primary efficacy analyses were based on the overall mITT population • The primary endpoint was analysed using a MMRM • The statistical model included treatment group, visit, region, number of classes of failed prior preventive treatments, and treatment group by visit interaction as categorical fixed effects. It also included the baseline MMDs and baseline-by-visit interaction as covariates • Restricted maximum likelihood method was used, and the within-patient correlation was modelled using the unstructured covariance matrix • Treatment effect and treatment comparison were estimated by the LS Means and their difference in LS Means, along with their SE and 95% confidence interval, and the p-value corresponding to the between-treatment group difference • A fixed-sequence procedure was used for multiple comparisons to control the family-wise error rate at α = 0.05 for each set of primary and secondary endpoint comparisons between atogepant 60 mg QD versus placebo • Other efficacy analyses were performed at the nominal significance level without adjusting for multiplicity	• Baseline was defined as the number of migraine days during the last 28 days prior to the randomisation date • The primary efficacy analyses were based on the overall mITT population • The primary endpoint was analysed using a MMRM • The statistical model included treatment group, visit, region, acute migraine medications during the baseline period, current and past use of migraine prevention medications and the number of medications failed with unique mechanisms of action, and treatment group by visit interaction as categorical fixed effects. It also included the baseline MMDs and baseline-by-visit interaction as covariates • Restricted maximum likelihood method was used, and the within-patient correlation was modelled using the unstructured covariance matrix • Treatment effect and treatment comparison were estimated by the LS Means and their difference in LS Means, along with their SE and 95% confidence interval, and the p-value corresponding to the between-treatment group difference • The overall type I error rate for multiple comparisons across the two atogepant doses and the primary and secondary efficacy endpoints was controlled at the 0.05 level using a graphical approach • Other efficacy analyses were performed at the nominal

Trial	ELEVATE	PROGRESS
		significance level without adjusting for multiplicity
Sample size, power calculation	• A planned enrolment of 150 patients per treatment group provided a 97% power to detect the treatment difference between atogepant and placebo for the primary efficacy endpoint • Treatment differences from placebo in change from baseline in mean MMDs were assumed to be −1.7 days for the US and -1.6 days for the EU, respectively, and the standard deviation was assumed as 3.5 days • A fixed-sequence procedure was used for multiple comparisons to control the familywise Type I error rate at a 0.05 level. The dropout rate was assumed to be 15%	• A planned enrolment of 250 patients randomised per treatment group provided ≥96% power to detect the treatment difference between each of the two atogepant doses (assumed equally effective) and placebo for the primary efficacy endpoint • Treatment difference from placebo in change and standard deviation from baseline in mean MMDs were assumed to be −2 days and 5.5 days, respectively • Overall type I error was controlled at 5% and two-sided t-tests were conducted at a 0.025 significance level
Data management, patient withdrawals	Patients could request to withdraw from the study at any time, or they could be withdrawn at the discretion of the study doctor or sponsor due to failure to comply with instructions or safety concerns. Missing data for patients who discontinued the study treatment due to any reason were assumed to be MAR and were handled using a MMRM approach.	

Source: AbbVie Data on File. PROGRESS CSR [Section 9.5], Protocol [Sections 7.3, 7.6] Statistical Analysis Plan [Section 10.2, 14.0];[137] AbbVie Data on File. ELEVATE CSR [Section 9.5], Protocol [Section 9.2], Statistical Analysis Plan [Sections 2.1, 9.3].[147]
Abbreviations: ATO: atogepant; BID: twice daily; CFB: change from baseline; EU: European Union; LS: least squares; MAR: missing-at-random; MMDs: monthly migraine days; MMRM: mixed model for repeated measures; QD: once daily; SE: standard error; US: United States.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

Full details of the SLR, including methods and results of the quality assessment can be found in Section D.1 of Appendix D. A summary of the quality assessments conducted based on the University of York's Centre for Reviews and Dissemination (CRD) checklist for RCTs for PROGRESS and ELEVATE trials are presented in Table 11.

Table 11: Assessment of quality and risk of bias in the ELEVATE and PROGRESS trials

Criteria	Risk of bias	
	ELEVATE	PROGRESS
Was randomisation carried out appropriately?	Yes	Yes
	Randomisation was performed using IWRS	Randomisation was performed using IWRS
Was the concealment of treatment allocated adequate?	Yes	Yes
	Atogepant tablets and matching placebo were provided in identical blister cards to maintain masking of the study	Atogepant tablets and matching placebo were provided in identical blister cards to maintain masking of the study
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
	The demographics were generally balanced between treatment groups	Demographic and baseline headache characteristics of all groups were similar
Were the care providers, participants, and outcomes assessors blind to treatment allocation?	Yes	Yes
	This was a double-blinded randomised control trial where both participants and Investigators were blinded	This was a double-blinded randomised control trial where both participants and Investigators were blinded
Were there any unexpected imbalanced in dropouts between groups?	No	No
	Authors do not report any unexpected imbalances in dropouts	Authors do not report any unexpected imbalances in dropouts
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
	All outcomes measured were previously reported by authors	All outcomes measured were previously reported by authors
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes
	The efficacy analysis was carried out by Off-Treatment Hypothetical Estimand Population/ overall mITT	It includes mITT population for both safety and efficacy

Abbreviations: IWRS: Interactive Web Response System; mITT: modified intention-to-treat.

B.2.6 Clinical effectiveness results of the relevant studies

As discussed in Section B.1.1, migraine is a disease continuum and clinical experts have highlighted that data in patients with <15 headache days per month (i.e., EM) and patients with ≥15 headache days per month (i.e., CM) are complementary in evaluating the efficacy and safety of migraine treatments and should thus be viewed holistically. Clinical advice received by the EAG as part of the NICE appraisal of eptinezumab in migraine (TA871) also indicates that there is no reason for the relative treatment effect of interventions to differ between EM and CM.[12] Clinical experts consulted by AbbVie further confirmed that there is no biological rationale for a CGRP inhibitor to be effective in only one of the two EM and CM subpopulations.

This sentiment is supported by data submitted in the appraisal of another oral CGRP inhibitor, rimegepant (TA906), whereby a recommendation was made in the preventive treatment of EM based on a mixed population of both EM (77.3%) and CM patients (22.7%).[15] Within-trial analyses demonstrated no statistically signficant evidence that the odds ratios for response differed between EM and CM patients, and the EAG concluded that the use of the overall mixed population (EM and CM) rather than the EM subgroup is reasonable. The use of EM data in support of decision-making in a CM population is also supported by the ongoing appraisal of rimegepant for the treatment of acute migraine (ID1539), in which the NICE committee stated that although the relevant treatment efficacy data were collected in patients with EM, the trial results are generalisable to patients with CM.[149]

Furthermore, the appropriateness of overall mITT data in decision-making for a treatment-failure subgroup has been accepted and preferred by the NICE committee in the appraisal of rimegepant in the preventive treatment of EM (TA906), in which a recommendation was made for patients with 3+ TF based on data collected within an overall mITT study population which excluded patients with no response to at least 2 preventive treatments.[15] This decision falls in line with decision-making for rimegepant for the treatment of acute migraine (ID1539), in which a recommendation has been made for patients in whom ≥2 triptans have been tried but did not work well enough. Although treatment failure subgroup data were available for patients who had stopped 2 or more triptans because they had not worked; the ERG and NICE committee preferred to use the overall mITT data to inform the efficacy in the model. The larger dataset, the avoidance of risk of bias associated with post-hoc analyses, and the ability to incorporate all available trial data were noted as advantages of the overall mITT data.[149] Given that results from the atogepant ELEVATE trial indicate consistent clinical outcomes across EM overall mITT and 3+ TF mITT populations and there is an accepted clinical confluence of the EM and CM sub-indications, and the results from the 3+ TF mITT population of ELEVATE and overall mITT population of PROGRESS are considered broadly generalisable to 3+ TF CM patients.

A summary of the key clinical outcomes from the ELEVATE study for the 3+ TF mITT subgroup and the overall mITT population are presented in Table 12. Data from the overall mITT population in the PROGRESS trial is provided in Table 13. All scope-defined efficacy outcomes available from this study are summarised in these tables. The primary outcome of CFB in mean MMDs across the 12-week treatment period is discussed in Section B.2.6.1, and the secondary outcomes are discussed in Section B.2.6.2.

Table 12: Overview of key clinical effectiveness results from ELEVATE

Outcome		3+ TF mITT subgroup			Overall mITT population		
		Placebo (N=[redacted])	Atogepant 60 mg QD (N=[redacted])	TE[a] (95% CIs)	Placebo (N=[redacted])	Atogepant 60 mg QD (N=[redacted])	TE[a] (95% CIs)
Primary endpoint across the 12-week treatment period							
CFB in mean MMDs	LS Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secondary endpoint across the 12-week treatment period							
Achievement of ≥30% reduction in mean MMDs	Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Achievement of ≥50% reduction in mean MMDs	Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Achievement of ≥75% reduction in mean MMDs	Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB in mean MHDs	LS Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB in mean monthly acute MUDs	LS Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB in weekly migraine days during the first month of treatment	LS Mean (SE)	NA	NA	NA	[redacted]	[redacted]	[redacted]
CFB in PGI-S score (at Week 12)	LS Mean (SE)	NA	NA	NA	[redacted]	[redacted]	[redacted]
HRQoL at Week 12							
CFB in MSQ-RFR domain score	LS Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB in MSQ-RFP domain score	LS Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB in MSQ-EF domain score	LS Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CFB in HIT-6 total score	LS Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB in MIDAS total score	Mean (SE)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: AbbVie Data on File. ELEVATE CSR [Tables 14.2-1.2, 14.2-2.1.A, 14.2-2.2.A, 14.2-2.3.A, 14.2-3.4, 14.2-4.2.2.A, 14.2-4.2.3.A, 14.2-4.6.A, 14.2-4.11.A, 14.2-4.14.A, 14.2-5.11.A, 14.2-5.14.A, 14.2-5.15.A, 14.2-5.17.A]; [6] AbbVie Data on File. Atogepant Migraine MAAP 304 study_combined priority 1 2 3 analysis.[138, 148]

Footnotes: [a]TE was LSMD for all endpoints besides achievement of ≥50% reduction in mean MMDs where it was the odds ratio; *p<0.01; **p<0.001; ***p<0.0001; [b]Significant result, but no p-value reported.

Abbreviations: CFB: change from baseline; CI: confidence interval; HIT-6: Headache Impact Test; LSMD: least squares mean difference; max: maximum; min: minimum; mITT: modified intent-to-treat; MHD: monthly headache day; MIDAS: Migraine Disability Assessment; MMD: monthly migraine day; MSQ-EF: Migraine Specific Quality of Life Emotional Function; MSQ-RFP: Migraine Specific Quality of Life Role Function-Preventive; MSQ-RFR: Migraine Specific Quality of Life Role Function-Restrictive; MUD: medication use days; NA: not available; QD: once daily; SD: standard deviation; TE: treatment effect; TF: treatment failure.

Table 13: Overview of key clinical effectiveness results from PROGRESS

Outcome		Overall mITT population		
		Placebo (N=246)	Atogepant 60 mg QD (N=256)	TE[a] (95% CIs)
Primary endpoint across the 12-week treatment period				
CFB in mean MMDs	LS Mean (SE)	−5.05 (0.411)	−6.88 (0.406)	−1.82*** (−2.89, −0.75)
Secondary endpoint across the 12-week treatment period				
Achievement of ≥30% reduction in mean MMDs	Responders, n (%)	[redacted]	[redacted]	[redacted]
Achievement of ≥50% reduction in mean MMDs	Responders, n (%)	64 (26.0)	105 (41.0)	2.04*** (1.38, 3.00)
Achievement of ≥75% reduction in mean MMDs	Responders, n (%)	[redacted]	[redacted]	[redacted]
CFB in mean MHDs	LS Mean (SE)	−5.13 (0.405)	−7.00 (0.401)	−1.87*** (−2.93, −0.81)
CFB in mean monthly acute MUDs	LS Mean (SE)	−4.10 (0.392)	−6.23 (0.386)	−2.13**** (−3.13, −1.13)
CFB in weekly migraine days during the first month of treatment	LS Mean (SE)	[redacted]	[redacted]	[redacted]
CFB in PGI-S score (at Week 12)	LS Mean (SE)	[redacted]	[redacted]	[redacted]
HRQoL at Week 12				
CFB in MSQ-RFR domain score	LS Mean (SE)	[redacted]	[redacted]	[redacted]
CFB in MSQ-RFP domain score	LS Mean (SE)	[redacted]	[redacted]	[redacted]
CFB in MSQ-EF domain score	LS Mean (SE)	[redacted]	[redacted]	[redacted]
CFB in HIT-6 total score	LS Mean (SE)	[redacted]	[redacted]	[redacted]
CFB in MIDAS total score	Mean (SE)[b]	[redacted]	[redacted]	[redacted]

Source: AbbVie Data on File. PROGRESS CSR [Tables 30, 14.2-4.2.A.2, 14.2-3.2.2, 14.2-3.7.1, 14.2-4.22.A.1, 14.2-4.5.B.1, 14.2-4.8.B.1, 14.2-4.10.1, 14.2-4.14.B.1, 14.2-4.14.C.1, 14.2-4.23, 14.2-4.23.1];[137] AbbVie Data on File. Atogepant CM study 303 MAAP priority 1 to 3 analysis_updated with p value 09092022.[150]
Footnotes: [a]TE was LSMD for all endpoints besides achievement of ≥30%, ≥50% and ≥75% reduction in mean MMDs where it was the odds ratio: *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001
Abbreviations: CFB: change from baseline; CI: confidence interval; LSMD: least squares mean difference; HIT-6: Headache Impact Test; max: maximum; min: minimum; mITT: modified intent-to-treat; MHD: monthly headache day; MIDAS: Migraine Disability Assessment; MMD: monthly migraine day; MSQ-EF: Migraine Specific Quality of Life Emotional Function; MSQ-RFP: Migraine Specific Quality of Life Role Function-Preventive; MSQ-RFR: Migraine Specific Quality of Life Role Function-Restrictive; MUD: medication use days; NA: not available; QD: once daily; SD: standard deviation TF: treatment failure.

B.2.6.1 Primary outcome (CFB in MMDs)

As migraine attacks are associated with severe pain and a range of non-headache incapacitating symptoms which are highly disabling, a reduction in MMDs is a crucial outcome in the treatment of migraine.[151] In the ELEVATE study, reduction in Least Square (LS) mean MMDs across the 12-week treatment period was significantly greater in patients in the atogepant group compared with placebo (3+ TF mITT subgroup: [redacted] vs [redacted], [redacted]; overall mITT: [redacted] vs [redacted], [redacted] Figure 6). Data in the overall mITT population of the ELEVATE trial is in alignment with 3+TF mITT and therefore, supportive of observations made within the 3+ TF mITT subgroup.

Figure 6: CFB in LS mean MMDs across the 12-week treatment period in ELEVATE

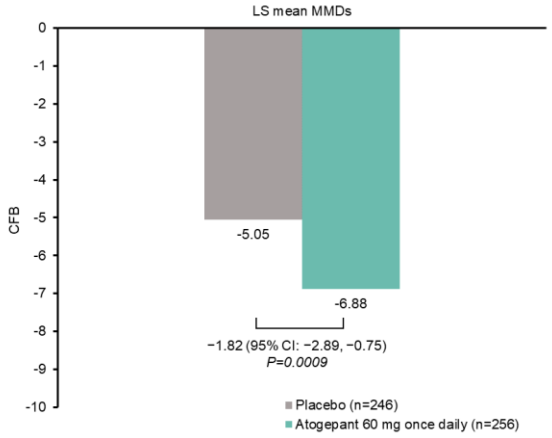
3+TF mITT **Overall mITT**

[redacted]

Source: AbbVie Data on File. ELEVATE CSR [Table 14.2-1.2];[138] ELEVATE CSR [Table 14.2-1.9].[138]
Abbreviations: CFB: change from baseline; CI: confidence interval; LS: least squares; mITT: modified intent-to-treat; MMDs: monthly migraine days; NR: not reported; TF: treatment failure.

In the PROGRESS study, a significantly greater reduction in LS mean MMDs was also observed across the 12-week treatment period in patients in the atogepant group compared with placebo (overall mITT: −6.88 vs −5.05, p=0.0009; Figure 7).

Figure 7: CFB in LS mean MMDs across the 12-week treatment period in PROGRESS



Source: AbbVie Data on File. PROGRESS CSR [Table 17].[137]

Abbreviations: CFB: change from baseline; CI: confidence interval; LS: least squares; mITT: modified intent-to-treat; MMDs: monthly migraine days.

B.2.6.2 Secondary and exploratory outcomes

Proportion of patients with ≥30%, ≥50%, and ≥75% reduction in LS mean MMDs

The American Headache Society defines success in migraine prevention as a reduction of at least 50% in MMDs.[40] Although the achievement of ≥30% reduction in LS mean MMDs can be used to inform negative stopping rules in the 3+ TF setting for CM (per NICE guidance), clinical experts have highlighted that the achievement of ≥50% reduction in LS mean MMDs also represents a clinically meaningful endpoint for CM patients.[5]

In the ELEVATE study, a significantly greater proportion of patients in the atogepant treatment group achieved ≥50% reduction in LS mean MMDs across the 12-week treatment period, compared to patients on placebo (3+ TF mITT: [redacted] vs [redacted], [redacted]; overall mITT: [redacted] vs [redacted], [redacted]Table 14). Data in the overall mITT population of the ELEVATE trial is in alignment with 3+ TF mITT and therefore, supportive of observations made within the 3+ TF mITT subgroup. In the PROGRESS study, a significantly greater proportion of patients in the atogepant group also achieved a ≥50% reduction in LS mean MMDs across the 12-week treatment period compared with placebo (overall mITT: 41.0% vs 26.0%, p=0.0003; Table 15

).

A summary of patients experiencing a ≥50% reduction, as well as a ≥30% and ≥75% reductions, in LS mean MMDs across the 12-week treatment period are presented in Table 14 for ELEVATE and **Error! Reference source not found.** for PROGRESS. Patients receiving atogepant were significantly more likely to achieve reductions in LS mean MMDs compared with patients receiving placebo across each of the response outcomes.

Table 14: Achievement of ≥30%, ≥50%, ≥75% reduction in LS mean MMDs across the 12-week treatment period in ELEVATE

Proportion of patients across 12 weeks, n (%)	3+TF mITT			Overall mITT		
	ATO 60 mg (n=[redacted])	Placebo (n=[redacted])	Odds ratio (95%CI)	ATO 60 mg (n=[redacted])	Placebo (n=[redacted])	Odds ratio (95%CI)
≥30% reduction in MMDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥50% reduction in MMDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥75% reduction in MMDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: AbbVie Data on File. ELEVATE CSR [Tables 14.2-4.2.2.A, 14.2-4.2.3.A];[138] ELEVATE Atogepant Migraine MAAP 304 study_combined priority 1 2 3 analysis;[148]
Abbreviations: ATO: atogepant; CI: confidence interval; mITT: modified intent-to-treat; MMDs: monthly migraine days; TF: treatment failure.

Table 15: Achievement of ≥30%, ≥50%, ≥75% reduction in LS mean MMDs across the 12-week treatment period in PROGRESS

Proportion of patients across 12 weeks, n (%)	PROGRESS		
	ATO 60 mg (n=256)	Placebo (n=246)	Odds ratio (95%CI)
≥30% reduction in MMDs	[redacted]	[redacted]	[redacted]
≥50% reduction in MMDs	105 (41.0)	64 (26.0)	2.04 (1.38, 3.00; p=0.0003)
≥75% reduction in MMDs	[redacted]	[redacted]	[redacted]

Source: AbbVie Data on File. PROGRESS CSR [Table 14.2-4.2.B.1, Table 14.2-3.3.1, Table 14.2-4.2.C.1].[137]
Abbreviations: ATO: atogepant; CI: confidence interval; mITT: modified intent-to-treat; MMDs: monthly migraine days.

CFB in MHDs

In the ELEVATE study, CFB in LS mean MHDs across the 12-week treatment period was significantly greater in patients in the atogepant group compared with placebo (3+ TF mITT: [redacted] vs [redacted], [redacted]; overall mITT: [redacted] vs [redacted], [redacted] Figure 8). Data in the overall mITT population of ELEVATE is in alignment with 3+TF mITT and therefore, supportive of observations made within the 3+ TF mITT subgroup.

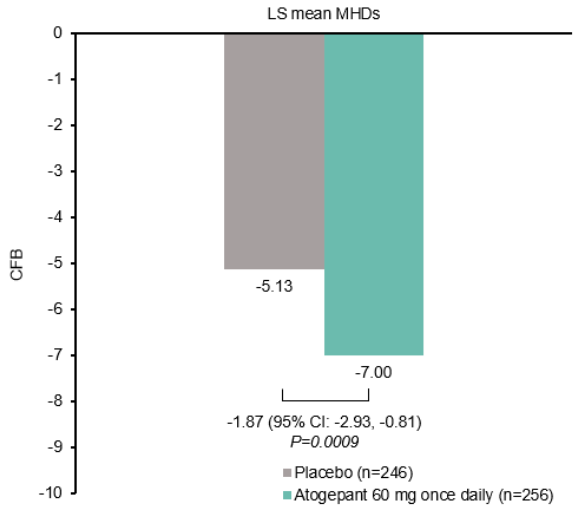
Figure 8: CFB in LS mean MHDs across the 12-week treatment period in ELEVATE

3+TF mITT **Overall mITT**

Source: AbbVie Data on File. ELEVATE CSR [Table 14.2-2.2.A];[138] ELEVATE Atogepant Migraine MAAP 304 study_combined priority 1 2 3 analysis;[148]
Abbreviations: CFB: change from baseline; CI: confidence interval; LS: least squares; mITT: modified intent-to-treat; MHDs: monthly headache days; TF: treatment failure.

In the PROGRESS study, patients in the atogepant group also had a significantly greater reduction in LS mean MHDs across the 12-week treatment period compared with placebo (overall mITT: −7.00 vs −5.13, p=0.0009, Figure 9).

Figure 9: CFB in LS mean MHDs across the 12-week treatment period in PROGRESS



Source: AbbVie Data on File. PROGRESS CSR [Table 19].[137]
Abbreviations: CFB: change from baseline; CI: confidence interval; LS: least squares; mITT: modified intent-to-treat; MHDs: monthly headache days.

CFB in monthly acute MUDs

Frequent use of acute migraine medications can lead to chronic daily migraine and medication overuse headache in patients with migraine.[152] In the ELEVATE study, CFB in LS mean monthly acute MUDs across the 12-week treatment period was significantly greater in patients in the atogepant group compared with placebo (3+ TF mITT: [redacted] vs [redacted], [redacted]; overall mITT: [redacted] vs [redacted], [redacted] Figure 10). Data in the overall mITT population of the ELEVATE trial is in alignment with 3+TF mITT and therefore, supportive of observations made within the 3+ TF mITT subgroup.

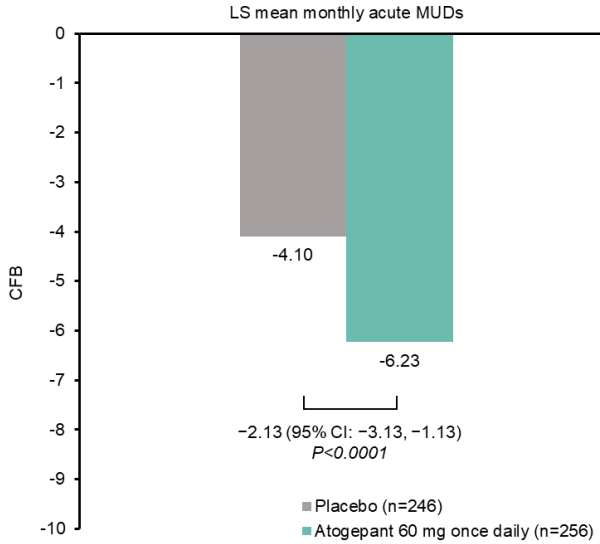
Figure 10: CFB in LS mean monthly acute MUDs across the 12-week treatment period in ELEVATE

3+TF mITT **Overall mITT**

Source: AbbVie Data on File. ELEVATE CSR [Table 14.2-2.3.A];[138] ELEVATE Atogepant Migraine MAAP 304 study_combined priority 1 2 3 analysis;[148]
Abbreviations: CFB: change from baseline; CI: confidence interval; LS: least squares; mITT: modified intent-to-treat; MUDs: medication use days; TF: treatment failure.

In the PROGRESS study, patients in the atogepant group had a greater reduction in LS mean monthly acute MUDs across the 12-week treatment period compared with placebo (overall mITT: −6.23 vs −4.10, p<0.0001; Figure 11).

Figure 11: CFB in LS mean monthly acute MUDs across the 12-week treatment period in PROGRESS



Source: AbbVie Data on File. PROGRESS CSR [Table 21].[137]
Abbreviations: CFB: change from baseline; CI: confidence interval; LS: least squares; mITT: modified intent-to-treat; MUDs: medication use days.

CFB in weekly migraine days during the first month of treatment

CFB in LS mean weekly migraine days was significantly greater in patients in the atogepant group compared with placebo in both ELEVATE (overall mITT: [redacted] vs [redacted], [redacted]; Figure 12) and PROGRESS studies (overall mITT: [redacted] vs [redacted], [redacted]; Figure 12; data not available in 3+ TF mITT subgroup of ELEVATE). ELEVATE and PROGRESS thus demonstrate the rapid efficacy of atogepant, significantly reducing weekly migraine days by a greater extent than placebo within the first month of treatment. Rapid efficacy has further been demonstrated in the proportion of patients with a migraine day during the first week of treatment. In the ELEVATE and PROGRESS studies, the atogepant group also had a significantly lower proportion of patients with a migraine day than the placebo group from 1 day after the initial dose (overall mITT; Table 16).

Figure 12: CFB in LS mean weekly migraine days during the first month of treatment in ELEVATE and PROGRESS

ELEVATE

PROGRESS

Source: AbbVie Data on File. ELEVATE CSR [Table 14.2-4.14.A];[138] PROGRESS CSR [Table 14.2-4.10.1].[137]
Abbreviations: CFB: change from baseline; CI: confidence interval; LS: least squares; mITT: modified intent-to-treat.

Table 16: Proportion of patients with a migraine day during the first week of treatment in ELEVATE and PROGRESS

Proportion of patients during the first week, n (%)	ELEVATE			PROGRESS		
	ATO 60 mg (N=[redacted])	Placebo (N=[redacted])	Odds ratio (95%CI)	ATO 60 mg (N=256)	Placebo (N=246)	Odds ratio (95%CI)
Initial dose day	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 day after initial dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 days after initial dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 days after initial dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4 days after initial dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 days after initial dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 days after initial dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: AbbVie Data on File. ELEVATE CSR [Table 14.2-4.15.A];[138] PROGRESS CSR [Table 14.2-4.11.1].[137]
Abbreviations: ATO: atogepant; CI: confidence interval; mITT: modified intent-to-treat.

CFB in PGI-S score

PGI-S measures a patient's global impression of the severity of their migraine symptoms, where a higher score indicates a greater severity. Patients in the atogepant group had a significantly greater reduction in LS mean PGI-S score across the 12-week treatment period compared with placebo in both the ELEVATE study (overall mITT: [redacted] vs [redacted], [redacted]; Figure 13) and the

PROGRESS study (overall mITT: [redacted] vs [redacted], [redacted], Figure 13; data not available in 3+ TF mITT subgroup of ELEVATE).

Figure 13: CFB in LS mean PGI-S score at Week 12 in ELEVATE and PROGRESS

ELEVATE **PROGRESS**

Source: AbbVie Data on File. ELEVATE CSR [Table 14.2-5.14.A];[138] PROGRESS CSR [Table 14.2-4.23.1].[137]
Abbreviations: CFB: change from baseline; CI: confidence interval; LS: least squares; mITT: modified intent-to-treat; PGI-S: patient global impression of severity scale.

B.2.6.3 HRQoL outcomes

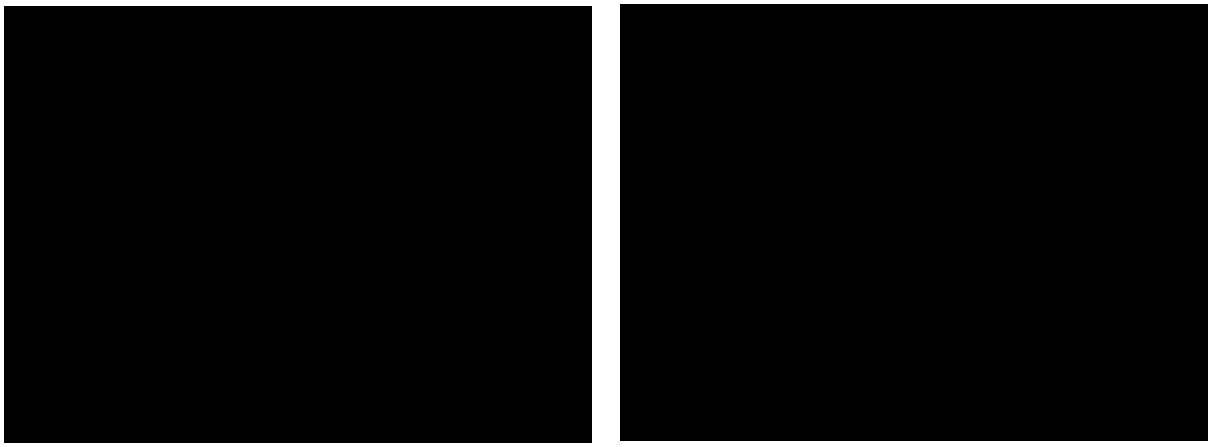
HRQoL outcomes were measured using the MSQ v2.1, HIT-6, and MIDAS questionnaires (as described in Table 5) which are recommended in international guidelines for the assessment of treatment response.[40, 112, 116-118] As specified in B.1.3.3, HRQoL measures are particularly important in the assessment of migraine by representing both migraine severity and/or patient disability which would not otherwise be captured by outcomes assessing migraine frequency alone. Across ELEVATE and PROGRESS, patients in the atogepant group reported significantly better HRQoL outcomes compared with patients in the placebo group in the overall mITT population. In the ELEVATE study, these data were in alignment with findings in the 3+ TF mITT population, and therefore can be considered supportive of the observations made in this patient subgroup. Improvements in HRQoL indicative of reduced migraine severity and/or patient disability is further supported by significant improvements in CFB in moderate/severe MHDs and CFB in monthly cumulative headache hours observed across both ELEVATE and PROGRESS studies (Appendix G); as well as CFB in PGI-S score (Section B.2.6.2)

CFB in MSQ v2.1 Role Function – Restrictive domain score (MSQ-RFR)

MSQ-RFR assesses the impact of migraines in terms of limiting one's daily social and work-related activities, whereby a higher score indicates a better HRQoL. In the ELEVATE study, significantly greater improvement in LS mean MSQ-RFR score were observed at Week 12 in the atogepant group compared with placebo (3+TF mITT: [redacted] vs [redacted], [redacted]; overall mITT: [redacted] vs [redacted], [redacted] Figure 14). The difference in improvement between atogepant and placebo is considerably higher than the minimally important difference in MSQ-RFR score (3.2 points for both EM and CM), indicating that this improvement is clinically meaningful.[153] Data in the overall mITT population of the ELEVATE trial is in alignment with 3+TF mITT and therefore, supportive of observations made within the 3+ TF mITT subgroup.

Figure 14: CFB in LS mean MSQ-RFR score at Week 12 in ELEVATE

3+TF mITT **Overall mITT**



Source: AbbVie Data on File. ELEVATE CSR [Table 14.2-3.1.A];[138]ELEVATE Atogepant Migraine MAAP 304 study_combined priority 1 2 3 analysis;[148]
Abbreviations: CFB: change from baseline; CI: confidence interval; LS: least squares; mITT: modified intent-to-treat; MSQ-RFR: Migraine-Specific Quality of Life Role Function – Restrictive domain; TF: treatment failure.

In the PROGRESS study, patients in the atogepant group also had a significantly greater improvement in LS mean MSQ-RFR score across the 12-week treatment period compared with placebo (overall mITT: [redacted] vs [redacted], [redacted], Figure 15).

Figure 15: CFB in LS mean MSQ-RFR score at Week 12 in PROGRESS

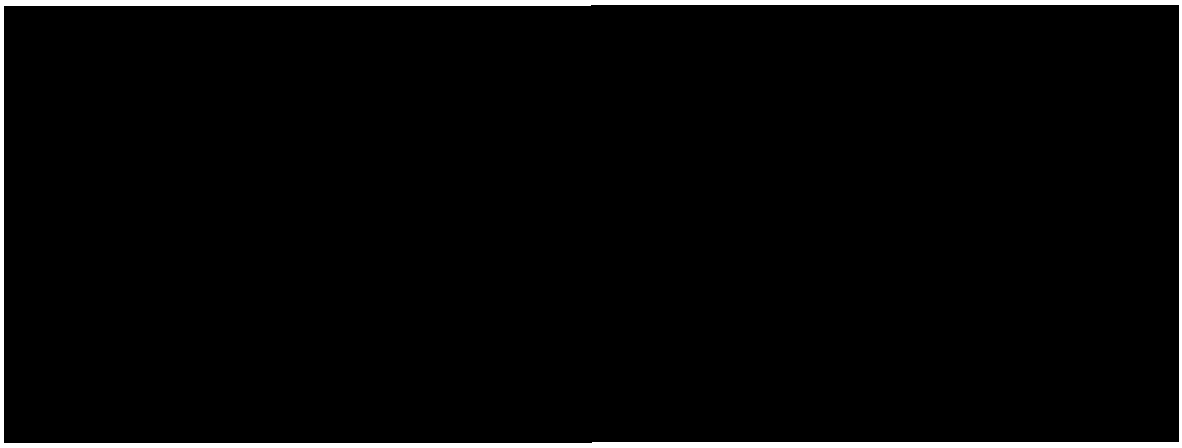
Source: AbbVie Data on File. PROGRESS CSR [Table 14.2-3.7.1].[137]
Abbreviations: CFB: change from baseline; CI: confidence interval; LS: least squares; mITT: modified intent-to-treat; MSQ-RFR: Migraine-Specific Quality of Life Role Function – Restrictive domain.

CFB in MSQ v2.1 Role Function – Preventive domain score (MSQ-RFP)

MSQ-RFP assesses the impact of migraines in terms of preventing one's daily social and work-related activities, whereby a higher score indicates a better HRQoL. In the ELEVATE study, a significantly greater improvement in LS mean MSQ-RFP score was observed at Week 12 in the atogepant group compared with placebo (3+TF mITT: [redacted] vs [redacted], [redacted]; overall mITT: [redacted] vs [redacted], [redacted]Figure 16). The difference in improvement between atogepant and placebo is considerably higher than the minimally important difference in MSQ-RFP score (4.6 points for both EM and CM), indicating that this improvement is clinically meaningful.[153] Data in the overall mITT population of the ELEVATE study is in alignment with 3+TF mITT and therefore, supportive of observations made within the 3+ TF mITT subgroup.

Figure 16: CFB in LS mean MSQ-RFP score at Week 12 in ELEVATE

3+TF mITT **Overall mITT**



Source: ELEVATE CSR [Table 14.2-5.15.A];[138] AbbVie Data on File. ELEVATE Atogepant Migraine MAAP 304 study_combined priority 1 2 3 analysis.[148]
Abbreviations: CFB: change from baseline; CI: confidence interval; LS: least squares; mITT: modified intent-to-treat; MSQ-RFP: Migraine-Specific Quality of Life Role Function – Preventive domain; TF: treatment failure.

In PROGRESS study, patients in the atogepant group had a significantly greater improvement in LS mean MSQ-RFP score across the 12-week treatment period compared with placebo (overall mITT: [redacted] vs [redacted], [redacted], Figure 17).

Figure 17: CFB in LS mean MSQ-RFP score at Week 12 in PROGRESS

Source: AbbVie Data on File. PROGRESS CSR [Table 14.2-4.14.B.1].[137]
Abbreviations: CFB: change from baseline; CI: confidence interval; LS: least squares; mITT: modified intent-to-treat; MSQ-RFP: Migraine-Specific Quality of Life Role Function – Preventive domain.

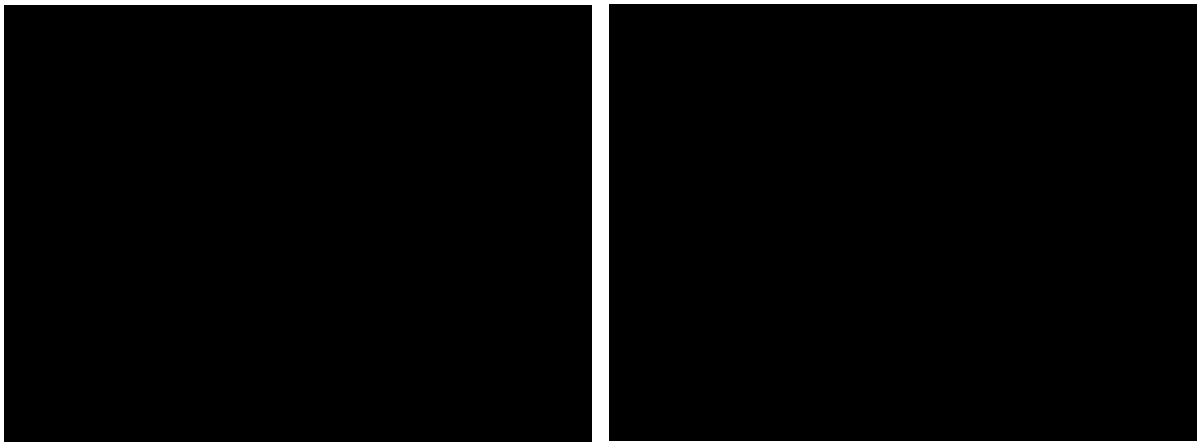
CFB in MSQ v2.1 Emotional Function (MSQ-EF)

MSQ-EF assesses patients' emotions associated with migraines, whereby a higher score indicates a better HRQoL. In the ELEVATE study, a significantly greater improvement in LS mean MSQ-EF score was observed at Week 12 in the atogepant group compared with placebo (3+ TF mITT: [redacted] vs [redacted], [redacted]; overall mITT: [redacted] vs [redacted], [redacted]Figure 18). The difference in improvement between atogepant and placebo is considerably higher than the minimally important difference in MSQ-EF score (7.5 points for both EM and CM), indicating that

this improvement is clinically meaningful.[153] Data in the overall mITT population of ELEVATE is in alignment with 3+ TF mITT and therefore, supportive of observations made within the 3+ TF mITT subgroup.

Figure 18: CFB in LS mean MSQ-EF score at Week 12 in ELEVATE

3+TF mITT **Overall mITT**



Source: AbbVie Data on File. ELEVATE CSR [Table 14.2-5.17.A];[138] ELEVATE Atogepant Migraine MAAP 304 study_combined priority 1 2 3 analysis.[148]
Abbreviations: CFB: change from baseline; CI: confidence interval; LS: least squares; mITT: modified intent-to-treat; MSQ-EF: Migraine-Specific Quality of Life Emotional Function; TF: treatment failure.

In the PROGRESS study , patients in the atogepant group had a significantly greater improvement in LS mean MSQ-EF score across the 12-week treatment period compared with placebo (overall mITT: [redacted] vs [redacted], [redacted]; Figure 19).

Figure 19: CFB in LS mean MSQ-EF score at Week 12 in PROGRESS

PROGRESS

Source: AbbVie Data on File. PROGRESS CSR [Table 14.2-4.14.C.1].[137]
Abbreviations: CFB: change from baseline; CI: confidence interval; LS: least squares; mITT: modified intent-to-treat; MSQ-EF: Migraine-Specific Quality of Life Emotional Function.

CFB in HIT-6 scores

HIT-6 is a measure of the impact of headaches on ability to function, whereby a higher score is associated with a greater impact on functioning and hence lower HRQoL. In the ELEVATE study,

a significantly greater improvement in LS mean HIT-6 score was observed at Week 12 in the atogepant group compared with placebo (3+ TF mITT: [redacted] vs [redacted], [redacted]; overall mITT: [redacted] vs [redacted], [redacted] Figure 20). The difference in improvement between atogepant and placebo is higher than the minimally important difference in HIT-6 (−1.5 points for both EM and CM), indicating that this improvement is clinically meaningful.[154, 155] Data in the overall mITT population of the ELEVATE study is in alignment with 3+TF mITT and therefore, supportive of observations made within the 3+ TF mITT subgroup.

Figure 20: CFB in LS mean HIT-6 score at Week 12 in ELEVATE

3+TF mITT **Overall mITT**

Source: AbbVie Data on File. ELEVATE CSR [Table 14.2-5.1.A];[138] ELEVATE Atogepant Migraine MAAP 304 study_combined priority 1 2 3 analysis.[148]
Abbreviations: CFB: change from baseline; CI: confidence interval; HIT-6: Headache Impact Test-6; LS: least squares; mITT: modified intent-to-treat; TF: treatment failure.

In the PROGRESS study, patients in the atogepant group had a significantly greater improvement in LS mean HIT-6 score across the 12-week treatment period compared with placebo (overall mITT: [redacted] vs [redacted], [redacted], Figure 21).

Figure 21: CFB in LS mean HIT-6 score at Week 12 in PROGRESS

Source: AbbVie Data on File. PROGRESS CSR [Table 14.2-3.7.1].[137]
Abbreviations: CFB: change from baseline; CI: confidence interval; HIT-6: Headache Impact Test-6; LS: least squares; mITT: modified intent-to-treat.

CFB in MIDAS total scores

MIDAS is a measure of headache-related disability over a three-month period, whereby a higher score is associated with a greater degree of disability due to headaches and hence lower HRQoL. In the ELEVATE study, the reduction in LS mean MIDAS score was numerically greater at Week 12 in the atogepant group compared with placebo (3+ TF mITT: [redacted] vs [redacted], [redacted]; overall mITT: not reported; Figure 22). The difference in improvement between atogepant and placebo is considerably higher than the minimally important difference in MIDAS (−4.5 points for both EM and CM), indicating that this improvement is clinically meaningful.[156]

Figure 22: CFB in LS mean MIDAS score at Week 12 in ELEVATE

3+TF mITT[a]

Footnotes: [a]The LS mean values for the CFB in MIDAS score were not reported for the overall mITT population in ELEVATE. However, the LS mean difference between atogepant and placebo across the 12-week treatment period was reported to be −[redacted] (95% CI: −[redacted], −[redacted]; p=[redacted]).

Source: AbbVie Data on File. ELEVATE CSR [Table 14.2-5.11.A];[138] ELEVATE Atogepant Migraine MAAP 304 study_combined priority 1 2 3 analysis.[148]
Abbreviations: CFB: change from baseline; CI: confidence interval; LS: least squares; MIDAS: Migraine Disability Assessment; mITT: modified intent-to-treat; TF: treatment failure.

In the PROGRESS study, patients in the atogepant group had a significantly greater reduction in LS mean MIDAS score across the 12-week treatment period compared with placebo (overall mITT: [redacted] vs [redacted], [redacted]; Figure 23).

Figure 23: CFB in LS mean MIDAS score at Week 12 in PROGRESS
PROGRESS

Source: AbbVie Data on File. PROGRESS CSR [Table 14.2-4.22.A.1].[137]
Abbreviations: CFB: change from baseline; CI: confidence interval; LS: least squares; MIDAS: Migraine Disability Assessment; mITT: modified intent-to-treat.

B.2.7 Other pre-planned subgroup analyses

To identify any variation in the efficacy of atogepant, the primary endpoint was analysed by several demographic and disease characteristics (as shown in Table 4). Across the majority of demographic and disease characteristic subgroups, treatment with atogepant showed greater reduction in LS mean MMDs across the 12-week treatment period compared with placebo for both trials. For the PROGRESS trial, the sample sizes for some subgroup categories were too small to infer clinical meaningful difference. Full results are presented in Appendix E.

B.2.8 Meta-analysis

The ELEVATE trial was a Phase 3, multicentre RCT evaluating the efficacy, safety, and tolerability of atogepant for the prophylaxis of migraine in patients with EM in whom 2 to 4 classes of oral preventive treatments have previously failed. PROGRESS was the only trial identified in the SLR evaluating the efficacy and safety of atogepant for the prevention of migraine in adults with CM, therefore no meta-analysis was necessary. An additional trial, ADVANCE, was identified in the SLR, which evaluated the efficacy and safety of atogepant for the prevention of migraine in adults with EM. However, given the overall mITT population of this study included very few patients in whom ≥3 prior preventive treatments have failed (atogepant 60 mg QD [n=[redacted]; placebo [n=[redacted]), a standard meta-analysis was not considered. Given the lack of head-to-head RCT data for atogepant vs the relevant comparators in UK clinical practice, a network meta-analysis was performed to indirectly compare the efficacy, HRQoL and safety of atogepant versus relevant comparators, and includes all three atogepant trials (Section B.2.9).

B.2.9 Indirect and mixed treatment comparisons

As atogepant and the relevant comparators have not been studied in head-to-head RCTs, NMAs have been conducted to provide comparative evidence in both EM and CM populations. NMAs have been conducted for efficacy, HRQoL and safety outcomes. HRQoL outcomes are particularly important in migraine because unlike migraine frequency-related endpoints, they represent migraine severity as well as the level of patient disability.

B.2.9.1 Identification of comparator studies

As reported in Section B.2.1 and in line with the NICE methods guide, two SLRs were conducted in May 2020 and updated in September 2022 to identify efficacy data of treatments in patients with EM or CM to support an initial company submission in February 2023. Across the original SLR and subsequent updates, a total of 200 unique trials were identified in episodic migraine and 32 in chronic migraine. Full details of the SLR methodology and studies included in the NMA are provided in Appendix D.

B.2.9.2 Eligibility for the NMA

Studies considered for inclusion in the NMA were informed by the clinical SLR. The clinical SLR captured data from all potentially relevant studies from a global perspective, and thus a number of studies were not eligible for inclusion in the NMA (e.g., those not reporting relevant outcomes, or those investigating treatments that are not licenced for the treatment of EM or CM or investigated licenced treatments that did not represent relevant comparators for atogepant). The NMAs included studies investigating treatments that had been approved by the Food and Drug Administration or the European Medicines Agency for prophylaxis of migraine, which were specified in the NICE final scope associated with this submission. As discussed in Section B.1, SC CGRP mAbs are considered to be relevant comparators for atogepant across EM and CM. However, botulinum toxin type A was included in the NMA as a NICE-recommended treatment for the CM subset of patients. While eptinezumab and rimegepant are recommended by NICE, these recommendations had not been published at the time of scoping and these treatments are not considered established clinical practice.[15, 16]

Table 17: Summary of eligibility criteria for the NMA

Criteria	Inclusion criteria	Exclusion criteria
Patient population	Adult patients (age ≥18 years) with episodic/chronic migraine: • Overall mITT population • 3+ TF mITT subgroup (EM only)	Dissimilar populations
Treatments	Report at least two treatments of interest according to licensed EMA and FDA doses: • Atogepant • Fremanezumab • Erenumab • Galcanezumab • Botulinum toxin type A[a] • Placebo	Treatments not licensed for the treatment of EM or CM, not specified in the NICE final scope or had not received final guidance from NICE when relevant SLRs were performed
Endpoint	• CFB in MMDs • CFB in MUDs • ≥50% reduction in MMDs • ≥30% reduction in MMDs (CM only) • CFB in HIT-6 total score • CFB in MSQ-RFR • CFB in MSQ-RFP	No results of interest reported

	• CFB in MSQ-EF • TEAEs • All-cause discontinuation	
Trial design	• RCTs	• Trials with small numbers of patients (approximately <30 patients per treatment arm) were considered for exclusion as outcomes from these studies are likely to be less representative of the EM/CM population • Open-label trials were considered for exclusion

Footnotes: Eligibility criteria for the NMA reported here differ from the SLR; SLR eligibility criteria are presented in Appendix D; [a]SC CGRP mAbs are considered to be relevant comparators to the decision problem across EM + CM (see Section B.1). However, botulinum toxin type A was included in the NMA as a NICE-recommended treatment for the CM subset of patients.
Abbreviations: CFB: change from baseline; CM: chronic migraine; EM: episodic migraine; EMA: European Medicines Agency; FDA: Food and Drug Administration; HIT-6: Headache Impact Test-6; mITT: modified intent-to-treat; MMD: monthly migraine days; MSQ-EF: Migraine-Specific Quality of Life Emotional Function; MSQ-RFP: Migraine-Specific Quality of Life Role Function – Preventive domain; MSQ-RFR: Migraine-Specific Quality of Life Role Function – Restrictive domain; MUD: medication use days; NMA: network meta-analysis; RCT: randomised controlled trial; TEAE: treatment-emergent adverse event; TF: treatment failure.

Episodic migraine

The clinical SLR identified 31 trials as being potentially relevant for inclusion in the episodic migraine NMA. A total of 15 studies were excluded from the evidence base based on the eligibility criteria presented in Table 17. Therefore, 16 of the original 31 studies were included in NMAs for either the 3+ TF mITT subgroup population or the overall mITT population.

Available endpoint data for all trials considered for inclusion in the NMAs are presented in Appendix D. Twelve trials were excluded because they did not investigate at least two treatments of interest (including exploring combination therapies or irrelevant doses of treatments of interest).[157-168] Three trials were excluded on the basis of trial design alone; one study was excluded based on inclusion of a mixed population of EM/CM patients,[169] and two studies were excluded because they were long-term extension study of other trials included in the NMA (and therefore could result in double counting if included).[170, 171] The reasons for exclusion from the NMAs are summarised in Table 18, and full summary of studies excluded from evidence base is presented in Appendix D. The trials included in the EM NMA (overall mITT [including treatment failure study populations] and 3+ TF mITT populations) are summarised in Table 19.

Table 18: Summary of studies excluded from EM evidence base by category of exclusion

Category of exclusion*	Number excluded	Number remaining
Studies identified in SLR with treatments of interest	-	31
Treatments (i.e., combination therapy, irrelevant dose)	12	19
Endpoint data	-	19
Trial design (i.e., open label; small study)	3	16
Total	**15**	**16**

Footnotes: [a]Some studies could be excluded based on multiple categories; they are only assigned one category for counting.

Abbreviations: EM: episodic migraine; SLR: systematic literature review.

Table 19: Summary of study design for studies included in the EM NMA (overall mITT population and 3+ TF mITT subgroup)

Study name	Year	Treatment	Phase	Study setting	Blinding	Double-blind period (weeks)	Includes data for overall mITT population	Includes data for 3+ TF mITT
ELEVATE[138]	2022	• Atogepant 60 mg QD • Placebo	Phase 3	Multi-centre	Double blind	12	Yes[c]	Yes
ADVANCE[144]	2021	• Atogepant 10 mg QD • Atogepant 30 mg QD • Atogepant 60 mg QD • Placebo	Phase 3	Multi-centre	Double blind	12	Yes	No
CGP-MD-01[172]	2020	• Atogepant 10 mg QD • Atogepant 30 mg (QD and BID) • Atogepant 60 mg (QD and BID) • Placebo	Phase 2b/3	Multi-centre	Double blind	12	Yes	No
STRIVE[173]	2017	• Erenumab 70 mg QM • Erenumab 140 mg QM • Placebo	Phase 3	Multi-centre international	Double blind	24	Yes	No
LIBERTY[174]	2018	• Erenumab 140 mg QM • Placebo	Phase 3b	Multi-centre international	Double blind	12	Yes[c]	Yes
HALO EM[175]	2018	• Fremanezumab 225 mg QM[a] • Fremanezumab 675 mg Q3M • Placebo	Phase 3	Multi-centre international	Double blind	12	Yes	No
Bigal 2015a[176]	2015	• Fremanezumab 225 mg QM[a] • Placebo	Phase 2b	Multi-centre	Double blind	12	Yes	No

FOCUS[177]	2019	• Fremanezumab 225 mg QM[a] • Fremanezumab 675 mg Q3M • Placebo	Phase 3	Multi-centre international	Double blind	12	Yes[c]	Yes
EVOLVE-1[178]	2018	• Galcanezumab 120 mg QM[b] • Galcanezumab 240 mg QM • Placebo	Phase 3	Multi-centre	Double blind	24	Yes	No
EVOLVE-2[179]	2018	• Galcanezumab 120 mg QM[b] • Galcanezumab 240 mg QM • Placebo	Phase 3	Multi-centre international	Double blind	24	Yes	No
CONQUER[180]	2020	• Galcanezumab 120 mg QM[b] • Placebo	Phase 3b	Multi-centre international	Double blind	12	Yes[c]	Yes
Sakai 2019	2019	• Erenumab 28 mg • Erenumab 70 mg • Erenumab 140 mg • Placebo	Phase 2	Multi-centre	Double blind	24	Yes	No
Wang 2021 (EMPOwER) [181]	2021	• Erenumab 70 mg • Erenumab 140 mg • Placebo	Phase 3	Multi-centre	Double blind	12	Yes	No
Sakai 2021a[182]	2021	• Fremanezumab 225 mg monthly • Fremanezumab 675 mg once every 3 months • Placebo	Phase 2/3	Multi-centre	Double blind	12	Yes	No
Hu 2022 (PERSIST)[183]	2022	• Galcanezumab 120 mg • Placebo	Phase 3	Multi-centre	Double blind	12	Yes	No

Sakai 2020a[184]	2020	• Galcanezumab 240/120 mg • Galcanezumab 240 mg • Placebo	Phase 2	Multi-centre	Double blind	24	Yes	No

Footnotes: [a]Fremanezumab regimen is 675 mg initial dose followed by 225 mg once a month. [b]Galcanezumab regimen is a 240 mg loading dose followed by 120 mg once a month. [c] Trial only included patients with between two and four prior preventive migraine treatment failures.
Abbreviations: 3+ TF: patients with ≥3 prior preventive treatment failures; BID: twice a day; EM: episodic migraine; mITT: modified intention-to-treat; NMA: network meta-analysis; QD: once a day; QM: once a month; Q3M: once per quarter.

Chronic migraine

The clinical SLR identified 24 trials as being potentially relevant for inclusion in the chronic migraine NMA. A total of 14 studies were excluded from the evidence base based on the eligibility criteria presented in Table 17. Therefore, 10 of the original 24 studies were included in NMAs for the overall mITT population.

Available endpoint data for all trials considered for inclusion in the NMAs is presented in Appendix D. Seven trials were excluded because they did not investigate at least two treatments of interest.[185-190] One trial was excluded due to a lack of data for relevant endpoints.[191] Four trials were excluded on the basis of trial design alone; three studies were excluded based on small sample size (n <30) and one study was excluded due to open-label study design.[192-195] Two studies were excluded since MOH was required for inclusion in the trials.[196, 197] The reasons for exclusion from the NMAs are summarised in Table 20, and full summary of studies excluded from evidence base is presented in Appendix D. The trials included in the NMA (overall mITT population including treatment failure study populations) are summarised in Table 21.

Table 20: Summary of studies excluded from CM evidence base by category of exclusion

Category of exclusion[a]	Number excluded	Number remaining
Studies identified in SLR	-	24
Treatments	7	17
Endpoint data	1	16
Trial design (i.e., open label; small study)	4	12
Population	-	12
MOH required	2	10
Total	**14**	**10**

Footnotes: [a]Some studies could be excluded based on multiple categories; they are only assigned one category for counting.
Abbreviations: CM: chronic migraine; MOH: medication overuse headache; SLR: systematic literature review.

Table 21: Summary of study design for studies included in the CM NMA (overall mITT population)

Study name	Year	Treatment	Phase	Study setting	Blinding	Double-blind period (weeks)	Includes data for overall mITT
PROGRESS[198]	NA	• Atogepant 30 mg BID • Atogepant 60 mg QD • Placebo	Phase 3	Multi-centre international	Double blind	12	Yes
PREEMPT 1[199]	2010	• Botulinum toxin type A 155–195 U • Placebo	Phase 3	Multi-centre international	Double blind	24	Yes
PREEMPT 2[200]	2010	• Botulinum toxin type A 155–195 U • Placebo	Phase 3	Multi-centre international	Double blind	24	Yes
REGAIN[201]	2018	• Galcanezumab 120 mg QM[b] • Placebo	Phase 3	Multi-centre international	Double blind	12	Yes
HALO CM[202]	2017	• Fremanezumab 225 mg QM[c] • Fremanezumab 675 mg Q3M • Placebo	Phase 3	Multi-centre international	Double blind	12	Yes
Tepper 2017[203]	2017	• Erenumab 70 mg • Erenumab 140 mg • Placebo	Phase 2	Multi-centre international	Double blind	12	Yes
Bigal 2015b[204]	2015	• Fremanezumab 225 mg QM[c] • Placebo	Phase 2b	Multi-centre US	Double blind	12	Yes
FOCUS[177]	2019	• Fremanezumab 225 mg QM[a] • Fremanezumab 675 mg Q3M • Placebo	Phase 3	Multi-centre international	Double blind	12	Yes[d]
CONQUER[180]	2020	• Galcanezumab 120 mg QM[b] • Placebo	Phase 3b	Multi-centre international	Double blind	12	Yes[d]

Sakai 2021[205]	2021	• Fremanezumab 225 mg • Fremanezumab 675 mg • Placebo	Phase 3	Multi-centre	Double blind	24	Yes

Footnotes: [a]For efficacy endpoints including CFB and ≥50% response some trials used the whole treatment period whereas some evaluated endpoints in for example the last month of the treatment period; [b]Galcanezumab regimen is a 240 mg loading dose followed by 120 mg once a month; [c]Fremanezumab regimen is a starting does of 675 mg followed by 225 mg for subsequent doses**.** [d]Trial only included patients with between two and four prior preventive migraine treatment failures.
Abbreviations: 3+ TF: patients with ≥3 prior preventive treatment failures; BID: twice a day; CM: chronic migraine; mITT: modified intention-to-treat; NMA: network meta-analysis; QD: once a day; QM: once a month; Q3M: once per quarter.

B.2.9.3 Network of evidence

Network diagrams are presented in Appendix D for the EM (3+ TF mITT) and CM (overall mITT population) NMAs for the CFB in MMDs, ≥50% reduction in MMDs, ≥30% reduction in MMDs (CM only) and CFB in monthly acute MUDs endpoints.

HRQoL outcomes were only appraised in overall mITT due to limited publicly available 3+ TF HRQoL data for comparators. Network diagrams are presented in Appendix D for CFB in MSQ (RFR, RFP and EF) and CFB in HIT-6 total score in the overall mITT population.

Network diagrams are also presented in Appendix D for TEAEs and all-cause discontinuation endpoints in the overall safety population. NMAs for TEAEs and all-cause discontinuation NMAs are appropriate in the overall safety population, with clinical experts indicating that no difference in safety or tolerability would be expected across lines of treatment therapy.[5]

B.2.9.4 Heterogeneity across included trials

Study design

Trials included in the EM and CM NMAs were double-blind, multicentre studies; most commonly Phase 3 studies, although some Phase 2, 2b, 3b, 2b/3 and 2/3 studies were also included. Study duration varied across the trials. However, as presented in Table 19 and Table 21, the majority of studies included a 12-week double-blind treatment phase (availability of endpoint data is shown in Appendix D). Across the trials included in the CM NMAs, most included probable migraines and allowed enrolment of patients with MOH. Studies that exclusively enrolled patients with MOH were excluded from the analysis as described in Section B.2.9.2.

The ELEVATE, FOCUS, CONQUER and LIBERTY trials only included patients with between two and four prior preventive migraine treatment failures. Data from these studies were included in the overall mITT NMAs conducted for efficacy, HRQoL, TEAEs and all-cause discontinuation endpoints, as data reported for these treatment failure-specific studies were comparable to those of other included studies and the inclusion of all patients relevant to the treatment failure population maximises the strength of the network. The remaining trials enrolled patients in whom preventive migraine treatment had or had not failed or did not report eligibility criteria based on prior failures.

Considering inclusion and exclusion criteria, trials typically enrolled patients aged between 18 and 65 years (baseline mean age of trial patients is reported in plots in Appendix D). The definition of EM and CM was consistent across most trials. The typical definition of CM included ≥8 MMD and ≥15 mean MHD, and the typical EM definition included 4–14 mean MMDs and <15 mean MHDs. The Bigal 2015a EM trial exclusively enrolled patients with 8–14 mean MMDs and MHDs. The criteria used to define a migraine headache also varied considerably across trials (see discussion of endpoint definitions below), but were often based on International Classification of Headache Disorders (ICHD) criteria. Some trials did not report MHD inclusion criteria (EVOLVE-1, EVOLVE-2, CONQUER and Hu 2022 [PERSIST]). No trials were excluded from the analysis based on differences in trial inclusion and exclusion criteria, with the exception of studies exclusively enrolling patients with MOH.

Assessment timepoints

All primary NMA analyses were based on the efficacy assessed at the primary endpoint of each trial or where subgroup data of interest from a trial was only reported at a single timepoint. The

primary assessment timepoints for included endpoints are presented in Appendix D, the most common primary timepoint was at 12 weeks. However, this varied between studies.

Considering the trials included in the EM efficacy NMAs in the 3+ TF mITT subgroup (ELEVATE, CONQUER, FOCUS and LIBERTY), the primary endpoint was assessed from 1 to 12 weeks in all trials except LIBERTY, where the endpoint was assessed from 9 to 12 weeks. Considering the trials included in the HRQoL NMAs in the overall population, endpoints in Sakai 2019 and Sakai 2020 were assessed from 13 to 24 weeks, and from 9 to 12 weeks in LIBERTY and Wang 2021 (EMPOwER). Considering the trials included in the CM NMAs, Tepper 2017 calculated CFB using the difference at Weeks 9 to 12. The 9–12-week outcome was treated as 1–12 and no adjustments were made for length of efficacy outcomes. The PROGRESS trial calculating CFB as the change in MMDs from baseline to each post-baseline month averaged over the three study months. Furthermore, the assessment timepoint was 24 weeks for the primary endpoints of the PREEMPT 1 and 2 trials investigating botulinum toxin type A; these data were included in the NMAs alongside the 12-week data for atogepant and the SC CGRP mAbs.

Safety and tolerability outcomes and all-cause discontinuation used in the analysis were typically reported across the total treatment period, varying between 12–24 weeks for EM and CM, as per Table 19 and Table 21, respectively.

Patient population

The characteristics summarised below were identified as potential prognostic factors and treatment effect modifiers, as identified in a previous NMA conducted in EM.[206] Generally, data were not comprehensively reported specifically for EM patients with 3+ TFs. Further details on potential heterogeneity of studies included in the NMA and the baseline characteristics of the studies included are presented in Appendix D.

Age: Age was identified in the previous NMA as a possible effect modifier. However, it was judged to be an unlikely effect modifier in the trials identified for these analyses due to the age range being fairly similar across the trials. Average age across trials considered for the EM overall mITT NMAs was approximately 41 years and ranged from approximately 44–46 years across the trials considered for the EM 3+ TF mITT NMAs. Mean age ranged from 40.73 to 46.8 years across trials considered for the CM overall mITT NMAs.

Sex: There was some variation among trials with regards to the proportion of female patients, which was identified in the previous NMA as a possible effect modifier. The proportion of female patients was between 80–90% for trials considered for the EM overall mITT NMAs. This proportion ranged from 80.9% to 87.7% across trials considered in the CM overall mITT NMAs. However, as most trials were performed in a predominantly female population, it was judged to be an unlikely effect modifier in the trials identified for these analyses.

Concomitant therapy: Concomitant therapies were determined to be a potential effect modifier; however, the literature displayed mixed results with a number of trials including, and others excluding, patients with concomitant preventive medications. A summary of concomitant treatment for the trials included in these analyses is provided in Appendix D.

Duration of treatment: Duration of treatment was considered to be a potential effect modifier depending on the mechanism of action of the treatment. Duration of treatment may have a minor effect modification for treatments with immediate effect. The duration of double-blinded treatment

varied between trials; however, the initial treatment period prior to response assessment is used for the NMA and was broadly consistent across trials as noted above.

Race: As described in Section B.2.9.2, one study in CM and five in EM were performed in entirely Asian populations. These studies were associated with a range of differences in patient population characteristics (not race alone), as well as some deviations from the mean values calculated across all trials in terms of age, race and body mass index. Additionally, the studies in CM were associated with differences in the number of baseline MMDs compared with the overall mean baseline MMDs across all trials. Thus, including these trials in the NMA could introduce some heterogeneity and represents a limitation of the NMA, but were included to maximise the strength of the network. Across the remaining trials, patients were predominantly white, and the distribution was reasonably homogeneous.

Baseline migraine days: Across the trials considered for the EM overall mITT NMAs, baseline mean MMDs was typically between 7–10 days. Bigal 2015a reported a higher mean MMDs at baseline (approximately 11.5 days), but this was not unexpected given it exclusively enrolled patients with 8–14 mean MMDs and MHDs. FOCUS only reported mean number of MMDs at baseline for the total EM and CM (between 14.1 and 14.3 days). Across the trials considered for the CM overall mITT NMAs, mean MMDs at baseline ranged from 15.66 and 19.45 days. The overall pooled mean baseline MMD was 17.88 in the CM overall mITT population, with substantial variation in baseline MMD across trials from the pooled mean. Similar to the values for the overall mITT population, the mean MMD at baseline across the trials relevant to the 3+ TF mITT population in EM was between 9–10 days.

Other characteristics: In addition to the above characteristics, the following characteristics were identified as potential effect modifiers:

- **Comorbidities**: limited data were available to compare patients' comorbidities across trials
- **Duration of disease**: limited data were available for patients' duration of disease
- **Year of study publication**: publication year ranged from 2015 to 2022 across EM trials and from 2010 to 2020 (excluding unpublished atogepant trials) across CM trials

Number of prior treatment failures

Within the overall mITT populations, there was heterogeneity in the proportion of patients with prior preventive treatment failures. Across the studies included in the EM overall mITT NMAs, excluding those studies that only enrolled patients with 2–4 prior treatment failures, the proportion of patients with no prior preventive treatment failures ranged from 48.02% in ADVANCE to 81.58% in the EVOLVE-1 trial. ADVANCE had correspondingly higher proportions of patients with prior preventive treatment failures than comparator trials. As expected, studies that only enrolled patients with 2–4 prior treatment failures (ELEVATE, FOCUS, CONQUER and LIBERTY) had higher proportions of patients with prior treatment failures. In the 3+ TF mITT populations, these same four studies were included. Nonetheless, there was limited heterogeneity across these trials, with the ELEVATE, FOCUS and CONQUER trials enrolling patients with 2, 3 or 4 prior preventive treatment failures, and LIBERTY enrolling patients with 2 or >2 prior preventive treatment failures.

Across the studies included in the CM overall mITT NMAs, excluding those studies that only enrolled patients with 2–4 prior treatment failures (FOCUS and CONQUER) the proportion of patients with no prior preventive treatment failures ranged from [redacted]% in PROGRESS to 49.28% in the REGAIN trial. PROGRESS had a correspondingly higher proportion of patients with one or

two prior treatment failures compared with comparator trials, but a smaller proportion of patients with ≥3 prior treatment failures. There was also heterogeneity in whether trials reported prior treatments by medication or by class.

Endpoint definitions

There was variation in the definition of endpoints across the trials included in the NMA and definitions are reported in full in Appendix D.

The majority of CM trials defined a migraine day as ≥4 continuous hours of headache meeting ICHD criteria for migraine (PREEMPT 1 and 2 used the ICHD-2 criteria, whereas other trials used ICHD-3). STRIVE, LIBERTY, EVOLVE-1 and EVOLVE-2 defined a migraine day as a migraine lasting ≥30 minutes with ≥2 pain features (e.g., throbbing) and ≥1 associated symptoms (e.g., nausea/vomiting). Similarly, the CONQUER and REGAIN trials defined a migraine day as a headache lasting ≥30 minutes with features meeting ICHD-3 criteria for migraine or probable migraine. While in EM trials, the ADVANCE, CGP-MD-01, ELEVATE, PROGRESS and HALO studies specified that patients must have ≥2 continuous hours of migraine headache (or no minimum duration if an acute, migraine-specific medication was used).

Multiple types of data were reported for all-cause discontinuation. Some studies reported study withdrawal, where others reported treatment discontinuation. Overall, there are various sources of heterogeneity identified between the trials included in the NMA, which have potential to confound the results of these analyses.

Placebo efficacy

Variation in placebo efficacy was observed across the trials included in the NMA. A detailed comparison of placebo response rates across the trials included in the EM and CM overall mITT and 3+ TF mITT NMAs are presented in Appendix D.

Across EM trials, there were differences in placebo efficacy for certain outcomes; the Bigal 2015, CGP-MD-01 and ADVANCE trials reported higher efficacy for placebo (greater CFB in MMDs and MUDs) than STRIVE, EVOLVE-2 and HALO EM. The high placebo efficacy rates in the Bigal 2015 trial are likely due to the enrolment of patients with 8–14 mean MMDs and MHDs (e.g., due to regression to the mean). Placebo response was generally lower for studies that only enrolled patients with 2–4 prior treatment failures, which is to be expected given the patients within these studies have a more extensive experience of treatment failure. Similarly, in CM trials, there was a notable difference in placebo efficacy between PREEMPT and PROGRESS trials and trials investigating SC CGRP mAbs in both overall mITT and 3+ TF mITT populations. The PREEMPT and PROGRESS trials reported consistently higher efficacy for placebo (greater CFB in MMDs and MUDs and higher proportions of patients achieving ≥50% reduction in MMDs) than REGAIN, FOCUS and CONQUER.

UK clinical experts noted that the high placebo efficacy observed in atogepant trials may be due to the more frequent, oral administration of atogepant, in contrast to CGRP mAbs that are administered by SC injection. Prior appraisals in migraine have also noted that placebo effects may be impacted by differences in mode of administration.[8] The experts also highlighted that the PROGRESS (2019–2022) trial was conducted during the COVID-19 pandemic. Lockdown restrictions could have led to fewer opportunities for patients to see clinicians outside of a trial setting and it is uncertain as to whether this could have a differential impact on patients receiving placebo compared to those receiving an active treatment in a trial setting, where patients may feel supported during mandated clinician visits.[5] The high placebo efficacy associated with

botulinum toxin type A may also be due to its mode of administration, which requires a higher number of more invasive injections than the SC CGRP mAbs.[207, 208] These differences in placebo efficacy may bias the NMA results in favour of SC CGRP mAbs, meaning that it is important to consider baseline risk adjustment via meta-regressions to account for heterogeneity of this placebo effect, as discussed in Section B.2.9.5 below.

B.2.9.5 Methods

The NMA used Bayesian methods to estimate the relative efficacy, safety, and tolerability of atogepant compared with existing treatments. Given the heterogeneity identified within the NMA networks, both fixed effect (FE) and random effects (RE) models were fitted for each endpoint. The RE models include a parameter to include a between-trial standard deviation (SD) to allow for the possibility of heterogeneity between studies. Baseline risk meta-regressions were also explored to account for difference in placebo effect that was observed across the included trials, which may represent a proxy for cross-trial variability in multiple (measured and unmeasured) confounders.[209, 210] This is in line with the approach taken in the recent NICE appraisal of rimegepant for preventing migraine (TA906) in which the EAG preferred the use of a RE baseline risk-adjusted NMA.[15] In a Bayesian NMA, 'statistically significant' indicates a result in which the 95% CrI of a comparison does not include the null value (0 in the case of mean differences, and 1 in the case of odds/hazard ratios).

For each of the RE models, a vague or non-informative uniform (0, 5) distribution was used as the prior distribution for the between-study SD; this prior distribution assumes that any value between 0 and 5 are equally probable. This is in line with the recommendations to allow the posterior distribution to be primarily driven by the data.

In the EM overall data for NMA results used in scenario analyses, there were no treatment comparisons informed by independent direct and indirect evidence. In the CM overall data used in the base case NMAs, there are no instances where it would be theoretically possible to find inconsistency.

NMAs were performed on the following endpoints: CFB in MMDs, ≥50% and ≥30% reduction in MMDs (CM only), CFB in monthly acute MUDs, CFB in MSQ (RFR, RFP and EF), CFB in HIT-6 total score, treatment-emergent AEs (TEAEs), and all-cause discontinuation/study withdrawal. NMA results for relative treatment effects were reported as MDs for CFB endpoints (CFB in MMDs, monthly acute MUDs, MSQ [-RFR, -RFP and -EF] and HIT-6 total score, and ORs for binary efficacy endpoints (≥50% and ≥30% reduction in MMDs), whereas binary safety and tolerability endpoints (TEAEs and all-cause discontinuation) were summarised using both ORs and HRs.

All models for dichotomous outcomes (≥30%/≥50% reduction in MMDs, TEAEs, and all-cause discontinuation) used median as the point estimate. This is because those models often have skewed posterior distributions for the parameters of interest. For continuous outcomes (CFB in MMDs, CFB in MUDs, CFB in MSQ and CFB in HIT-6), median and mean have the same expected value; but the mean has lower variance, and thus the mean was used.

Meta-analyses were conducted which allow the estimation of the absolute effect for placebo for each outcome, especially as placebo rates for oral preventive therapies have been on the rise.[211] These were combined with the estimated relative treatment effects (for each treatment versus placebo) to estimate the absolute effect for each treatment; the absolute effects for atogepant

were included in the base case economic analysis. All relative treatment effect results in Section B.2.9.6 are presented as each treatment versus atogepant.

Full details of the methodology used in the NMA are presented in Appendix D.

B.2.9.6 Results

Model fit statistics

Statistical assessments of heterogeneity were based on model fit comparisons of FE and RE models with and without baseline risk-adjustment using DIC and total residual deviance (Table 22–Table 24) for EM and CM. Baseline risk-adjusted models did not converge in the 3+ TF EM efficacy NMAs given the sparse networks and limited data available to inform the regression coefficients, so were not considered further. Model fit was similar across the converging candidate models for all endpoints across both EM and CM analyses. Given the heterogeneity between the trials included in the NMA and in line with clinical and health economic expert opinion at an advisory board, RE models were more suitable.[5] Whilst baseline risk-adjusted models may be theoretically appropriate given the differences in placebo response observed across trials included in the NMAs, these models were not considered in the base case, given regression coefficients were not significant and model fit statistics for these models did not show meaningful improvements over unadjusted models.

For completeness, the detailed model fit statistics and results of comparisons based on FE and baseline risk-adjusted models are presented in Appendix D. Supplementary NMA results for the comparison of atogepant versus botulinum toxin type A are presented in Appendix O.

Table 22: Model fit statistics – EM efficacy outcomes

Outcome	Model	3+ TF mITT subgroup		
		DIC	Residual Deviance	SD
CFB in MMD	FE	[redacted]	[redacted]	[redacted]
	RE	[redacted]	[redacted]	[redacted]
	FE + BR	DNC	DNC	DNC
	RE + BR	DNC	DNC	DNC
≥50% reduction in MMDs	FE	[redacted]	[redacted]	[redacted]
	RE	[redacted]	[redacted]	[redacted]
	FE + BR	DNC	DNC	DNC
	RE + BR	DNC	DNC	DNC
CFB in monthly acute MUDs	FE	[redacted]	[redacted]	[redacted]
	RE	[redacted]	[redacted]	[redacted]
	FE + BR	DNC	DNC	DNC
	RE + BR	DNC	DNC	DNC

Footnotes: For each continuous endpoint, a normal likelihood with an identity link function was fit to the difference in mean change from baseline data for the endpoint of interest. For each binary endpoint an analysis of odds was performed using a binomial likelihood with a logit link function.

Abbreviations: BR: baseline-risk adjusted; CFB: change from baseline; DIC: deviance information criterion; EM: episodic migraine; FE: fixed effect; mITT: modified intent-to-treat; MMD: monthly migraine days; MUD: medication use days; RE: random effect; SD: standard deviation.

Table 23: Model fit statistics – EM HRQoL and safety outcomes

Outcome	Model	Overall mITT		
		DIC	Residual Deviance	SD
MSQ-RFR	FE	[redacted]	[redacted]	[redacted]
	RE	[redacted]	[redacted]	[redacted]
MSQ-RFP	FE	[redacted]	[redacted]	[redacted]
	RE	[redacted]	[redacted]	[redacted]
MSQ-EF	FE	[redacted]	[redacted]	[redacted]
	RE	[redacted]	[redacted]	[redacted]
HIT-6	FE	[redacted]	[redacted]	[redacted]
	RE	[redacted]	[redacted]	[redacted]
TEAE	FE (logit)	[redacted]	[redacted]	[redacted]
	FE (cloglog)	[redacted]	[redacted]	[redacted]
	RE (logit)	[redacted]	[redacted]	[redacted]
	RE (cloglog)	[redacted]	[redacted]	[redacted]
All-cause disc.	FE (logit)	[redacted]	[redacted]	[redacted]
	FE (cloglog)	[redacted]	[redacted]	[redacted]
	RE (logit)	[redacted]	[redacted]	[redacted]
	RE (cloglog)	[redacted]	[redacted]	[redacted]

Footnotes: For each continuous endpoint, a normal likelihood with an identity link function was fit to the difference in mean change from baseline data for the endpoint of interest. For each binary endpoint an analysis of odds was performed using a binomial likelihood with a logit link function. For safety endpoints an analysis of hazards was performed using a binomial likelihood with a cloglog link.
Abbreviations: BR: baseline-risk adjusted; CFB: change from baseline; DIC: deviance information criterion; DNC: did not converge; EM: episodic migraine; FE: fixed effect; HIT-6: Headache Impact Test-6; IP: informative prior; mITT: modified intent-to-treat; MMD: monthly migraine days; MSQ-EF: Migraine-Specific Quality of Life Emotional Function; MSQ-RFP: Migraine-Specific Quality of Life Role Function – Preventive domain; MSQ-RFR: Migraine-Specific Quality of Life Role Function – Restrictive domain; MUD: medication use days; RE: random effect; SD: standard deviation; TEAE: treatment-emergent adverse events; VP: vague prior.

Table 24: Model fit statistics – CM (efficacy, HRQoL and safety outcomes)

Outcome	Model	Overall mITT population		
		DIC	Residual Deviance	SD
CFB in MMD	FE	[redacted]	[redacted]	[redacted]
	RE	[redacted]	[redacted]	[redacted]
	FE + BR	[redacted]	[redacted]	[redacted]
	RE + BR	[redacted]	[redacted]	[redacted]

≥50% reduction in MMDs	FE	[redacted]	[redacted]	[redacted]
	RE	[redacted]	[redacted]	[redacted]
	FE + BR	[redacted]	[redacted]	[redacted]
	RE + BR	[redacted]	[redacted]	[redacted]
≥30% reduction in MMDs	FE	[redacted]	[redacted]	[redacted]
	RE	[redacted]	[redacted]	[redacted]
	FE + BR	[redacted]	[redacted]	[redacted]
	RE + BR	[redacted]	[redacted]	[redacted]
CFB in monthly acute MUDs	FE	[redacted]	[redacted]	[redacted]
	RE	[redacted]	[redacted]	[redacted]
	FE + BR	[redacted]	[redacted]	[redacted]
	RE + BR	[redacted]	[redacted]	[redacted]
MSQ-RFR	FE	[redacted]	[redacted]	[redacted]
	RE	[redacted]	[redacted]	[redacted]
MSQ-RFP	FE	[redacted]	[redacted]	[redacted]
	RE	[redacted]	[redacted]	[redacted]
MSQ-EF	FE	[redacted]	[redacted]	[redacted]
	RE	[redacted]	[redacted]	[redacted]
HIT-6	FE	[redacted]	[redacted]	[redacted]
	RE	[redacted]	[redacted]	[redacted]
TEAE	FE (logit)	[redacted]	[redacted]	[redacted]
	FE (cloglog)	[redacted]	[redacted]	[redacted]
	RE (logit)	[redacted]	[redacted]	[redacted]
	RE (cloglog)	[redacted]	[redacted]	[redacted]
All-cause disc.	FE (logit)	[redacted]	[redacted]	[redacted]
	FE (cloglog)	[redacted]	[redacted]	[redacted]
	RE (logit)	[redacted]	[redacted]	[redacted]
	RE (cloglog)	[redacted]	[redacted]	[redacted]

Footnotes: For each continuous endpoint, a normal likelihood with an identity link function was fit to the difference in mean change from baseline data for the endpoint of interest. For each binary endpoint an analysis of odds was performed using a binomial likelihood with a logit link function. For safety endpoints an analysis of hazards was performed using a binomial likelihood with a cloglog link.

Abbreviations: BR: baseline-risk adjusted; CFB: change from baseline; CM: chronic migraine; DIC: deviance information criterion; FE: fixed effect; HIT-6: Headache Impact Test-6; IP: informative prior; mITT: modified intent-to-treat; MMD: monthly migraine days; MSQ-EF: Migraine-Specific Quality of Life Emotional Function; MSQ-RFP: Migraine-Specific Quality of Life Role Function – Preventive domain; MSQ-RFR: Migraine-Specific Quality of Life Role Function – Restrictive domain; MUD: medication use days; NR: no response; RE: random effect; SD: standard deviation; TEAE: treatment-emergent adverse events; VP: vague prior.

Efficacy NMAs (EM and CM)

A summary of the results from the efficacy NMAs across EM and CM are presented in Table 25, with no significant differences between atogepant and any relevant comparator observed. Mean reduction in MMDs, odds of achieving ≥50% and ≥30% reduction in MMDs and mean reduction in monthly acute MUDs for atogepant were similar to other active treatments. Point estimates of the treatment effect of atogepant or any relevant comparator were generally close to the null (a mean difference of 0 for CFB endpoints or an OR of 1 for binary endpoints). Across EM and CM, point estimates marginally favoured either atogepant or comparators, with the credible intervals crossing null.

Further results are presented within Appendix D, including the results of the sensitivity analyses discussed in Section B.2.9.7 and fixed effects model results.

Table 25: Relative effect of atogepant 60 mg QD compared to treatments recommended for both EM and CM – efficacy outcomes (RE model)

ATO 60 mg vs,	EM	CM
	3+ TF mITT	Overall mITT
CFB in MMD, MD (95% CrI)		
Placebo	[redacted]	[redacted]
Erenumab 140 mg QM	[redacted]	[redacted]
Fremanezumab 225 mg QM[a]	[redacted]	[redacted]
Fremanezumab 675 mg Q3M	[redacted]	[redacted]
Galcanezumab 120 mg QM[b]	[redacted]	[redacted]
≥50% reduction in MMDs, OR (95% CrI)		
Placebo	[redacted]	[redacted]
Erenumab 140 mg QM	[redacted]	[redacted]
Fremanezumab 225 mg QM[a]	[redacted]	[redacted]
Fremanezumab 675 mg Q3M	[redacted]	[redacted]
Galcanezumab 120 mg QM[b]	[redacted]	[redacted]
≥30% reduction in MMDs, OR (95% CrI)		
Placebo	[redacted]	[redacted]
Erenumab 140 mg QM	[redacted]	-
Fremanezumab 225 mg QM[a]	[redacted]	[redacted]
Fremanezumab 675 mg Q3M	[redacted]	[redacted]
Galcanezumab 120 mg QM[b]	[redacted]	[redacted]
CFB monthly acute MUDs, MD (95% CrI)		
Placebo	[redacted]	[redacted]
Erenumab 140 mg QM	[redacted]	[redacted]
Fremanezumab 225 mg QM[a]	[redacted]	[redacted]

Fremanezumab 675 mg Q3M	[redacted]	[redacted]
Galcanezumab 120 mg QM[b]	[redacted]	[redacted]

Footnotes: No statistically significant differences in any outcomes were observed between atogepant and comparators across EM and CM in both the 3+ TF mITT and mITT populations; [a]Fremanezumab regimen is 675 mg initial dose followed by 225 mg once a month. [b]Galcanezumab regimen is a 240 mg loading dose followed by 120 mg once a month.

Abbreviations: ATO: atogepant; CFB: change from baseline; CM: chronic migraine; EM: episodic migraine; MD: mean difference; mITT: modified intent-to-treat; MMD: monthly migraine days; MUD: medication use days; NA: not applicable; OR: odds ratio; QD: once daily; QM: once a month; Q3M: once per quarter; RE: random effect; TF: treatment failure.

HRQoL NMAs (EM and CM)

HRQoL measures are particularly important in the assessment of migraine by representing both migraine severity and/or patient disability which would not otherwise be captured by outcomes assessing migraine frequency alone, and are recommended by international guidelines for the assessment of response to preventive treatments.[40, 112, 116-118]

Results of the HRQoL NMAs across EM and CM are presented below (Table 26). HRQoL outcomes were only appraised in overall mITT, due to limited publicly available 3+ TF HRQoL data for comparators. The HRQoL NMA results in the EM population are generally indicative of better, and in some cases significantly superior HRQoL for atogepant versus selected comparators. In the CM population, point estimates marginally favoured active comparators, but the results were not statistically significant in any of these cases.

Table 26: Relative effect of atogepant 60 mg QD compared to treatments recommended for both EM and CM – HRQoL outcomes (RE model overall mITT)

ATO 60 mg vs	EM	CM
CFB in MSQ-RFR, MD (95% CrI)[a]		
Placebo	[redacted]	[redacted]
Erenumab 140 mg QM	[redacted]	[redacted]
Fremanezumab 225 mg QM[b]	[redacted]	[redacted]
Fremanezumab 675 mg Q3M	[redacted]	[redacted]
Galcanezumab 120 mg QM[c]	[redacted]	[redacted]
CFB in MSQ-RFP, MD (95% CrI)[d]		
Placebo	[redacted]	[redacted]
Erenumab 140 mg QM	[redacted]	[redacted]
Fremanezumab 225 mg QM[b]	[redacted]	[redacted]
Fremanezumab 675 mg Q3M	[redacted]	[redacted]
Galcanezumab 120 mg QM[c]	[redacted]	[redacted]
CFB in MSQ-EF, MD (95% CrI)[d]		
Placebo	[redacted]	[redacted]
Erenumab 140 mg QM	[redacted]	[redacted]
Fremanezumab 225 mg QM[b]	[redacted]	[redacted]
Fremanezumab 675 mg Q3M	[redacted]	[redacted]
Galcanezumab 120 mg QM[c]	[redacted]	[redacted]
CFB in HIT-6, MD (95% CrI)		
Placebo	[redacted]	[redacted]
Erenumab 140 mg QM	[redacted]	[redacted]
Fremanezumab 225 mg QM[b]	[redacted]	[redacted]
Fremanezumab 675 mg Q3M	[redacted]	[redacted]

Statistically significant differences in any outcomes were observed between atogepant and comparators across EM and CM are **bolded**.
Footnotes: [a]EM results derived from the RE model with an informative prior. [b]Fremanezumab regimen is 675 mg initial dose followed by 225 mg once a month. [c]Galcanezumab regimen is a 240 mg loading dose followed by 120 mg once a month. [d]CM results derived from the RE model with an informative prior.

Abbreviations: ATO: atogepant; CFB: change from baseline; CM: chronic migraine; EM: episodic migraine; HIT-6: Headache Impact Test-6; MD: mean difference; mITT: modified intent-to-treat; MSQ-EF: Migraine-Specific Quality of Life Emotional Function; MSQ-RFP: Migraine-Specific Quality of Life Role Function – Preventive domain; MSQ-RFR: Migraine-Specific Quality of Life Role Function – Restrictive domain; OR: odds ratio; QD: once daily; QM: once a month; Q3M: once per quarter; RE: random effect; TF: treatment failure.

Safety NMAs (EM and CM)

Results of the safety NMAs across EM and CM are presented below (Table 27). In the overall safety population, no statistically significant differences in the hazard of TEAEs or all-cause discontinuation were observed between atogepant and any relevant comparator in either EM or CM, and point estimates of the treatment effect were generally close to the null (a hazard ratio or odds ratio of 1). Point estimates favoured either atogepant or active comparators, but in no cases were the results statistically significant.

Table 27: Relative effect of atogepant 60 mg QD compared to treatments recommended for both EM and CM – safety and tolerability outcomes (RE model overall mITT)

ATO 60 mg vs	Cloglog (HR)		Logit (OR)	
	EM	CM	EM	CM
TEAEs (95% CrI)				
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg QM	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 225 mg QM[a]	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 675 mg Q3M	[redacted]	[redacted]	[redacted]	[redacted]
Galcanezumab 120 mg QM[b]	[redacted]	[redacted]	[redacted]	[redacted]
All-cause discontinuation (95% CrI)				
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg QM	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 225 mg QM[a]	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 675 mg Q3M	[redacted]	[redacted]	[redacted]	[redacted]
Galcanezumab 120 mg QM[b]	[redacted]	[redacted]	[redacted]	[redacted]

No statistically significant differences in any outcomes were observed between atogepant and active comparators across EM and CM.
Footnotes: [a]Fremanezumab regimen is 675 mg initial dose followed by 225 mg once a month. [b]Galcanezumab regimen is a 240 mg loading dose followed by 120 mg once a month.
Abbreviations: ATO: atogepant; CFB: change from baseline; CM: chronic migraine; EM: episodic migraine; HR: hazard ratio; MMD: monthly migraine days; QD: once daily; QM: once a month; Q3M: once per quarter; RE: random effect; TF: treatment failure.

B.2.9.7 Sensitivity analyses

Sensitivity analyses were conducted to explore the effect of alternative model selections as well as the consistency between the 3+ TF and overall mITT populations in EM. The sensitivity analyses were performed on key efficacy outcomes from the NMA (CFB in MMD and ≥50%/≥30% reduction in MMDs). Overall, conclusions were unchanged relative to the base case, demonstrating the results of the NMA to be robust. The full results of the sensitivity analysis are provided in Appendix D.2.5.4.

Baseline risk-adjusted models (EM and CM):

Baseline-risk adjusted models failed to converge for the EM 3+ TF mITT population and so results are not presented further. For the CM overall mITT population, as in the unadjusted NMAs, no statistically significant differences were found between atogepant and relevant comparators for efficacy endpoints (Appendix D.2.5.4).

Overall mITT population (EM only):

NMAs were also run in the EM overall mITT population to provide supportive evidence. Results presented in Appendix D.2.5.4 are aligned with results in the 3+ TF mITT population, with no statistically significant differences being found between atogepant and relevant comparators for efficacy endpoints.

B.2.9.8 Uncertainties in the indirect and mixed treatment comparison

The analysis was based on the clinical SLR described in Section B.2.1 that was conducted to identify RCTs assessing the efficacy and safety of atogepant in adult patients (≥18 years of age) with migraine, ensuring that all relevant data were identified using a systematic approach. The SLR identified the relevant trials, and all evidence considered was from RCTs to ensure a high quality of data. As such, all studies included within the analyses were randomised trials, generally implying within-study validity of the evidence base.

Nonetheless, there were differences in baseline characteristics and trial design, assessment timepoints, extent of endpoint availability, and variation in endpoint definitions. Such differences may confound the output of the NMAs (both for the 3+ TF mITT subgroup for EM and the overall mITT population for EM and CM) and may suggest that random effects models might better reflect the uncertainty in NMA results. Baseline-risk adjusted analyses were explored for EM and CM overall mITT populations, however analysis of the model fit statistics favoured the unadjusted analyses performed. Results from these analyses are presented in Appendix D.

B.2.9.9 Conclusions of the indirect treatment comparisons

Across EM and CM RE NMAs, no statistically significant differences in efficacy endpoints were observed between atogepant compared to all relevant active comparators available in patients with 4 or more migraine days per month (galcanezumab, erenumab, fremanezumab). RE models were suitable for these analyses, given the heterogeneity identified across the included trials, as reported in Section B.2.9.4. The results observed in the EM 3+ TF mITT subgroup were corroborated by those reported in the EM overall mITT subgroup; no statistically significant differences were observed between atogepant and any relevant comparator, and point estimates of the treatment effect were generally close to the null.

Furthermore, across EM and CM RE NMAs (overall mITT population), the HRQoL NMA results were generally indicative of better and in some cases significantly superior HRQoL for atogepant versus selected comparators. Unlike migraine frequency-related endpoints, HRQoL measures represent migraine severity as well as the level of patient disability and are recommended by international guidelines for the assessment of response to preventive treatments.[40, 112, 116-118]

Similarly, no statistically significant differences in safety endpoints were observed between atogepant compared to all relevant active comparators across EM and CM NMAs (overall mITT population). Rates of TEAEs were extremely low across all treatments, and thus numerical differences in hazards or odds are not likely to translate into meaningful differences in absolute TEAE rates.

Taken together, the NMAs demonstrate atogepant to have similar efficacy and safety to the relevant comparators in patients with ≥3 prior preventive treatment failures, with credible intervals overlapping between atogepant and comparators across the vast majority of assessed endpoints. Additionally, in EM, atogepant demonstrated statistically significantly superior HRQoL versus all three CGRP mAbs in at least one HRQoL measure.

B.2.10 Adverse reactions

All TEAEs were summarised using Medical Dictionary for Regulatory Activities (MedDRA®, version 24.0). The number and proportion of patients with reported TEAEs were summarised by MedDRA® primary system organ class (SOC) and preferred term (PT). TEAEs are defined as those which began or increased in severity after the first dose of study drug and occurred no more than 30 days after the last dose of study drug. A patient with more than one AE reported for the same PT is counted only once for that term. All AEs presented in this section were treatment-emergent, unless otherwise noted. The following sections summarise the safety data from PROGRESS and ELEVATE.

B.2.10.1 ELEVATE

Atogepant was generally well-tolerated by patients with EM, and the overall safety results were consistent with the safety profile of other CGRP inhibitors. A total of [redacted] patients ([redacted]) in the atogepant group and [redacted] patients ([redacted]) in the placebo group experienced at least one TEAE. Among these patients, the atogepant group reported a greater proportion of patients with treatment-related TEAEs compared to the placebo group ([redacted] vs [redacted]). While a higher proportion of patients in the atogepant group experienced treatment-emergent serious AEs (TESAEs) as compared with the placebo group ([redacted] vs [redacted]), none of these TESAEs were considered to be treatment-related. The rates of TEAEs resulting in treatment discontinuation were low and comparable across the atogepant and placebo groups ([redacted] vs [redacted]), and no deaths were reported in either treatment group. Table 28 provides a summary of the TEAEs from the ELEVATE trial.

Table 28: Overall summary of adverse events (safety population)

n (%)	ATO 60 mg QD (N=[redacted])	Placebo (N=[redacted])
TEAEs	[redacted]	[redacted]
Treatment-related TEAEs	[redacted]	[redacted]
Deaths	[redacted]	[redacted]
TESAEs	[redacted]	[redacted]

Treatment-related TESAEs	[redacted]	[redacted]
TEAEs leading to treatment discontinuation	[redacted]	[redacted]

Source: AbbVie Study 304 ELEVATE CSR, 2022.[138]
Abbreviations: ATO: atogepant; QD: once daily; TEAE: treatment-emergent adverse event; TESAEs: treatment-emergent serious adverse events.

AEs reported by ≥2% of patients receiving atogepant

The most common AEs reported with atogepant include [redacted], [redacted], and [redacted] (Table 29). The incidence rates of [redacted] and [redacted] were greater in the atogepant group than placebo. No common TEAEs leading to treatment discontinuation (≥1% of patients) were reported in either atogepant group or placebo group.

Table 29: AEs reported by ≥2% of patients receiving atogepant (safety population)

Most Frequent TEAE (≥2%), n (%)	ATO 60 mg QD (N=[redacted])	Placebo (N=[redacted])
Constipation	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Migraine	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]

Source: AbbVie Study 304 ELEVATE CSR, 2022.[138]
Abbreviations: AEs: adverse events; ATO: atogepant; QD: once daily; TEAE: treatment-emergent adverse event.

AEs of interest

Alanine transaminase (ALT) and aspartate transaminase (AST) are enzymes in the liver which are critical indicators for liver injury, whereby liver damage is associated with elevations in ALT and AST levels.[212] Telcagepant, a first generation gepant, failed in clinical trials due to hepatotoxicity.[213] It is thus crucial to assess ALT and AST levels to investigate if atogepant causes liver injury. No hepatic safety issues related to atogepant were identified, with no patient reporting post-baseline ALT or AST elevations ≥3 x upper limit of normal (ULN). Generally, elevated ALT and/or AST laboratory test results were more frequent in the placebo group compared with the atogepant group (Table 30). In both treatment groups, patients most frequently had elevations that were less than 1.5 x ULN. There were no potential Hy's law cases, indicating that treatment with atogepant does not pose a high risk of fatal drug-induced liver injury on patients.

Table 30: AEs of interest (safety population)

ALT or AST (U/L), n/N1 (%)	ATO 60 mg QD (N=[redacted])	Placebo (N=[redacted])
≥1 x ULN	[redacted]	[redacted]
≥1.5 x ULN	[redacted]	[redacted]
≥2 x ULN	[redacted]	[redacted]

≥3 x ULN	[redacted]	[redacted]
≥5 x ULN	[redacted]	[redacted]
≥10 x ULN	[redacted]	[redacted]
≥20 x ULN	[redacted]	[redacted]

Source: AbbVie Study 304 ELEVATE CSR, 2022.[138]
Abbreviations: AEs: adverse events; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ATO: atogepant; n: number of patients within a specific category; N1: number of patients with ≥1 non-missing post-baseline value; QD: once daily; U/L: upper limit; ULN: upper limit of normal.

B.2.10.2 PROGRESS

Atogepant was generally well-tolerated in patients with CM, and the overall safety results were consistent with the safety profile of other CGRP inhibitors with no new safety signals identified.[137] A total of 165 patients (63.2%) in the atogepant group and 126 patients (49.4%) in the placebo group experienced at least one TEAE. Among these patients, the atogepant group reported a greater proportion of patients with treatment-related TEAEs compared with the placebo group (17.2% vs 13.3%). While a higher proportion of patients in the atogepant group experienced TESAEs as compared with the placebo group (2.7% vs 1.2%), none of these TESAEs were considered to be treatment-related. The rates of TEAEs resulting in treatment discontinuation were low and comparable across the atogepant and placebo groups (3.4% vs 3.9%), and no deaths were reported in either treatment group. Table 31 provides a summary of the TEAEs from the PROGRESS trial.

Table 31: Overall summary of adverse events (safety population)

n (%)	ATO 60 mg QD (N=261)	Placebo (N=255)
TEAEs	165 (63.2)	126 (49.4)
Treatment-related TEAEs	45 (17.2)	34 (13.3)
Deaths	0 (0)	0 (0)
TESAEs	7 (2.7)	3 (1.2)
Treatment-related TESAEs	[redacted]	[redacted]
TEAEs leading to treatment discontinuation	9 (3.4)	10 (3.9)

Source: AbbVie Study 303 PROGRESS CSR, 2022.[137]
Abbreviations: ATO: atogepant; QD: once daily; TEAE: treatment-emergent adverse event; TESAEs: treatment-emergent serious adverse events.

AEs reported by ≥2% of patients receiving atogepant

The most common AEs reported with atogepant include constipation, nausea, and dizziness (Table 32). The incidence rate of constipation, nausea and decreased appetite were greater in the atogepant group than placebo. In general, constipation with atogepant was mild or moderate in severity and discontinuation due to [redacted] was infrequent. There were no TESAEs of nausea and discontinuation due to [redacted] was infrequent.

Table 32: AEs reported by ≥2% of patients receiving atogepant (safety population)

Most Frequent TEAE (≥2%), n (%)	ATO 60 mg QD (N=261)	Placebo (N=255)
Constipation	26 (10.0)	8 (3.1)
Nausea	25 (9.6)	9 (3.5)
Dizziness	12 (4.6)	8 (3.1)

Nasopharyngitis	11 (4.2)	11 (4.3)
Decreased appetite	9 (3.4)	0 (0.0)
Fatigue	8 (3.1)	7 (2.7)
Pyrexia	8 (3.1)	3 (1.2)
Urinary tract infection	6 (2.3)	3 (1.2)
Abdominal pain	5 (1.9)	3 (1.2)
Diarrhea	5 (1.9)	6 (2.4)
Insomnia	5 (1.9)	5 (2.0)
COVID-19	4 (1.5)	5 (2.0)
Migraine	4 (1.5)	5 (2.0)
Abdominal pain upper	3 (1.1)	5 (2.0)
Arthralgia	3 (1.1)	6 (2.4)
Back pain	3 (1.1)	0 (0.0)
Upper respiratory tract infection	2 (0.8)	6 (2.4)

Source: AbbVie Study 303 PROGRESS CSR, 2022.[137]
Abbreviations: AEs: adverse events; ATO: atogepant; QD: once daily; TEAE: treatment-emergent adverse event; TESAEs: treatment-emergent serious adverse events.

AEs of interest

No hepatic safety issues related to atogepant were identified during the study. Generally, elevated ALT and/or AST laboratory test results were more frequent in the placebo group compared with the atogepant group (Table 33). In both treatment groups, patients most frequently had elevations that were less than 1.5 x ULN. There were no potential Hy's law cases.

A total of 1 patient in the placebo group reported a TEAE of suicidal ideation and a TESAE of suicide attempt. No patients in the atogepant treatment groups reported a TEAE of suicidal ideation. No patients in the atogepant 60 mg QD treatment group reported a TEAE of suicide attempt.

Table 33: AEs of interest (safety population)

ALT or AST (U/L), n/N1 (%)	ATO 60 mg QD (N=261)	Placebo (N=255)
≥1 x ULN	18/257 (7.0)	30/254 (11.8)
≥1.5 x ULN	6/257 (2.3)	13/254 (5.1)
≥2 x ULN	3/257 (1.2)	6/254 (2.4)
≥3 x ULN	2/257 (0.8)	1/254 (0.4)
≥5 x ULN	2/257 (0.8)	0 (0.0)
≥10 x ULN	0 (0.0)	0 (0.0)

Source: AbbVie Study 303 PROGRESS CSR, 2022.[137]
Abbreviations: Aes: adverse events; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ATO: atogepant; n: number of patients within a specific category; N1: number of patients with ≥1 non-missing post-baseline value; QD: once daily; TEAE: treatment-emergent adverse event; TESAE: treatment-emergent serious adverse event; U/L: upper limit; ULN: upper limit of normal.

B.2.11 Ongoing studies

There are currently two ongoing studies investigating the efficacy and safety of atogepant in adult migraine patients within its UK marketing authorisation patient population.[1] Both trials are Phase

3, open-label extension studies (NCT04686136 [estimated study completion date: September 13, 2024] and NCT04437433 [estimated study completion date: June 14, 2024]) evaluating the long-term and tolerability of atogepant in adults with EM or CM.[214, 215] NCT04686136 included patients who had previously participated in either ELEVATE or PROGRESS without significant protocol deviations and NCT04437433 in Japanese adults with EM or CM. The study included Japanese adults who had previously participated in the PROGRESS trial without significant protocol deviations, and *de novo* EM participants (4–14 MMDs) in Japan.

B.2.12 Interpretation of clinical effectiveness and safety evidence

Background

In alignment with prior technology appraisals in migraine, this submission targets a subgroup of the marketing authorisation for atogepant to focus on adult patients who have ≥4 migraine days a month and for whom ≥3 prior preventive treatments have failed.[1] The appropriate comparators for atogepant in this population are SC CGRP mAbs galcanezumab, erenumab and fremanezumab, which can be associated with slow rates of drug clearance, discontinuation, restricted access, and an intrusive/inconvenient route of administration (Section B.1.3.3).[2, 37-40] Atogepant is the first once daily, oral treatment designed for the preventive treatment of migraine. Atogepant would offer a key alternative to SC CGRP mAbs, addressing the unmet need for a more convenient, oral treatment option for patients with ≥3 prior preventive treatment failures, whilst offering comparable health benefits and safety.

Efficacy evidence

In the ELEVATE trial, which was powered to assess efficacy in patients with EM who have experienced 2–4 prior treatment failures, atogepant demonstrated significantly improved efficacy compared with placebo across the 12-week treatment period in the 3+ TF mITT subgroup across the primary (CFB in MMDs) and secondary/exploratory endpoints (≥50% reduction in MMDs, CFB in MHDs, MUDs, MSQ score, PGI-S, HIT-6 score and MIDAS score). These results are supported by data collected in the overall mITT populations, where significant reductions in monthly MMDs, MHDs and acute MUDs, migraine duration (cumulative headache hours), migraine severity (moderate/severe migraines), and HRQoL outcomes were observed for atogepant versus placebo.

In the PROGRESS trial, atogepant demonstrated significantly improved efficacy compared with placebo across the 12-week treatment period in the overall mITT population across the primary (CFB in MMDs) and secondary endpoints (≥30% reduction in MMDs, ≥50% reduction in MMDs, CFB in MHDs, MUDs, MSQ score, PGI-S, HIT-6 score and MIDAS score).

ELEVATE and PROGRESS also demonstrate the rapid efficacy of atogepant, which significantly reduced weekly migraine days by a greater extent than placebo within the first month of treatment. Compared to placebo, a significantly lower proportion of patients with a migraine day was also observed for atogepant from 1 day after initial dose. Pre-specified subgroup analyses confirmed efficacy across all assessed subgroups (including BMI, disease severity, and treatment history) (Section B.2.7). These positive outcomes were also observed despite the high placebo efficacy observed in the PROGRESS study compared with studies investigating SC CGRP mAbs (see Section B.2.9.4 and Appendix D).

Safety evidence

Atogepant demonstrated an acceptable safety and tolerability profile in patients with EM and CM. The most common adverse events (AEs) were consistent with the known safety profile of other CGRP inhibitors and no new safety signals were identified.

Indirect treatment comparison

As atogepant and the relevant comparators (galcanezumab, erenumab, fremanezumab) have not been studied in head-to-head RCTs, an NMA was conducted to provide comparative evidence in both EM and CM patients. Given heterogeneity identified across the trials included in the NMAs (Section B.2.9.4), and in line with expert opinion received at an advisory board, RE models were suitable.[5] Across EM and CM RE NMAs, no statistically significant differences in efficacy endpoints were observed between atogepant compared to all relevant active comparators (Section B.2.9.6). Conversely, in the EM RE NMAs, atogepant demonstrated statistically significantly superior HRQoL versus relevant comparators in at least one HRQoL measure. Unlike migraine frequency-related endpoints, HRQoL measures represent migraine severity as well as the level of patient disability and are recommended by international guidelines for the assessment of response to preventive treatments.[40, 112, 116-118] Finally, no statistically significant differences in safety endpoints were observed between atogepant compared to all relevant active comparators across EM and CM NMAs (overall safety population).

Atogepant and the SC CGRP mAbs (galcanezumab, erenumab, fremanezumab) are all designed to suppress CGRP activity, and thus UK clinical experts anticipated that the technologies would have similar efficacy.[5] The NMAs demonstrate atogepant to have similar efficacy and safety to the relevant comparators in patients with ≥3 prior preventive treatment failures, with credible intervals overlapping between atogepant and comparators across all assessed endpoints. Clinical experts agreed that these results suggest atogepant has broadly similar efficacy to existing SC CGRP mAbs.[5] Notably, the NMA did not capture differences in additional adverse events such as injection site reactions, which would be associated with SC CGRP mAbs but not atogepant, therefore potentially underestimating the benefit of atogepant in this regard.[120-122]

B.2.13 Conclusions of the clinical effectiveness results

Overall, the clinical effectiveness results of the ELEVATE (3+ TF mITT population) and PROGRESS (overall mITT inclusive of 3+ TF mITT population) trials demonstrate that atogepant is effective in the prevention of EM and CM; with reductions in migraine frequency (monthly MMDs, MHDs), duration (cumulative headache hours), and severity (moderate/severe migraines); as well as acute medication use (acute MUDs). Together, improvements in these clinical outcomes translate into significant improvements in HRQoL and PGI-S. This is despite the high placebo efficacy observed in the PROGRESS study compared to other trials investigating SC CGRP mAbs (which have lower placebo efficacy, see Section B.2.9.4).

As discussed in Sections B.2.6.1 to B.2.6.3, [redacted] in the 3+ TF mITT subgroup of the Phase 3 trial, ELEVATE, which was powered to assess efficacy in patients with EM who have experienced prior preventive treatment failures. In the 3+ TF mITT subgroup of ELEVATE, [redacted] was observed across CFB in MMDs, ≥30%/≥50%/≥75% reduction in MMDs, CFB in MHDs, CFB in monthly acute MUDs, and HRQoL outcomes (MSQ v2.1 and HIT-6). In the Phase 3 trial PROGRESS, [redacted] across the same endpoints. Given results from the ELEVATE trial indicate consistent clinical outcomes in EM patients in overall mITT and 3+ TF mITT populations, the results from the overall mITT population of PROGRESS are considered broadly generalisable to 3+ TF CM patients.

Given that migraine is a disease continuum, clinical experts further indicated that data in EM and CM are complementary in the evaluation of the efficacy and safety of migraine treatments. This is in agreement with clinical advice received by the External Assessment Group (EAG) as part of the NICE appraisal of eptinezumab in migraine (TA871), where clinical experts suggested there is no reason to believe that the relative treatment effect of interventions would differ between EM and CM, and with recent NICE decision-making for another oral CGRP inhibitor, rimegepant (as outlined in Section B.2.6).[12, 15] Therefore, the clinical effectiveness results presented show that atogepant is an effective treatment for the prevention of migraine in patients with 3+ TF across both EM and CM, with a similar efficacy and safety profile to established injectable therapies in addition to the added benefit of a simple, once daily oral route of administration.

B.3 Cost effectiveness

Summary of the cost-effectiveness analysis

- A cost-effectiveness model was developed to assess the cost-effectiveness of atogepant in the prevention of migraine in both EM and CM.
- In line with prior NICE appraisals of SC CGRP mAbs, the model adopted a semi-Markov approach with six health states: 'On treatment before response assessment', 'Off treatment before response assessment', 'Off treatment non-responder', 'On treatment responder', 'Off treatment after response assessment and 'Death', over a lifetime time horizon.
- The analysis was conducted from an NHS/PSS perspective, with a lifetime time horizon and costs and outcomes were discounted at 3.5% per annum
- Efficacy data for atogepant were derived from the relevant populations of the ELEVATE and PROGRESS trials, with efficacy data for CGRP mAbs relative to atogepant derived from the base case NMAs (Section B.2.9.3).
- Utility values for all health states were derived from observed MSQ v2.1 values in the overall mITT patient population from relevant trials, and then mapped to EQ-5D-3L.
- Costs included in the model comprised drug acquisition, drug administration, and health state costs.
- A supplementary economic analysis for atogepant versus botulinum toxin type A (in CM only) is presented in Appendix O.

Base case cost-effectiveness results

- At PAS price, atogepant was found to be cost-effective compared to all relevant comparators in EM, yielding INHB for atogepant versus galcanezumab (120 mg), erenumab (140 mg) and fremanezumab (225 mg or 675 mg) of [redacted], [redacted], [redacted] and [redacted], respectively at a willingness-to-pay threshold of £20,000.
- At the same willingness-to-pay threshold in the CM population, atogepant was cost-effective compared to galcanezumab (120 mg), erenumab (140 mg), fremanezumab (225 mg or 675 mg) with a INHB of [redacted], [redacted], [redacted] [redacted], respectively.
- The base case fully incremental analysis in the EM and CM populations showed atogepant to be most cost-effective treatment option at PAS price and were consistent with the pair-wise analysis, with a fully incremental [redacted] saved per QALY forgone as compared to fremanezumab 225 mg in EM and [redacted] saved per QALY forgone as compared to erenumab 140 mg QM in CM, with all other comparators [redacted]. Fully incremental analyses should however be interpreted with caution given small incremental costs and QALYs between comparators.

Sensitivity and scenario analyses

- Probabilistic sensitivity analyses (PSA) and deterministic sensitivity analyses (DSA) were conducted to assess uncertainty in the economic analysis and demonstrate that the base case cost-effectiveness results were robust to an extensive number of scenario analyses
- The results of the PSA were similar to the base case, with atogepant remaining cost-effective versus all comparators and having a probability of cost-effectiveness of [redacted] at a WTP threshold of £30,000 per QALY.
- Scenario analyses conducted to address sources of uncertainty in the model such as an analysis which included extended induction demonstrated that whilst there was variation in the NHB, the cost-effectiveness conclusions were unchanged with the resulting NHBs remaining cost-effective at a willingness-to-pay threshold of £30,000 per QALY in all scenarios tested.

Conclusion

- The cost-effectiveness analysis demonstrates that atogepant would offer a cost-effective alternative to SC CGRP mAbs, addressing the unmet need for an oral treatment option for patients with ≥3 prior preventive treatment failures, with reduced or minimal budget impact.

B.3.1 Published cost-effectiveness studies

An economic SLR was conducted on 17 August 2020, and then updated twice (on 7 January 2022 and 4 November 2022) to identify all relevant literature published on previous economic models of comparable therapies for the prevention of migraine to support an initial company submission in February 2023.

The SLR was conducted following current best practices, as recommended by the Cochrane Collaboration.[216] The reporting of the methods and results of the SLR were done in line with the guidance provided by NICE and the PRISMA guidelines.[217-219] Full details of the economic SLR search strategy, study selection process and results are reported in Appendix H for economic evaluations.

In total, 20 unique UK economic evaluations of therapies for the prevention of migraine were identified in the SLR, the details of which are presented in Table 34. No prior economic evaluations were identified for atogepant in the population of relevance to this submission.

Table 34: Summary list of published cost-effectiveness studies (UK)

Study	Year	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Episodic migraine						
Galcanezumab Company Submission, NICE[220]	2020	CUA; Semi-Markov model; Lifetime time horizon (25 years); 3.5% discount rate; 4 health states	Patients with EM with at least 3 failed migraine preventive therapies	Galcanezumab vs BSC • Data redacted	Galcanezumab vs BSC • Data redacted	Galcanezumab vs BSC: £29,230
Fremanezumab Company Submission, NICE[221]	2019	CUA; Semi-Markov model and decision tree; 10-year time horizon; 3.5% discount rate; 3 health states	Patients with EM with at least 3 failed migraine preventive therapies	Fremanezumab vs BSC • Data redacted	Fremanezumab vs BSC • Data redacted	Fremanezumab vs BSC: £13,954
Erenumab Company Submission, NICE[222]	2018	CUA; Markov model and decision tree; 10-year time horizon; 3.5% discount rate; 2 health states	Patients with EM with at least 3 failed migraine preventive therapies	Erenumab vs BSC • Data redacted	Erenumab vs BSC • Data redacted	Erenumab (140 mg) vs BSC: £40,662
Skroumpelos – Cost-Effectiveness of Fremanezumab for the Treatment of Migraine in England From a Healthcare System Perspective[223]	2021	CUA; Semi-Markov model; 10-year time horizon; 3.5% discount rate; 28 health states (MMDs)	Adult patients with EM	Fremanezumab vs BSC • NR	Fremanezumab vs BSC • NR	Fremanezumab vs BSC: £14,408
Skroumpelos – Scenario analyses on major impactful and uncertain inputs of the cost-effectiveness model of fremanezumab from a healthcare system perspective in England[224]	2021	CUA; Semi-Markov model; 10-year time horizon; 3.5% discount rate; 28 health states (MMDs)	Adult patients with EM with at least 2 failed migraine preventive therapies	Fremanezumab vs BSC • NR	Fremanezumab vs BSC • NR	Fremanezumab vs BSC: £13,062

Galcanezumab Company Submission, SMC[225]	2021	CMA; Semi-Markov model; 25-year time horizon; discount rate NR; 6 health states	Patients with EM with at least 3 failed migraine preventive therapies	Galcanezumab vs fremanezumab (225 mg or 675 mg) • NR	Galcanezumab vs fremanezumab (225 mg or 675 mg) • NR	Galcanezumab vs fremanezumab (225 mg or 675 mg): NR
Fremanezumab Company Submission, SMC[226]	2020	CUA; Semi-Markov model; 10-year time horizon; discount rate NR; 2 health states	Patients with EM with at least 3 failed migraine preventive therapies	Fremanezumab vs BSC • NR	Fremanezumab vs BSC • NR	Fremanezumab vs BSC (with PAS): £10,300
Erenumab Company Submission, SMC[227]	2019	CUA; Semi-Markov model and decision tree; 10-year time horizon; 3.5% discount rate; 2 health states	Patients with EM with at least 3 failed migraine preventive therapies	Erenumab vs BSC • Data redacted	Erenumab vs BSC • Data redacted	Erenumab (140 mg; with PAS) vs BSC: £40,667
Chronic migraine						
Skroumpelos – Cost-Effectiveness of Fremanezumab for the Treatment of Migraine in England From a Healthcare System Perspective[223]	2021	CUA; Semi-Markov model; 10-year time horizon; 3.5% discount rate; 28 health states (MMDs)	Adult patients with CM	Fremanezumab vs BSC • NR Fremanezumab vs botulinum toxin type A • NR	Fremanezumab vs BSC • NR Fremanezumab vs botulinum toxin type A • NR	Fremanezumab vs BSC: £11,880; Fremanezumab vs botulinum toxin type A: £16,716
Skroumpelos – Scenario analyses on major impactful and uncertain inputs of the cost-effectiveness model of fremanezumab from a healthcare system perspective in England[224]	2021	CUA; Semi-Markov model; 10-year time horizon; 3.5% discount rate; 28 health states (MMDs)	Adult patients with CM with at least 2 failed migraine preventive therapies	Fremanezumab vs BSC • NR	Fremanezumab vs BSC • NR	Fremanezumab vs BSC: £13,062
Skroumpelos – The Cost-Effectiveness of Fremanezumab in Patients with Migraine Who Have	2021	CUA; Semi-Markov model; 10-year time horizon; 3.5% discount rate; health states NR	Adult patients with CM with at least 2 failed migraine	Fremanezumab vs BSC • NR	Fremanezumab vs BSC • NR	Fremanezumab vs BSC: £11,471

Failed Two or More Previous Migraine Preventive Therapies From a UK Healthcare System Perspective[228]			preventive therapies			
Galcanezumab Company Submission, NICE[220]	2020	CUA; Semi-Markov model; Lifetime time horizon (25 years); 3.5% discount rate; 4 health states	Adult patients with CM with at least 3 failed migraine preventive therapies	Galcanezumab vs BSC • Data redacted Galcanezumab vs botulinum toxin type A • Data redacted	Galcanezumab vs BSC • Data redacted Galcanezumab vs botulinum toxin type A • Data redacted	Galcanezumab vs BSC: £8,080; Galcanezumab vs botulinum toxin type A: £2,560
Hollier-Hann – Updated cost-effectiveness analysis of onabotulinumtoxinA for the prevention of headache in adults with chronic migraine who have previously received three or more preventive treatments in the UK[229]	2020	CUA; Markov model; 2-year time horizon; 3.5% discount rate; 13 health states	Adult patients with CM with at least 3 failed migraine preventive oral therapies	Botulinum toxin type A vs BSC • Botulinum toxin type A: 1.23 • BSC: 1.15	Botulinum toxin type A vs BSC • Botulinum toxin type A: £2,861 • BSC: £1,649	Botulinum toxin type A vs BSC: £16,306
Fremanezumab Company Submission, NICE[221]	2019	CUA; Semi-Markov model; 10-year time horizon; 3.5% discount rate; 3 health states	Adult patients with CM	Fremanezumab vs BSC • Data redacted	Fremanezumab vs BSC • Data redacted	Fremanezumab vs BSC: £11,825
Erenumab Company Submission, NICE[222]	2018	CUA; Markov model and decision tree; 10-year time horizon; 3.5% discount rate; 2 health states	Adult patients (18–65 years) with CM with at least 3 failed migraine preventive oral therapies	Erenumab vs BSC • Data redacted Erenumab vs botulinum toxin type A • Data redacted	Erenumab vs BSC • Data redacted Erenumab vs botulinum toxin type A • Data redacted	Erenumab (140 mg; with PAS) vs BSC: £13,340; Erenumab (140 mg; with PAS) vs botulinum toxin type A: £17,832
Batty - The cost-effectiveness of onabotulinumtoxinA for the prophylaxis of headache in	2013	CUA; Markov model; 2-year time horizon; 3.5% discount rate; 13 health states	Adult patients with CM	Botulinum toxin type A vs BSC • Botulinum toxin type A: 1.34	Botulinum toxin type A vs BSC • Botulinum toxin type A:	Botulinum toxin type A vs BSC: £15,028

adults with chronic migraine in the UK[230]				• BSC: 1.24	£3,077 • BSC: £1,680	
Botulinum toxin type A Company Submission, NICE[231]	2011	CUA; Markov model; 2-year time horizon; 3.5% discount rate; 6 health states	Adult patients with CM with at least 1 failed migraine preventive oral therapies	Botulinum toxin type A vs BSC • Botulinum toxin type A: 1.31 • BSC: 1.22	Botulinum toxin type A vs BSC • Botulinum toxin type A: £2,376 • BSC: £1,809	Botulinum toxin type A vs BSC in patients with ≥1 preventive treatment failure: £5,828; Botulinum toxin type A vs BSC in patients with ≥3 preventive treatment failure: £6,083
Galcanezumab Company Submission, SMC[225]	2021	CMA; Semi-Markov model; 10-year time horizon; 3.5% discount rate; health states NR	Adult patients with CM with at least 3 failed migraine preventive therapies	Galcanezumab vs fremanezumab (225 mg or 675 mg) • NR	Galcanezumab vs fremanezumab (225 mg or 675 mg) • NR	Galcanezumab vs fremanezumab (225 mg or 675 mg): NR
Erenumab Company Submission, SMC[227]	2019	CUA; Markov model and decision tree; 10-year time horizon; discount rate NR; 2 health states	Adult patients (18–65 years) with ≥12-month history of CM	Erenumab vs BSC • Data redacted Erenumab vs botulinum toxin type A • Data redacted	Erenumab vs BSC • Data redacted Erenumab vs botulinum toxin type A • Data redacted	Erenumab (140 mg; with PAS) vs BSC: £13,345; Erenumab (140 mg; with PAS) vs botulinum toxin type A: £17,823
Botulinum toxin type A Company Submission, SMC[232]	2017	CUA; Semi-Markov model; 10-year time horizon; discount rate NR;	Adult patients (18–70 years) with CM with at least 3 failed migraine preventive oral therapies	Botulinum toxin type A vs BSC • Incremental QALY: 0.12	Botulinum toxin type A vs BSC • Incremental cost: £1,301	Botulinum toxin type A vs BSC: £10,816

Abbreviations: BSC: best supportive care; CUA: cost-utility analysis; CM: chronic migraine; CMA: cost-minimisation analysis; EM: episodic migraine; ICER: incremental cost-effectiveness ratio; NR: not reported; PAS: patient access scheme; QALY: quality-adjusted life year; UK: United Kingdom.

B.3.2 Economic analysis

B.3.2.1 Patient population

A *de novo* cost-effectiveness model was developed to assess the cost-effectiveness of atogepant in adults for the prevention of migraine if:[2-4]

- They have 4 or more migraine days a month
- At least 3 preventive drug treatments have failed (3+ TF)

The economic analysis considered patients with EM and CM, in line with the decision problem defined in Section B.1.1 and the EMA and MHRA licensed indication for atogepant. In line with the approach taken in previous appraisals (TA260, TA659, TA682, TA764, TA871, TA906),[2-4, 12, 13, 15] the patient population considered in the economic analyses is separated by EM (defined as <15 headache days per month) and CM (defined as ≥15 headache days per month, in addition to ≥8 migraine days per month) sub-indications.

B.3.2.2 Model structure

The cost-effectiveness model was constructed in Microsoft Excel and adopted a simple, semi-Markov state transition model with six model states, in line with the model structures used in the NICE technology appraisals (TAs) for galcanezumab (TA659),[2] erenumab (TA682)[3] and fremanezumab (TA764).[4]

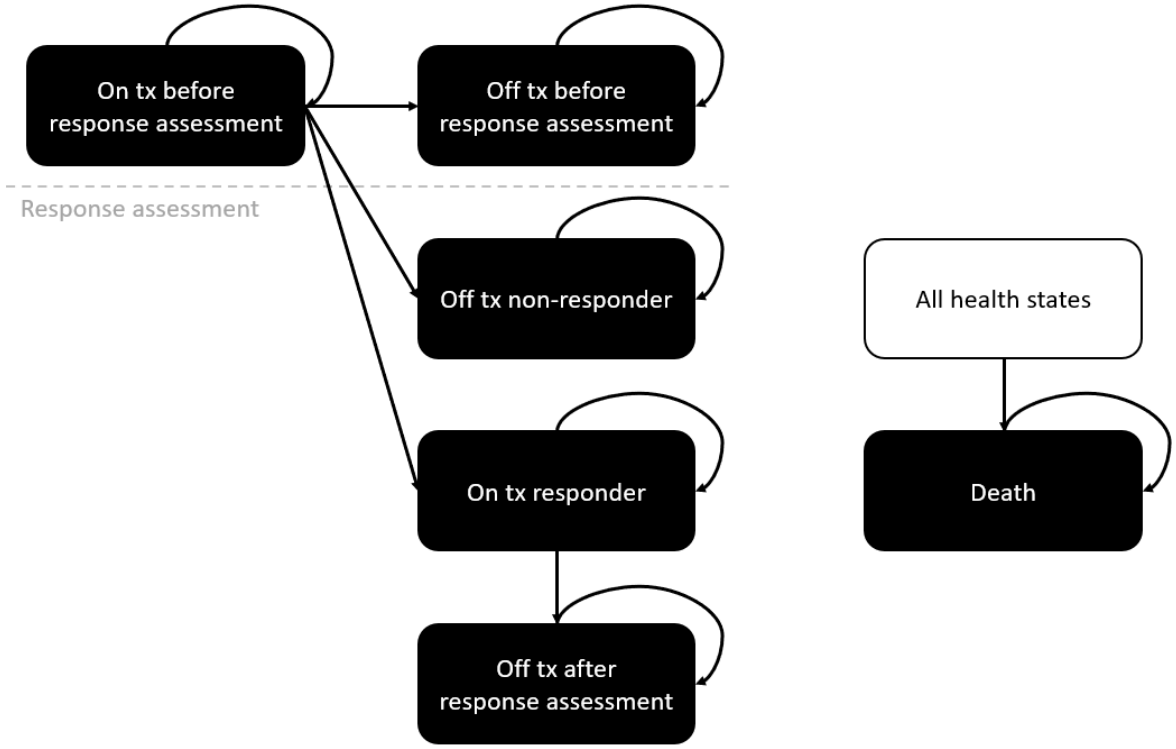
The model was composed of multiple health states, notably differing in the mean number of MMDs experienced by patients residing in each state:

- **On treatment before response assessment:** All patients are assumed to enter the model in this health state where they receive therapy, and remain until response assessment, death or treatment discontinuation. Week 12 was the modelled response assessment timepoint for atogepant, in line with expected stopping rules in clinical practice, and the ELEVATE and PROGRESS trials, where response was evaluated by the primary and secondary endpoints across a 12-week treatment period.[6, 137, 138] Response assessment was also modelled at 12 weeks for galcanezumab, erenumab and fremanezumab, in line the respective SmPCs and the negative stopping rules implemented in their respective NICE appraisals.[2-4, 129-131] After the 12-week response assessment (24 weeks for botulinum toxin type A), no patients remain in this health state. Response for botulinum toxin type A in the supplementary analysis (Appendix O) was assessed at 24 weeks to align with the 24-week assessment timepoint for the primary endpoint of the PREEMPT 1 and 2 trials and the timepoint used to inform the negative stopping rule for botulinum toxin type A in TA260.[13, 199, 200] After the 12-week response assessment (24 weeks for botulinum toxin type A), no patients remain in this health state.
- **Off treatment before response assessment:** Patients transition to this health state from 'On treatment before response assessment' should they discontinue treatment (for example, due to loss of efficacy or AEs) during the first 12 weeks, and thus, before response is assessed. They remain in this health state for the rest of the model time horizon or until death. As a simplifying assumption based on available data, this discontinuation was informed by all-cause discontinuation rates in the overall mITT population NMA.

- **Off treatment non-responder:** At 12 weeks, patients are only modelled to continue receiving treatment should they demonstrate treatment response, and therefore a lack of treatment response determines whether a patient transitions to this health state and would subsequently discontinue treatment. This is a semi-absorbing health state; patients entering it remain in the health state for remainder of the time horizon or until death, whichever occurs first.
- **On treatment responder:** In line with the 'Off treatment non-responder' health state, patients enter this health state if they demonstrate a treatment response across the initial 12-week treatment period and remain on treatment. However, patients can subsequently transition from this state to both 'Off treatment after response assessment' and 'Death' health states, as determined by long-term discontinuation rates (post response assessment), and UK population mortality rates, respectively.[233] The long-term discontinuation rates used are derived from relevant trial data and are discussed in further detail in Section B.3.3.6.
- **Off treatment after response assessment:** As stated above, patients transition to this health state in accordance with long-term discontinuation rates, applied as a per-cycle probability. This is a semi-absorbing health state; patients entering it remain in the health state for remainder of the time horizon or until death, whichever occurs first.
- **Death:** In line with previous TAs for migraine prevention, the model assumes that patients with migraines do not experience an increased risk of mortality.[2-4] As previously stated, patients can transition to this health state from any other and the associated probability of this occurring is applied uniformly using UK general population mortality rates.

In all off-treatment states, patients are assumed to receive BSC. A diagram depicting the semi-Markov modelling approach is presented in Figure 24 below.

Figure 24: Semi-Markov model structure



Footnotes: The response assessment pictured occurs at Week 12 and is applied as a one-off probability.
Abbreviations: tx: treatment.

Features of the cost-effectiveness analysis

Each health state in the model is associated with particular drug acquisition and drug administration costs, as well as MMD distributions that vary over time. Utility weights and MMD-related resource costs are applied in accordance with the number of MMDs experienced by patients residing in these states (as per TA659, TA682, TA764, TA906).[2-4, 15] This is necessary because the relationships between MMDs and MMD-related resource use costs are non-linear.[2] By aggregating the utility weights and MMD-related resource use costs in line with the proportion of patients experiencing a given number of MMDs, the utility weights and MMD-related resource use costs are calculated for each health state. These MMD-specific costs and utilities are then combined with the MMD-independent drug acquisition and drug administration costs for each treatment. Total costs and quality-adjusted life years (QALYs) associated with each treatment are then estimated by aggregating the utility weights and costs associated with each health state by state occupancy over time. The reasons for entering and exiting a health state, and the cost components that are considered in these states are detailed in Table 35.

Table 35: Summary of efficacy, cost and QALY modelling assumptions

Health state	Health state entry	Health state exit	Costs and QALY input
On treatment before response assessment	• Starting point for all patients	• Response assessment at Week 12 • All-cause discontinuation before response assessment • General population mortality	• All patients incur active treatment acquisition and administration costs • All other costs and QALYs are based on the MMD distribution in this health state
Off treatment before response assessment	• All-cause discontinuation before response assessment	• General population mortality	• No active treatment costs • All costs and QALYs are based on the MMD distribution used in this health state
Off treatment non-responder	• Response rates per treatment	• General population mortality	• No active treatment costs • All costs and QALYs are based on the MMD distribution used in this health state
On treatment responder	• Response rates per treatment	• All-cause discontinuation after response assessment • General population mortality	• All patients incur active treatment acquisition and administration costs where relevant • All other costs and QALYs are based on the MMD distribution in this health state
Off treatment after response assessment	• All-cause discontinuation after response	• General population mortality	• No active treatment costs • All costs and QALYs

	assessment		are based on the MMD distribution used in this health state
Death	• General population mortality	• None	• None

Abbreviations: AE: adverse event; MMD: monthly migraine day; QALY: quality-adjusted life year.

In line with the NICE reference case,[234] the base case analysis was conducted from the perspective of the National Health Service (NHS) and Personal Social Services (PSS). A lifetime time horizon was chosen given the chronic nature of migraine, and to align with the NICE reference case.[235] Additionally in previous appraisals, EAGs have concluded that a lifetime time horizon is appropriate to capture all relevant costs and outcomes associated with interventions for the prevention of migraine.[2, 16] A 28-day cycle length was considered in the base case to accurately capture the dosing schedule of atogepant and to align with a common dosing regimen duration among relevant comparators. Due to a longer cycle length, a half-cycle correction is included. Costs and effects were discounted at 3.5% annually.[236] The economic analysis is conducted using recent estimates of resource use and treatment costs available from published sources, including National Schedule of NHS Costs 2021–2022, PSS Research Unit 2022 and the Monthly Index of Medical Specialties 2023.[237-242]

As laid out in greater detail in Section B.1.1, the features of the analysis were based on previous NICE evaluations including:

EM and CM preventive treatments:

- Galcanezumab (TA659)[2]
- Erenumab (TA682)[3]
- Fremanezumab (TA764)[4]

CM preventive treatments:

- Botulinum toxin type A (TA260)[13]

A summary of the key features of these four appraisals and justification for the design of the cost-effectiveness analysis for atogepant in the prevention of EM and CM is provided in Table 36. More recently, eptinezumab and rimegepant have received NICE recommendations for the prevention of migraine in adults, signifying that selected details of these appraisals may be relevant to the current evaluation of atogepant. However, they are not considered to be comparators as these treatments do not constitute established clinical practice as discussed in Section B.1.1.[15, 16]

Table 36: Features of the economic analysis in previous evaluations in the prevention of migraine

Factor	Previous evaluations					
	TA659 galcanezumab	TA682 erenumab	TA764 fremanezumab	TA260 botulinum toxin type A	TA871 eptinezumab	TA906 rimegepant (preventive)
Date of publication	November 2020	March 2021	February 2022	June 2012	March 2023	July 2023
Is the treatment a relevant comparator for this appraisal?	Yes	Yes	Yes	No	No	No
Model structure	Semi-Markov	Decision tree plus Markov	Semi-Markov	Markov	Discrete event simulation	Decision tree plus Markov
Time horizon	45 years (lifetime)	Lifetime	58 years (lifetime)	2 years	82 years (lifetime)	20 years
Cycle length	30 days	12 weeks	28 days	12 weeks	NA	28 days
Half-cycle correction	Not included	• Yes for disease management and indirect costs • No for treatment costs	Not reported	Yes	No	No
Source of utilities	Patient-level MSQ v2.1 data from the CONQUER study mapped onto EQ-5D-3L scores.	Patient-level MSQ v2.1 data from Study 295, STRIVE and ARISE studies mapped to EQ-5D scores.	Patient-level MSQ data from FOCUS trial mapped to EQ-5D-3L scores.	Patient-level MSQ data from PREEMPT clinical trials.	Patient-level MSQ data from DELIVER trial mapped to EQ-5D-3L scores.	Patient-level MSQ data from BHV3000-201 study mapped to EQ-5D-3L scores.
Source of costs	• Intervention costs were based on the UK list price including a	• Intervention costs were based on the UK list price • Comparator	• BNF • PSSRU • National Schedule of	• BNF • PSSRU • National Schedule of	• Intervention costs were based on the UK list price • Comparator	• BNF • PSSRU • National Schedule of

	confidential discount • Comparator costs (drug and administration) were taken from the BNF and MIMS • Other costs were taken from the BNF, National Tariff, PSSRU	costs were taken from the BNF and NHS National Tariff • Other costs were taken from the National Tariff, PSSRU 2016, NHWS survey, BNF	NHS Costs	NHS Costs	costs were taken from the BNF and NHS National Tariff	NHS Costs
Resource use	Trial-specific data and Lipton *et al.* (2018)	NHWS survey	NHWS survey	International Burden of Migraine study	NHWS EU	NHWS survey
Health effects measure	QALYs	QALYs	QALYs	QALYs	QALYs	QALYs
Annual discount rate	3.5%	3.5%	3.5%	3.5%	3.5%	3.5%
Perspective	NHS/PSS	NHS/PSS	NHS/PSS	NHS	NHS/PSS	NHS/PSS

Abbreviations: BNF: British National Formulary; EAG: External Assessment Group; EU: European Union; HRQoL: health-related quality-of-life; mAbs: monoclonal antibodies; MIMS: Monthly Index of Medical Specialities; MMDs: monthly migraine days; MSQ: migraine-specific quality-of-life questionnaire; NA: not applicable; NICE: National Institute for Health and Care Excellence; NHB: net health benefit; NHS: National Health Service; NHWS: National Health and Wellness Survey; NMB: net monetary benefit; PSS: Personal Social Services; PSSRU: Personal Social Services Research Unit; QALY: quality-adjusted life year; SC: subcutaneous; TA: technology appraisal; UK: United Kingdom.

Table 37: Features of the economic analysis in the current evaluation

Factor	Current evaluation	
	Chosen values	Justification
Model structure	Semi-Markov	Model structure was closely aligned to that used in previous evaluations
Time horizon	Lifetime	A lifetime horizon was chosen to align with the NICE reference case and previous appraisals (TA659, TA682, TA764 and TA871)[2-4, 12]
Cycle length	28 days	Cycle length was chosen to accurately capture the dosing schedule of atogepant
Half-cycle correction	Yes	To increase accuracy of modelling, considering cycle length of 28 days
Source of utilities	Patient-level MSQ v2.1 data from the ELEVATE and PROGRESS studies mapped onto EQ-5D-3L scores	MSQ v2.1 was considered the most appropriate instrument to estimate utilities, in line with previous evaluations. The MSQ v2.1 assesses the HRQoL of patients over the previous 4 weeks, whereas the EQ-5D-5L questionnaire assesses the HRQoL of a patient on the day treatment is administered. This makes the MSQ v2.1 more suitable to estimate utilities by MMDs, because migraine severity can vary substantially on a daily basis, and also is in line with prior appraisals detailed in Table 36
Source of costs	• MIMS 2023 • PSSRU 2022 • National Schedule of NHS Costs 2021–2022	These are established sources of drug costs within the NHS. SC treatment administration costs were included (10% of costs applied after cycle 1).
Resource use	NHWS survey	In line with previous evaluations and EAG recommendations therein
Health effects measure	QALYs; NHBs	In line with NICE reference case, and preference for NHBs
Annual discount rate	3.5%	As per NICE reference case
Perspective	NHS/PSS	As per NICE reference case

Abbreviations: EAG: External Assessment Group; HRQoL: health-related quality-of-life; MIMS: Monthly Index of Medical Specialities; MSQ: migraine-specific quality-of-life questionnaire; NICE: National Institute for Health and Care Excellence; NHB: net health benefit; NHS: National Health Service; NHWS: National Health and Wellness Survey; PSS: Personal Social Services; PSSRU: Personal Social Services Research Unit; QALY: quality-adjusted life year; SC: subcutaneous; TA: technology appraisal; UK: United Kingdom.
Source: National Schedule of NHS Costs 2021–2022;[237] Monthly Index of Medical Specialties 2023;[239] PSSRU Unit Costs of Health and Social Care;[238] NICE health technology evaluations: the manual.[234]

B.3.2.3 Intervention technology and comparators

Atogepant

The intervention, atogepant is to be administered at a dose of 60 mg QD for both EM and CM. Additionally, atogepant 10 mg QD is licensed for patients who require dose modifications, or for special populations with severe renal impairment or end-stage renal disease. However, as this is considered outside of the scope of this present submission, the economic model assesses atogepant 60 mg QD in its base case. Week 12 was the modelled response assessment timepoint for atogepant, in line with expected stopping rules in clinical practice, and the ELEVATE and PROGRESS trials, where response was evaluated by the primary and secondary endpoints across a 12-week treatment period.[137, 138] For EM, responders are those patients with a ≥50% reduction from baseline in three-monthly average MMDs. For CM, patients are defined as responders if they experience ≥30% reduction from baseline in three-monthly average MMDs.

Comparators

Relevant comparators across EM and CM included galcanezumab, erenumab and fremanezumab (225 mg monthly or 675 mg every three months) for the prophylaxis of migraine in adults who have ≥4 migraine days a month and in whom ≥3 prior preventive treatments have failed. Response assessment was modelled at 12 weeks for galcanezumab, erenumab and fremanezumab, in line with their respective SmPCs and the negative stopping rules implemented in their respective NICE appraisals.[2-4, 129-131]

In addition, botulinum toxin type A is recommended for a subset of patients with CM, in those with headaches on at least 15 days per month of which at least 8 days are with migraine.[2-4] However, the proportion of patients with CM receiving botulinum toxin type A is expected to decline considerably following the introduction of CGRP mAbs and oral CGRP inhibitors due to capacity constraints related to in-clinic administration of botulinum toxin type A and the associated waiting lists which mean that the majority of newly treated patients are initiated on CGRP mAbs across the UK (B.1.3.3). Therefore, botulinum toxin type A is not considered a relevant comparator for atogepant, which is in line with the recent appraisal of eptinezumab (TA871),[12] whereby relevant comparators were ultimately deemed to be erenumab, fremanezumab, and galcanezumab, and not botulinum toxin type A. However, the results of a supplementary economic analysis of botulinum toxin type A are presented in Appendix O.

As introduced in Section B.1.1, galcanezumab, erenumab, and fremanezumab are recommended across both EM and CM and are appropriate comparators for this submission. The suitability of these comparators has been validated with UK clinical experts at an advisory board. The rationale for the selection of these comparators include:

- Galcanezumab, erenumab, and fremanezumab are all recommended for preventing migraine in adults for whom at least three preventive drug treatments have failed (TA659, TA682, and TA764)[2-4]
- Atogepant and the CGRP mAbs (galcanezumab, erenumab, and fremanezumab) are all designed to suppress CGRP activity. Thus, UK clinical experts at an advisory board were willing to consider atogepant as an alternative to a CGRP mAb and anticipated that the technologies would have similar efficacy and positioning[5]
- Atogepant and the CGRP mAbs can each be self-administered by the patient at home, and do not require in-clinic administration. Although, a subset of patients receiving CGRP mAbs

are not comfortable with self-injection, and continue to attend the clinic for administration by a healthcare professional[2, 133]

- A series of indirect comparisons were conducted to estimate the relative efficacy of atogepant against the full range of comparators recommended at publication of the final scope (please refer to Section B.2.8 for further details). Evidence from the indirect comparisons demonstrates that atogepant has similar health benefits to galcanezumab, erenumab, and fremanezumab across EM and CM, with no significant difference seen in efficacy endpoints. Additionally, in EM, atogepant demonstrated statistically significantly superior HRQoL versus relevant comparators in at least one HRQoL measure

The more recently approved CGRP inhibitor therapies, eptinezumab (TA871) and rimegepant (TA906), have been excluded as comparators from the analysis on the basis that they are not considered as established clinical practice.[12, 15] This is discussed in further detail in Section B.1.1.

B.3.3 Clinical parameters and variables

The clinical parameters and variables used in the model are summarised in Table 38. Where possible, parameters for the comparators are informed by the NMAs (Section B.2.9). The NMAs presented in the base case are informed by data from 3+ TF patient population for EM (ELEVATE study), and the overall mITT population for CM (PROGRESS study), given that these populations were the most relevant data which were sufficiently powered to inform decision-making.

In a recent appraisal of another oral CGRP inhibitor for the prevention of migraine (TA906), rimegepant,[15] a recommendation was made based on a Phase 3 trial which excludes those with no response to at least two preventive treatments (i.e. an overall population that did not reflect the 3+ TF mITT subgroup). Furthermore, in the Final Appraisal Document of an ongoing appraisal of the same drug for treating acute migraine (ID1539), the EAG have maintained a preference for the use of an overall mITT analysis to inform the efficacy of rimegepant.[149] In the Committee slides of the same appraisal, the EAG indicated a preference for this larger sample size while citing a lack of patient stratification at randomisation and imbalances in baseline characteristics as subgroup limitations.[149]

Table 38: Clinical parameters used in the model

Input parameter	Input options	Data Source	Purpose
Discontinuation before response assessment	All-cause discontinuation applied on a per-cycle basis (base case)	Relevant EM and CM NMA inputs	This input parameter governs what proportion of patients moves to the 'Off treatment before response assessment' health state
	All-cause discontinuation applied as a one-off probability at the response assessment timepoint (scenario)	Relevant EM and CM NMA inputs	
Response rate	≥50% reduction in MMDs from baseline across the 12-week treatment period (EM) (base case)	Trial data from the ELEVATE (3+ TF mITT subgroup) and PROGRESS (overall mITT population) trial are used to inform values used for atogepant in EM and CM, respectively, with odds ratios from the NMAs applied to generate response rates for selected comparators	This input parameter governs what proportion of patients transition to 'Off treatment non-responder' and 'On treatment responder' after response assessment in Week 12 for all treatments
	≥30% reduction in MMDs from baseline across the 12-week treatment period (base case)		
	≥50% reduction in MMDs from baseline across the 12-week treatment period (scenario analysis)		
Discontinuation after response assessment	All-cause discontinuation (base case)	The long-term discontinuation rate for atogepant from LTS-302 (3.59%) is used for all active treatments due to a lack of suitable data to perform an NMA. This is in alignment with the approach taken in the NICE appraisals of erenumab (TA682), fremanezumab (TA764), and rimegepant (TA906).[3, 4, 15]	This input parameter governs what proportion of patients move to the 'Off treatment after response assessment' health state
Mean MMDs over time	Within each health state, the mean number of MMDs differs by response status and by treatment arm	• Baseline and non-responder mean MMD rates are derived from ELEVATE and PROGRESS. Non-responder mean MMDs for comparators are assumed to be equal to atogepant • Responder mean MMDs are treatment-specific and are calculated using the CFB in MMDs	This input parameter governs the number of MMDs patients experience over time within health states

		and response rates derived from NMA results	
MMD distribution	Mean MMDs are converted to an MMD distribution using a Poisson distribution	The distribution across MMDs is generated by applying a Poisson distribution to the mean MMDs described above	This input parameter determines how mean MMD rates are converted to distributions
Health state utilities	Utility values per MMD based on utility regression stratified by response status (base case) Utility values per MMD based on utility regression stratified by treatment (BSC only) (scenario)	• Utility values per MMD for atogepant and BSC are informed by ELEVATE (EM) and PROGRESS (CM) overall mITT populations • Utility values per MMD for other comparators are assumed to be equal to atogepant	This input parameter quantifies the quality-of-life impact of a given number of MMDs
Acute medication use	Number of MUDs per comparator calculated by using CFB in placebo MUDs plus the change from baseline in MUDs	For patients treated with placebo or atogepant, study data are used, while for comparators relevant NMA results are used	This input parameter determines the costs resulting from acute medication use over a patient's lifetime

Abbreviations: BSC: best supportive care; CFB: change from baseline; CM: chronic migraine; EM: episodic migraine; mITT: modified intention-to-treat; MMDs: monthly migraine days; MUDs: medication use days; NMA: network meta-analysis;.

B.3.3.1 Baseline characteristics

The baseline characteristics for the two populations in terms of age, gender distributions, baseline monthly MMDs and MUDs were derived from the ELEVATE and PROGRESS trials and are shown in Table 39.

Table 39: Baseline characteristics for the two populations used in the economic model

Characteristic	EM (3+ TF mITT)	CM (overall mITT)
Age, mean	[redacted]	42.1
Proportion female, %	[redacted]	87.5%
Pooled baseline MMDs (SD)	[redacted]	[redacted]
Pooled baseline monthly acute MUDs (SD)	[redacted]	[redacted]

Abbreviations: CM: chronic migraine; EM: episodic migraine; mITT: modified intent-to-treat; MMDs: monthly migraine days; MUDs: medication use days; SD: standard deviation; TF: treatment failure.
Source: AbbVie Data on File. Atogepant Migraine MAAP 304 study_combined priority 123 analysis.pdf. PROGRESS, Table 1-03-01-04, Table 2-03.01 and Table 2-07.01.

B.3.3.2 Discontinuation before response assessment

The proportion of patients who discontinue treatment before the response assessment (12 weeks for atogepant and SC CGRP mAbs) is applied as a per-cycle discontinuation rate prior to response assessment. In the base case, all-cause discontinuation rates are employed in line with the prior NICE evaluation for erenumab (TA682).[3] A scenario analysis where all-cause discontinuation was applied as a one-off probability at the response assessment timepoint was also explored.

For atogepant, absolute values for discontinuation are applied. SC CGRP mAbs are informed by a HR applied to each treatment relative to atogepant as the reference arm. In EM and CM, the probability of discontinuation before assessment for atogepant and SC CGRP mAbs is displayed in Table 40.

Table 40: Probability of discontinuation before response assessment for atogepant and relevant comparators in EM and CM

	EM		CM	
	HR (95% CrI)	Probability of disc.	HR (95% CrI)	Probability of disc.
Atogepant 60 mg QD (reference)	[redacted]	[redacted]	[redacted]	[redacted]
Galcanezumab 120 mg QM[a]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg QM	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 225 mg Q3M[b]	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 675 mg Q3M	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a]Galcanezumab regimen is a 240 mg loading dose followed by 120 mg once a month.
[b]Fremanezumab regimen is 675 mg initial dose followed by 225 mg once a month.
Abbreviations: CM: chronic migraine; CrI: credible interval; disc.: discontinuation; EM: episodic migraine; HR: hazard ratio; QD: every day; QM: every month; Q3M: every three months; RE: random effects; SC: subcutaneous.

B.3.3.3 Response

In the model, all patients are assumed to undergo a response assessment at 12 weeks for atogepant and SC CGRP mAbs. The results of this assessment determine whether patients move to the 'Off treatment non-responder' health state and discontinue treatment, or to the 'On treatment responder' health state and continue treatment. For the atogepant arm, the probability of response across 12 weeks derived from the relevant populations of ELEVATE or PROGRESS informs the proportion of responders for the atogepant arm in the model. For all other treatments, the odds ratio for each treatment versus atogepant is applied to the atogepant odds of response (calculated from the absolute probability of response) to calculate the log odds of response for each treatment, and ultimately the proportion of responders for each treatment. The proportion of responders and non-responders ultimately inform the calculation of response-specific MMDs.

Response is defined as:

- EM – ≥50% reduction from baseline in a three-month average of MMDs
- CM – ≥30% reduction from baseline in a three-month average of MMDs

These response assessment definitions are in line with previous NICE appraisals for the prophylaxis of migraine (TA659, TA682, TA764).[2-4] However, at an advisory board, clinicians noted that ≥50% reduction in MMDs was also clinically relevant for CM. As such, a scenario analysis was carried out in which the negative stopping rule for CM was based on a ≥50% response rate (Section B.3.11.3).

Table 41: Probability of ≥50% response in MMDs across the 12-week treatment period for atogepant and relevant comparators in EM

	RE	
	OR (95% CrI)	Probability response
Atogepant 60 mg QD (reference)	[redacted]	[redacted]
Galcanezumab 120 mg QM[a]	[redacted]	[redacted]
Erenumab 140 mg QM	[redacted]	[redacted]
Fremanezumab 225 mg Q3M[b]	[redacted]	[redacted]
Fremanezumab 675 mg Q3M	[redacted]	[redacted]

Footnotes: [a]Galcanezumab regimen is a 240 mg loading dose followed by 120 mg once a month.
[b]Fremanezumab regimen is 675 mg initial dose followed by 225 mg once a month.
Abbreviations: CrI: credible interval; EM: episodic migraine; MMDs: monthly migraine days; OR: odds ratio; QD: every day; QM: every month; Q3M: every three months; RE: random effects.

Table 42: Probability of ≥30% response in MMDs across the 12-week treatment period for atogepant and relevant comparators in CM

	RE	
	OR (95% CrI)	Probability response
Atogepant 60 mg QD (reference)	[redacted]	[redacted]
Galcanezumab 120 mg QM[a]	[redacted]	[redacted]
Erenumab 140 mg QM	[redacted]	[redacted]
Fremanezumab 225 mg Q3M[b]	[redacted]	[redacted]
Fremanezumab 675 mg Q3M	[redacted]	[redacted]

Footnotes: [a]Galcanezumab regimen is a 240 mg loading dose followed by 120 mg once a month.
[b]Fremanezumab regimen is 675 mg initial dose followed by 225 mg once a month.
Abbreviations: CM: chronic migraine; CrI: credible interval; MMDs: monthly migraine days; OR: odds ratio; QD: every day; QM: every month; Q3M: every three months; RE: random effects.

B.3.3.4 Mean MMDs over time by health state

Mean MMDs are anticipated to change over time, as patients transition from one health state to another. For each health state, the mean MMDs are specified as the patient enters a health state ('**Start MMDs**'), the mean MMDs that a patient transitions to during their occupancy of a given health state ('**End MMDs**'), and the duration of this transition can be altered in all health states apart from 'On treatment before response assessment' as the duration of this is fixed at 12 weeks for atogepant and SC CGRP mAbs in both EM and CM.

The assumptions applied to MMDs in each health state in the base case were determined in line with those used in the prior appraisal of galcanezumab, and are detailed in Table 43.[2] Inputs are derived from NMA results and relevant trial data (ELEVATE or PROGRESS).[136, 138]

For those in the 'On treatment before response assessment state', mean MMDs were informed by pooled baseline MMDs across the atogepant 60 mg and placebo arms of the ELEVATE 3+ TF and PROGRESS overall mITT populations for EM and CM, respectively. For those who transition to the 'Off treatment before response assessment' state during the 12-week treatment period, MMDs are initially informed by treatment-specific non-responder MMDs, where all SC CGRP mAb non-responder MMDs are assumed equal to atogepant (except in the case of adjustments made to non-responder MMDs to ensure the comparator-specific CFB in MMDs pooled across responders and non-responders is retained, as discussed below). MMDs then immediately revert to pooled baseline MMDs (i.e., by the next model cycle). This in line with the assumption made in the NICE appraisal of rimegepant (TA906).[15] For those who do not achieve response at the 12-week response assessment timepoint, patients are also assigned treatment-specific non-responder MMDs which are assumed to revert to pooled baseline MMDs after one cycle.

For patients who achieve response and transition to the 'On treatment responder' state, patients are assigned treatment-specific responder MMDs, with atogepant 60 mg and BSC inputs informed by the atogepant 60 mg and placebo arms of the ELEVATE 3+ TF and PROGRESS overall mITT populations for EM and CM, respectively. Comparator MMDs are derived by applying the CFB in MMDs (across responders and non-responders) from the NMAs to the reference atogepant 60 mg data to generate pooled MMDs for a given comparator. Mean MMDs for responders and non-responders are then derived from these pooled data using the treatment-specific response rate, and an assumption that non-responder MMDs are equal to that of atogepant.

Responder MMDs were restricted in the model such that they could not fall below a user-defined clinically plausible minimum MMD (1 MMD), and thus in cases where responder MMDs would be predicted to fall below this minimum based on the CFB in MMDs, adjustments would be made to non-responder MMDs to ensure the input CFB in MMDs is retained.

The CFB in MMDs across the 12-week treatment period in patients with EM and CM receiving atogepant or CGRP mAbs is displayed below (Table 44). It was assumed that those on treatment maintain the improved number of MMD achieved when response is established at Week 12, i.e. the distribution of MMD by responder status will be maintained over the full post-assessment period in line with the previous CGRP mAbs and rimegepant appraisals.

Patients who discontinue treatment during the post-assessment period (i.e., after achieving response) do not maintain treatment-specific responder MMDs, and efficacy is assumed to immediately revert to pooled baseline MMDs (i.e. by the next model cycle), in line with the approach taken in the NICE appraisal of rimegepant (TA906).[15] This reflects clinical practice, where treatment discontinuation post response-assessment would most likely follow loss of treatment response.

Table 43: MMD assumptions made per health state

Health state	Base case MMD assumptions	
	Start	**End**
On treatment before response assessment	Pooled baseline MMDs	Pooled baseline MMDs
Off treatment before response assessment	Treatment-specific non-responder MMDs[a]	Pooled baseline MMDs
Off treatment non-responder	Treatment-specific non-responder MMDs	Pooled baseline MMDs
On treatment responder	Treatment-specific responder MMDs	Treatment-specific responder MMDs
Off treatment after response assessment	Treatment-specific responder MMDs	Pooled baseline MMDs
Death	None	

[a]All non-responder MMDs for SC CGRP mAbs and botulinum toxin type A were assumed equal to atogepant.
Abbreviations: IV: intravenous; MMD: monthly migraine day; SC: subcutaneous.

Table 44: Change from baseline in mean MMDs across the 12-week treatment period to atogepant and relevant comparators in EM and CM

	EM (RE)		CM (RE)	
	Median CFB (95% CrI)	Mean MMDs	Median CFB (95% CrI)	Mean MMDs
Atogepant 60 mg QD (reference)	[redacted]	[redacted]	[redacted]	[redacted]
Galcanezumab 120 mg QM[a]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg QM	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 225 mg Q3M[b]	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 675 mg Q3M	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a]Galcanezumab regimen is a 240 mg loading dose followed by 120 mg once a month. [b]Fremanezumab regimen is 675 mg initial dose followed by 225 mg once a month.
Abbreviations: EM: episodic migraine; CM: chronic migraine; CFB: change from baseline; CrI: credible interval; EM: episodic migraine; MMDs: monthly migraine days; OR: odds ratio; QD: once daily; QM: every month; Q3M: every three months; RE: random effects.

B.3.3.5 Mean MMD distribution

The proportion of patients experiencing a given mean number of MMDs over time in different health states is critical to the generation of model results. This is because each MMD frequency incurs a specific utility value and healthcare resource use costs, and because the relationships between MMDs and resource use costs are likely to be non-linear.

The model uses the mean MMD value as the primary parameter to estimate MMD distributions over time, for each health state across all treatments. As mean MMD values for health states and treatments change over time, distributions are automatically adjusted when using this method. To estimate these MMD distributions, Poisson distributions were fitted to the mean MMD value. The Poisson distribution does not require any additional parameters, as the variance of the distribution is equal to its mean. An illustrative example of how Poisson distributions were fitted to observed values is shown in Figure 25.

Figure 25: Illustrative example of Poisson-distributed versus observed MMDs

Abbreviations: ATO60: atogepant 60 mg; MMDs: monthly migraine days; PBO: placebo.

B.3.3.6 Discontinuation after response assessment

In the model, discontinuation after response assessment is included as a constant probability of discontinuation per model cycle. Patients who discontinue stop receiving active treatment and move to the 'Off-treatment after response assessment' health state. As with discontinuation before response assessment, all-cause discontinuation rates are employed to inform treatment discontinuation after response assessment for both EM and CM.

In the base case, the probability of discontinuing treatment after response assessment across all interventions is set at a per-cycle probability of 3.59%, derived from the LTS-302 long-term safety and tolerability study of atogepant in EM.[243] The discontinuation rate was assumed equal across treatments, due to a lack of suitable data to perform an NMA, and in line with assumptions made in appraisals of erenumab, fremanezumab and rimegepant (TA682, TA764, TA906).[3, 4, 15] In the absence of long-term discontinuation rates in CM, the same probability was applied to CM patients. Per cycle discontinuation rates were calculated assuming a constant hazard of discontinuation over the 291.6-day mean treatment duration for atogepant in LTS-302 (Table 45).

Table 45: Observed discontinuation after response assessment

Type of discontinuation (per cycle)	ATO 60 mg QD
All-cause discontinuation	3.59%

Note: Values are based on mean treatment duration of 291.6 days for atogepant and 278.9 days for placebo. Discontinuation after response assessment for all active comparators was assumed equal to that used for atogepant. **Abbreviations:** ATO: atogepant; QD: once daily.

B.3.3.7 Acute medication use days

The number of monthly acute MUDs for each treatment in the base case is based on the change from baseline in numbers of acute MUDs for atogepant and SC CGRP mAbs derived from the NMA. Patients on active treatment are modelled as having treatment-specific MUDs until they discontinue treatment, after which they are assumed to have acute MUDs in line with patients not receiving active treatment for the remainder of the time horizon. The monthly acute MUDs used in the base case are presented in Table 46.

Table 46: Change from baseline in mean responder MUDs across the 12-week treatment period to atogepant and relevant comparators in EM and CM

Treatment	EM (RE)		CM (RE)	
Mean difference versus ATO	Median CFB in MUDs (95% CrI)	Mean MUDs	Median CFB in MUDs (95% CrI)	Mean MUDs
Atogepant 60 mg QD (reference)	[redacted]	[redacted]	[redacted]	[redacted]
Galcanezumab 120 mg QM[a]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg QM	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 225 mg Q3M[b]	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 675 mg Q3M	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a]Galcanezumab regimen is a 240 mg loading dose followed by 120 mg once a month; [b]Fremanezumab regimen is 675 mg initial dose followed by 225 mg once a month; [c]Values are based on imputed values.
Abbreviations: CFB: change from baseline; CM: chronic migraine; EM: episodic migraine; MUD: medication use day; QD: every day; QM: every month; Q3M: every three months; RE: random effects.

B.3.3.8 Adverse Events

AEs are typically costed in an economic model should they be of Grade ≥3 severity. As no AEs of Grade ≥3 from the relevant trials for atogepant or its comparators met the inclusion criteria for the model, AE costs are not considered in the base case of the economic model, in line with the prior appraisals (TA260, TA659, TA682, TA764, TA871, TA906).[2, 3, 12, 13, 15] This may represent a conservative assumption given the potential for injection site reactions and hypersensitivity reactions with CGRP mAbs.[120-122]

B.3.3.9 Mortality

Transition probabilities to the 'Death' health state are informed by age- and sex-matched general population mortality statistics from the Office for National Statistics 2018–2020.[233] No additional migraine specific-mortality was modelled, in line with prior NICE appraisals, and consistent with a published meta-analysis, which found no association between migraine and all-cause mortality.[244]

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

As previously discussed, HRQoL outcomes were measured using the MSQ v2.1 and HIT-6 questionnaires which are recommended in international guidelines for the assessment of treatment response.[40, 112, 116-118] As migraine severity and/or patient disability might not be captured by outcomes measuring migraine frequency alone, HRQoL measures are particularly important in the assessment of migraine (Section B.2.6.3).

Whilst HRQoL data were also collected via the EQ-5D-5L questionnaire in atogepant studies (ELEVATE and PROGRESS),[136, 138] MSQ v2.1 was considered the most suitable instrument to estimate utilities for the model, in line with the approach used in past migraine models (Table 36).[2-4, 7, 13, 15, 16] The MSQ v2.1 assesses the HRQoL of patients over the previous 4 weeks, whereas the EQ-5D-5L questionnaire assesses the HRQoL of a patient on the day treatment is administered. This makes the MSQ v2.1 more suitable to estimate utilities by MMDs, because migraine severity can vary substantially on a daily basis.[245] The EQ-5D-5L questionnaire would otherwise substantially underestimate the impact of MMDs on HRQoL, as patients are unlikely to attend clinical visits on a day when they have a migraine attack.[245, 246] The use of these data in the economic model is discussed in more detail in Section B.3.4.5.

B.3.4.2 Mapping

MSQ v2.1 data from the two relevant studies, ELEVATE and PROGRESS, were converted into utility values on the EQ-5D-3L scale, using the CM- and EM-specific mapping algorithms, previously described by Gillard *et al.* (2012).[18, 136, 138, 247, 248] Gillard *et al.* describes two different mapping algorithms for mapping MSQ v2.1 to the EQ-5D-3L. The first mapping algorithm considers only the three MSQ dimensions (role preventive, role restrictive, and emotional function). The second mapping algorithm considers the MSQ dimensions and additional covariates for age, sex, race, employment, headache medication use, and comorbidities. Both mapping methods were performed and included in the model as “Regression 1” (MSQ domains only) and “Regression 2” (MSQ domains and additional comorbidities) in the model. Previous models detailed in the TAs for both the erenumab[3] and fremanezumab[4] used “Regression 1”, stating that the respective studies that informed their studies did not provide the necessary information required for “Regression 2” on employment status or comorbidities. In order to align with the precedence set in these TAs, “Regression 1” utilities were used in the model base case. However, a scenario analysis was performed in which “Regression 2” utilities are used, as all studies relevant to atogepant report the necessary data.

B.3.4.3 Health-related quality-of-life studies

Utility values per MMD included in the base case were derived from MSQ v2.1 values obtained from the ELEVATE and PROGRESS studies, mapped to EQ-5D data using the algorithm presented in Gillard *et al.* (2012).[247, 248]

An SLR was conducted to identify relevant HRQoL data in patients with EM and CM. Searches were conducted on 7 January 2022 and then updated on 3 November 2022 to support an initial company submission in February 2023. The original SLR and SLR update were performed in accordance with a pre-specified protocol and the methodological principles of conduct for systematic reviews as detailed in the University of York CRD “Guidance for Undertaking Reviews

in Health Care".[249] Full details of the SLR search strategy, study selection progress and results are reported in Appendix I.

In total, 48 publications reporting on 44 unique studies were included in the original SLR and SLR update. However, given the most relevant and applicable HRQoL data to atogepant were provided by the above studies, no further extraction of HRQoL studies from the SLR was performed.

B.3.4.4 Adverse reactions

In line with previous evaluations in this indication, adverse events were not considered in the economic model. The safety profile of atogepant is described in Section B.3.3.8.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

In the economic analysis, MSQ v2.1 values mapped to EQ-5D per MMD via regression 1 from Gillard *et al.* (2012) are used to model patient HRQoL in the base case.[247] The model assigns a utility value to the number of MMDs per patient. The utility values for each model health state are then calculated by multiplying the utility values for each number of MMDs by the distribution of patients across MMDs over time in that health state. QALYs are then calculated by aggregating the utility values for the different health states over time over the time horizon selected.

For the utility values, relevant HRQoL inputs were available for atogepant and BSC, but not for the comparators. As an indirect comparison of HRQoL utility values was not feasible, the utility values for comparators would otherwise be assumed to be the same as atogepant 60 mg. This is due to MSQ regressions requiring individual patient data (IPD) to generate utility values per MMD. Associated IPD were only available from ELEVATE and PROGRESS,[138, 145] and thus utility values could only be generated for atogepant and placebo treatment groups. As only summary data were reported from the clinical trials of the CGRP mAbs (EM and CM) (and botulinum toxin type A in CM), no robust, equivalent utility values could be generated for these comparators. Similarly, whilst utility values are reported in prior appraisals for erenumab and fremanezumab,[3, 4] baseline utility differed, meaning that these values cannot be directly used in the model. Therefore, in the absence of treatment-specific IPD, response-specific utility values were considered more robust and included in the base case analysis (i.e. regression models included a coefficient for response). As they are stratified by response status, using response-specific utility values allows for more accurate differentiation between atogepant and its active comparators as it considers the proportion of responders from each comparator, as informed by the NMA.

A small utility decrement associated with route of administration was applied to CGRP mAbs to reflect differential utilities measured for each respective treatment regimen vs oral treatments, as collected within a recent UK vignette-based study of 400 participants (200 general population and 200 migraine patients).[135] Relative to atogepant, an average utility decrement of −0.01 is applied for CGRP mAbs (based on a reported utility for 1 injection per month). On review of the utility data, three headache specialists deemed the route of administration-related disutilities to be realistic, given the discomfort and/or anxiety associated with injectable treatments relative to taking an oral tablet. Reported disutilities were also deemed to be conservative, given that the oral treatments included in the study are unlikely to have as favourable tolerability profile as atogepant.

The NMA results for MSQ presented in Section B.2.9.6 indicate that atogepant is associated with better and in some cases statistically superior HRQoL outcomes (against all active comparators for MSQ-RFR, MSQ-RFP, MSQ-EF in EM and fremanezumab in CM). The assumption of equal utilities per number of MMDs is therefore likely to be conservative, biasing cost-effectiveness results in favour of CGRP mAbs.

Utility values estimated from mapping the observed MSQ v2.1 values from the overall mITT populations of ELEVATE and PROGRESS to EQ-5D-3L were considered the most suitable for inclusion in the model, the justification for which is described in Table 37 and Section B.2.6.3. Utility values were derived for atogepant (60 mg) versus placebo according to the number of MMDs experienced, and the resulting difference between these values, in both EM and CM. The relevant coefficients for regression 1 are presented in Table 47 and the resulting utility values for each MMD are presented in Table 48.

Table 47: Coefficients for Regression 1

MMDs and treatment	EM		CM	
	Coeff	SE	Coeff	SE
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
MMD	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CM: chronic migraine; Coeff: coefficient; EM: episodic migraine; MMD: monthly migraine days; SE: standard error.

Table 48: MSQ v2.1 utility regression inputs per MMD for EM and CM

MMD	EM				CM			
	Active treatment: non-responder	BSC: non-responder	Active treatment: responder	BSC: responder	Active treatment: non-responder	BSC: non-responder	Active treatment: responder	BSC: responder
0	[redacted]							
1	[redacted]							
2	[redacted]							
3	[redacted]							
4	[redacted]							
5	[redacted]							
6	[redacted]							
7	[redacted]							
8	[redacted]							
9	[redacted]							
10	[redacted]							
11	[redacted]							
12	[redacted]							
13	[redacted]							
14	[redacted]							
15	[redacted]							
16	[redacted]							
17	[redacted]							
18	[redacted]							
19	[redacted]							
20	[redacted]							
21	[redacted]							

22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: Utility values per MMD for the comparators are assumed to be identical to atogepant.
Abbreviations: ATO: atogepant; CM: chronic migraine; EM: episodic migraine; MMD: monthly migraine day; MSQ: migraine-specific quality-of-life questionnaire; QD: every day.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

To fully capture the costs associated with EM and CM, the following factors were accounted for: active treatment drug acquisition, active treatment drug administration, health resource use, acute medication use, and are discussed in further detail in the sections below.

An SLR was conducted to identify relevant cost or resource use studies for incorporation in the model. The searches were run on 7 January 2022 and updated on 4 November 2022 to support an initial company submission in February 2023. Full details of the SLR search strategy, study selection process and results are presented in Appendix J.

In total, 19 articles reporting on 16 unique studies were included in the original and SLR update. The following cost categories were included in the model:

- Drug acquisition costs
- Administration costs
- Health state-related resource use

The economic analysis was conducted from an NHS and PSS perspective and therefore included only costs that would be incurred by the NHS and PSS. Cost inputs were based on British National Formulary (BNF), National Schedule for NHS costs (2021–2022), and Personal Social Services Research Unit (PSSRU) 2022.[241, 250, 251]

B.3.5.1 Intervention and comparators' costs and resource use

Drug acquisition costs

Drug acquisition costs are applied to the model as a function of health state occupancy; only patients in the 'On treatment before response assessment' and 'On treatment responder' accrue these costs, and are therefore determined by the negative stopping rules based on response outlined in Section B.3.3.3. Drug acquisition costs per model cycle are calculated based on recommended doses and administration schedules for each treatment, multiplied by the unit cost of treatment packs and adjusted for cycle length to calculate a drug acquisition cost per cycle. Unit costs are sourced from the Monthly Index of Medical Specialties (MIMS) for the relevant treatments that have publicly available costs (galcanezumab, erenumab and fremanezumab).[252-254] The recommended dose and administration of respective drugs are informed by the ELEVATE and PROGRESS trials for atogepant and the relevant SmPC and/or other regulatory documentation for the comparators.[1, 120-122, 138, 145]

Table 49: Drug acquisition costs for atogepant and relevant comparators

Treatment	Form	Strength	Pack size	Frequency	Cost per pack
Atogepant	Tablet	60 mg	28	QD	List price: £463.68 PAS price: £[redacted]
Galcanezumab	Pre-filled pen	2 x 120 mg	1	Loading dose	£450.00
Galcanezumab	Pre-filled pen	120 mg	1	Every 28 days[a]	£450.00
Erenumab	Pre-filled pen	140 mg	1	Every 28 days[a]	£386.50
Fremanezumab	Pre-filled pen	225 mg	1	Every 28 days[a]	£450.00
Fremanezumab	Pre-filled pen	675 mg	1	Every 84 days[b]	£1,350.00

Footnotes: [a]Duration used in the model, equating to a clinical dosing schedule of once monthly; [b]Duration used in the model, equating to a clinical dosing schedule of once every three months.
Abbreviations: QD: every day; U: units.
Sources: Monthly Index of Medical Specialties (MIMS).[252-254]

Drug administration costs

Atogepant is administered orally and does not incur any drug administration costs. On the other hand, galcanezumab, erenumab and fremanezumab are administered via SC injection (base case analysis; Section B.3.2.3). Drug administration costs are thus applied to the comparators as detailed in Table 50.

For the CGRP mAbs, SC administration costs were included for all patients in the first cycle to account for the cost of training patients to use the SC device. Additionally, based on feedback from the NICE committee in the appraisal of galcanezumab (TA659) and subsequent implementation in the appraisal of rimegepant (TA906), administration costs are applied every cycle for 10% of patients to account for the assumption that not all patients are able to self-administer due to factors such as physical or mental disability, old age or a phobia of needles.[2, 15]

The drug administration method modelled for each treatment is based on clinical trials for atogepant and the relevant SmPCs for the comparators:[255-258]

- Oral: atogepant
- SC: erenumab, fremanezumab and galcanezumab

The costs for each administration method are sourced from PSSRU and National Schedule of NHS Costs in the base case, assuming no administration cost for oral treatments.[237, 238]

Table 50: Drug administration costs

Treatment	Method of administration	Cost per administration	Source/assumption
Atogepant	Oral administration	NA	Assumed to be zero
Galcanezumab	SC injection	£21.50[a]	PSSRU (2022): based on a 30-minute appointment with a Band 5 hospital-based nurse at an hourly rate of £43.00
Erenumab	SC injection		
Fremanezumab	SC injection		

Footnotes: [a]This cost is applied in full in the first cycle only. In Cycle 2, 10% of this cost is applied per cycle reflecting the assumption that not all patients are able to self-administer due to factors such as physical or mental disability, old age or a phobia of needles..
Abbreviations: IM: intramuscular; NA: not applicable; NHS: National Health Service; PSSRU: Personal Social Services Research Unit; SC: subcutaneous; U: units.
Sources: National Schedule of NHS Costs 2021–2022;[237] PSSRU Unit Costs of Health and Social Care.[238]

Drug monitoring costs

In the recent NICE appraisal of rimegepant (TA906), clinical expert opinion indicated that rimegepant could be initiated by a specialist in secondary care then later continued by a GP in primary care, with the NICE committee preferring to consider costs for both the secondary care specialist and primary care GP.[15]

Clinical expert opinion received in support of the appraisal of atogepant has been consistent in concluding that due to its oral route of administration, clinical effectiveness and tolerable safety profile, atogepant is also ideally placed for use in primary care. However, studies mapping the UK migraine referral pathway and clinical expert opinion indicates that the role and cost of the secondary care general neurologist has not yet been captured in prior migraine appraisals (Section B.1.3.3), and so additional potential resource efficiencies are not fully captured in migraine clinical care pathway. As described in Section B.1.3.3, unlike the CGRP mAbs, atogepant is anticipated to be used widely in the general neurology care setting, thereby relieving headache specialist capacity. Therefore, costs for 6-monthly therapeutic monitoring/disease management across three healthcare professionals (secondary care headache specialist & general neurologist, as well as primary care GP) were included in the base case analysis.

In the base case, SC CGRP mABs and atogepant were assumed to be initiated in secondary care (100% headache specialist for CGRP mAbs versus whereas 50%:50% split of headache specialist/general neurologist for atogepant). However, in line with anticipated prescribing behaviour, clinical follow-ups are assumed to be conducted by a GP for atogepant and a headache specialist for CGRP mAbs. These base case assumptions have been validated by three headache specialists, while alternative drug monitoring scenarios have also been explored (Table 67).

Costs for the following appointments, either with a headache specialist, general neurologist, or a GP, were included in the base case analysis:

- Treatment prescription/initiation (at 0 months) for atogepant (headache specialist/general neurologist) and CGRP mAbs (headache specialist)
- Response assessment at 3 months (i.e., 12 weeks) for atogepant (GP) and CGRP mAbs (headache specialist)
- Follow-up consultation every 6 months (i.e., 24 weeks) after for atogepant (GP) and CGRP mAbs (headache specialist), in line with available NICE guidance[42]

As a simplifying assumption, patients are assumed to no longer require follow-ups after discontinuing their respective treatment. Unit costs are presented in Table 52. Scenario analyses have been conducted varying the distribution of healthcare professionals conducting therapeutic monitoring in both EM and CM, see Section B.3.11.3 for more detail.

B.3.5.2 Health state unit costs and resource use

HCRU costs are calculated for each health state by multiplying the distribution of patients across MMDs by resource use per MMD value and the associated unit costs of each type of resource use. Healthcare resource use values by MMDs are sourced from the National Health and Wellness Survey (NHWS) to estimate the disease management resource use associated with each health state: hospitalisations, accident and emergency visits, general practitioner visits, nurse practitioner visits and neurologist visits. In the previous NICE evaluation of galcanezumab (TA659), the EAG recommended the use of the NHWS dataset for the following reasons:[2]

- The NHWS includes information on how resource use relates to frequency of headache. This avoids the use of strong assumptions about the relationship between migraine frequency and healthcare utilisation
- The NHWS study is likely to be representative of resource consumption in the NHS given the study was based in Europe, and in part was conducted in the UK
- The use of NHWS data is consistent with previous relevant NICE appraisals: erenumab (TA682),[3] fremanezumab (TA764)[4] and rimegepant (TA906)[15]

HCRU values

The resource values from this study are displayed by number of MMDs in Table 51.

Table 51: HCRU data from the NHWS

Number of MMDs	Resource use per MMD				
	GP visit	A&E visit	Hospitalisation	Nurse specialist visit	Neurologist visit
0	0.202	0.030	0.023	0.063	0.003
1–3	0.288	0.067	0.042	0.102	0.015
4–7	0.413	0.058	0.040	0.175	0.013
8	0.553	0.092	0.040	0.048	0.038
9–14	0.553	0.092	0.052	0.048	0.038
15–28	0.585	0.117	0.052	0.127	0.073

Abbreviations: A&E: accident and emergency; GP: general practitioner; MMD: monthly migraine day; NHWS: National Health and Wellness Survey.

Unit costs

Unit costs associated with resource use during each model health state were sourced from National Schedule of NHS Costs and the Unit Costs of Health and Social Care, published by the PSSRU.[237, 238, 259, 260] These costs are presented in Table 52.

Table 52: Disease management unit costs

Medical resource	Unit cost	Description
GP visits	£41.00	Based on contact lasting 9.22 minutes, including direct care staff costs, carbon emissions, and qualification costs
A&E visits	£236.69	VB08Z: Emergency Medicine, Category 2 Investigation with Category 1 Treatment. (Total HRGs)
Hospitalisation	£449.52	AA31E: Headache, Migraine or Cerebrospinal Fluid Leak, with CC Score 0–6. Day case (DC)
Nurse specialist visits	£43.00	60-minute appointment with a Band 5 community-based nurse at an hourly rate of £37.00
Neurologist visit	£184.23	WF01A: follow-up attendance – single professional. Neurology (service Code 400). Outpatient procedures

Sources: National Schedule of NHS Costs 2021–2022;[237] PSSRU.[238]
Abbreviations: A&E: accident and emergency; CC: currency code; GP: general practitioner; NHS: National Health Service; PSSRU: Personal Social Services Resource Unit.

Acute medication use costs

The drug acquisition and administration costs of acute medication were sourced from the drugs and pharmaceutical electronic market information tool (eMIT), or the British National Formulary (BNF).[119] Dosing information was sourced from online NHS resources.[261-264] The unit costs and dosing schedules used in the model are presented in Table 53.

The proportion of patients receiving each acute medication detailed below was not collected in the ELEVATE or PROGRESS studies. Therefore, these data were assumed to be equal to those in ADVANCE.[137, 138, 144] Acute medications were included in the model if ≥20% of patients were receiving them in arm of the trial. These medications and the proportion of patients receiving them are detailed in Table 54. In the model, the acute medication use of patients receiving active comparators was assumed to be equal to patients receiving atogepant. Acute medication costs are applied according to the number of acute MUDs as presented in Section B.3.3.7.

Table 53: Acute medication use costs

Acute Medication	Recommended dosing		Unit costs		Maximum daily cost
	Dose	Maximum frequency	Cost per pack	Pack size	
Ibuprofen	400 mg	Three times per day	£3.25	84 tablets	£0.12
Thomapyrin N®	One sachet	Three times per day	£6.61[a]	6 sachets	£3.31
Sumatriptan	50 mg	Six times per day	£1.03	6 tablets	£1.03
Paracetamol	1,000 mg	Four times per day	£0.22	32 tablets	£0.05

Footnotes: [a]The unit cost for Thomapyrin N® was not available online so the cost for aspirin with metoclopramide was used as a proxy.

Table 54: Acute Medication Use

Acute Medication	Patients receiving acute medication (%)	
	Placebo	ATO (60 mg QD)
Ibuprofen	[redacted]	[redacted]
Thomapyrin N®	[redacted]	[redacted]
Sumatriptan	[redacted]	[redacted]
Paracetamol	[redacted]	[redacted]

Abbreviations: ATO: atogepant; QD: every day.

B.3.5.3 Adverse reaction unit costs and resource use

As detailed in Section B.3.3.8, AE costs are not considered in the base case of the economic model.

B.3.5.4 Miscellaneous unit costs and resource use

No additional costs were considered in the base case of the economic model.

B.3.6 Severity

The expected quality-adjusted life expectancy (QALE) for the general population was calculated in line with the methods provided by McNamara *et al*. (2023).[265] The total life expectancy for the

modelled population was calculated using population mortality data from the Office for National Statistics for 2018–2020.[233] The total life expectancy was quality-adjusted using UK population norm values for EQ-5D as reported by Hernández Alava *et al*. (2022) through the NICE DSU.[266]

The total QALYs for the current migraine population receiving existing treatments were calculated from the economic model. The absolute QALY shortfall and proportional QALY shortfall compared to the population receiving treatment with existing treatments were below the threshold, therefore, no severity weights were used in the present analysis. The proportion of patients who are female and the mean starting age of patients, contributing to the QALY shortfall analysis, can be found in Table 39.

Table 55: Summary of QALY shortfall analysis (EM)

Treatment	Expected total QALEs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute Shortfall (AS)	Proportional Shortfall (PS)	Severity modifier vs comparator
Galcanezumab 120 mg QM[a]	[redacted]	[redacted]	[redacted]	[redacted]	NA
Erenumab 140 mg QM		[redacted]	[redacted]	[redacted]	NA
Fremanezumab 225 mg Q3M[b]		[redacted]	[redacted]	[redacted]	NA
Fremanezumab 675 mg Q3M		[redacted]	[redacted]	[redacted]	NA

Footnotes: [a]Galcanezumab regimen is a 240 mg loading dose followed by 120 mg once a month.
[b]Fremanezumab regimen is 675 mg initial dose followed by 225 mg once a month.
Abbreviations: AS: absolute shortfall; EM: episodic migraine; NA: not applicable; PS: proportional shortfall; QALE: quality-adjusted life expectancy; QALY: quality-adjusted life year.

Table 56: Summary of QALY shortfall analysis (CM)

Treatment	Expected total QALEs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute Shortfall (AS)	Proportional Shortfall (PS)	Severity modifier vs comparator
Galcanezumab 120 mg QM[a]	[redacted]	[redacted]	[redacted]	[redacted]	NA
Erenumab 140 mg QM		[redacted]	[redacted]	[redacted]	NA
Fremanezumab 225 mg Q3M[b]		[redacted]	[redacted]	[redacted]	NA
Fremanezumab 675 mg Q3M		[redacted]	[redacted]	[redacted]	NA

Footnotes: [a]Galcanezumab regimen is a 240 mg loading dose followed by 120 mg once a month. [b]Fremanezumab regimen is 675 mg initial dose followed by 225 mg once a month.
Abbreviations: AS: absolute shortfall; CM: chronic migraine; NA: not applicable; PS: proportional shortfall; QALE: quality-adjusted life expectancy; QALY: quality-adjusted life year.

B.3.7 Uncertainty

While this submission provides high-quality evidence for the cost-effectiveness of atogepant in the prevention of migraine, there are a limited number of areas in which there may be unresolved uncertainty.

Firstly, the lack of randomised efficacy evidence directly comparing atogepant to CGRP mAbs in the preventive treatment of migraine may lead to uncertainty around the clinical efficacy inputs informing the economic model. As a consequence of the lack of direct comparative evidence, the model efficacy inputs for comparators are based on the NMAs performed, which may be impacted by any between-study heterogeneity across the included studies (Section B.2.9.4).

Limited HRQoL data for CGRP mAbs (EM and CM) relevant to this submission were available, leading to the adoption of an assumption that the associated utility values are equal to those of atogepant. Given that the results of the NMA are indicative of potentially superior HRQoL for atogepant versus selected comparators (Section B.2.9.6), this assumption would likely bias analyses in favour of said comparators.

B.3.8 Managed access proposal

Atogepant is not expected to be a candidate for managed access.

B.3.9 Summary of base-case analysis inputs and assumptions

B.3.9.1 Summary of base-case analysis inputs

A summary of inputs for the base case analysis is presented in Table 57.

Table 57: Summary of variables applied in the economic model

Variable	EM	CM	Reference to section in submission
Model Settings			
Discount rate	3.5%		Section B.3.2
Time horizon	Lifetime (60 years)		
Perspective	NHS and PSS		
Patient characteristics			
Baseline patient age, years (SD)	[redacted]	42.1	Section B.3.3.1
Proportion female, %	[redacted]	87.5%	
Pooled baseline MMDs (SD)	[redacted]	[redacted]	
Pooled baseline monthly acute MUDs (SD)	[redacted]	[redacted]	
Clinical inputs			
Response assessment timepoints	12 weeks for atogepant and SC CGRP mAbs		Section B.3.3.3

Discontinuation before response assessment	Treatment-specific discontinuation rates are applied	Section B.3.3.2 (Table 40)
Discontinuation after response assessment	3.59%	Section B.3.3.6
Acute medication use days	Derived from the NMA	in Section B.3.3.7 (Table 46)
Adverse events	No AEs are included within the model	Section B.3.3.8
Mortality	No migraine specific-mortality was modelled	Section B.3.3.9
Utility inputs		
Utility values per MMD	*Various* – response-specific utility values applied per MMD derived by mapping MSQ v2.1 data to EQ-5D via regression 1 from Gillard *et al.* (2012)[247]	Section B.3.4.5
Cost inputs		
Acquisition costs		
List price: Cost per pack (atogepant)	£463.68	Section B.3.5.1
PAS price: Cost per pack (atogepant)	£[redacted]	
List price: Cost per pack (fremanezumab)	£450.00	
List price: Cost per pack (erenumab)	£386.50	
List price: Cost per pack (galcanezumab)	£450.00	
Administration costs		
Oral	£0.00	Section B.3.5.1
SC injection	£21.50	
Health state costs per cycle, mean		
Resource use per MMD	*Various* – applied per MMD based on NHWS data	Section B.3.5.2
Disease management costs		
GP visits	£41.00	
A&E visits	£236.69	
Hospitalisation	£449.52	
Nurse specialist visits	£43.00	
Neurologist visit	£184.23	

Abbreviations: CM: chronic migraine; CI: confidence interval; EM: episodic migraine; MMD: monthly migraine day; MSQ: migraine-specific quality-of-life questionnaire; NHWS: National Health and Wellness Survey.

B.3.9.2 Assumptions

A list of the key assumptions used in the base case analysis is provided in Table 58.

Table 58: Modelling assumptions

Assumption	Justification	Addressed in scenario analysis
Response to treatment with atogepant and the relevant comparators (SC CGRP mAbs) is assessed across 12 weeks (base case analysis across EM and CM).	Week 12 was the modelled response assessment timepoint for atogepant, in line with the ELEVATE and PROGRESS trials, where response was evaluated by the primary and secondary endpoints across a 12-week treatment period. [6, 137, 138] Week 12 was the modelled response assessment timepoint for galcanezumab, erenumab and fremanezumab, in line with the respective SmPCs and the negative stopping rules implemented in the respective NICE appraisals.[2-4, 129-131]	NA
A negative stopping rule for EM is based on ≥50% reduction in MMDs and those who do not reach this, discontinue at week 12. The negative stopping rule for CM is based on a ≥30% reduction in MMDs.	This assumption is in line with previous NICE appraisals for the prophylaxis of migraine (TA659, TA682, TA764).[2-4] However, at an advisory board, clinicians noted that ≥50% reduction in MMDs was also clinically relevant for CM.	A scenario analysis was carried out in which the negative stopping rule for CM was based on a ≥50% response rate.
Treatment efficacy (i.e., probability of responding to treatment, all-cause discontinuation before the response assessment) is based on the relevant atogepant trials and the base case NMAs (Section B.2.9.6.)	The NMAs were conducted in accordance with the NICE DSU guidelines.[267]	A range of scenario analyses were performed exploring alternative sources of efficacy data, based on different NMA analysis sets or assumptions around the imputation of missing NMA data
It is assumed that responders who discontinue in the post-response assessment period will experience an immediate reversion to baseline MMD following discontinuation.	In clinical practice, treatment discontinuation would most likely follow loss of treatment response, signifying that an immediate reversion to baseline MMD would be most appropriate to model this transition. This in line with the assumption made in the NICE appraisal of rimegepant (TA906).[15]	NA
It is assumed that responders who remain on-treatment maintain reduction in MMDs.	Maintenance of MMD reduction over the long-term is supported by open label extension studies for atogepant and mAbs and has been the assumption adopted in previous NICE appraisals.	NA

The per-cycle probability of discontinuation is assumed equal at 3.59% for patients in the 'on tx response' health state.	The per-cycle probability of discontinuation after response assessment was derived from the LTS-302 long-term safety and tolerability study of atogepant in EM. Prior appraisals of erenumab (TA682), fremanezumab (TA764) and rimegepant (TA906) also used their respective safety studies to inform per cycle probability of discontinuation for all active comparators.[3, 4, 15] In further alignment with the assumptions made in these appraisals, the discontinuation rate in the model was assumed equal across treatments, due to a lack of suitable data to perform an NMA.	A scenario analysis was carried out on the basis of applying the long-term discontinuation rate used in TA682 (0.44% per cycle)
AEs are equivalent among atogepant and the relevant comparators, and therefore not accounted for in the analysis.	As no AEs of Grade ≥3 from the relevant trials for atogepant or its comparators met the inclusion criteria for the model, AE costs are not considered in the base case of the economic model. Additionally, NMA data for AEs indicate that AEs incidence is similar in patients treated with atogepant and comparators, therefore AE costs were omitted from the analysis. This is also in line with other previous NICE appraisals for the prophylaxis of migraine (TA659, TA682, TA764).[2-4]	NA
Modelled mortality is based solely on ONS UK life table mortality rates; no additional migraine-specific mortality is applied and there is no effect of treatment on mortality	This aligns with prior NICE TAs in migraine prevention, and is supported by a published meta-analysis, which found no association between migraine and all-cause mortality.[244]	NA
Utility estimates per MMD are based on MSQ v2.1 mapped to EQ-5D. The resulting utility estimates were applied across atogepant and CGRP mAbs.	Relevant HRQoL inputs for the intervention and its comparators were only available for atogepant and BSC. The NMA results for MSQ presented in Section B.2.9.6 indicate that atogepant is associated with better and in some cases statistically superior HRQoL outcomes. The assumption of equal utilities per number of MMDs is therefore likely to be conservative.	A scenario analysis was carried out to investigate the use of an alternative regression model (regression model 2) rather than the regression model used in the base case (regression model 1) to map MSQ v2.1 values to EQ-5D-3L data.
Monitoring costs for atogepant and active comparators are accounted for in the analysis.	It is expected that atogepant is associated with lower monitoring costs when compared to SC CGRP mAbs, due in part to its oral route of administration. This assumption of healthcare resource use savings associated with monitoring has been validated as reasonable by clinical experts.	A range of scenario analyses exploring different assumptions around monitoring costs associated with treatment initiation have been carried out.

All patients receiving SC treatments incur the cost of administration in the first cycle. Thereafter, SC administration costs are applied for 10% of patients, treated with relevant treatments, to account for the assumption that not all patients are able to self-administer due to factors such as physical or mental disability, old age or a phobia of needles.	Based on feedback from the NICE committee in TA659, TA764 and TA906.	NA

Abbreviations: AE: adverse event; CM: chronic migraine; CGRP: calcitonin gene-related peptide; DSU: decision support unit; EM: episodic migraine; EQ-5D: European Quality of Life 5 Dimensions; HRQoL: health-related quality of life; mAbs: monoclonal antibodies; MMDs: monthly migraine days; MSQ: Migraine Specific Quality of Life Questionnaire; NICE: National Institute of Health and Care Excellence; NMAs: network meta analysis; ONS: Office of National Statistics; SC: subcutaneous; SmPC: Summary of product characteristics; TA: technology appraisal.

B.3.10 Base-case results cost-effectiveness analysis results

Table 59 and Table 61 present the base case pairwise results of the economic evaluation for the EM and CM populations at list price, respectively, and Table 60 and Table 62 present the base case pairwise results at atogepant PAS price. In both cases the PAS price of atogepant has been used. Comparators are also available with confidential discounts, but as these are not publicly available all comparators were included at list price. As some of the comparisons resulted in south-west (SW) quadrant incremental cost-effectiveness ratios (ICERs) representing cost savings per QALY forgone, to improve the readability of the results, the incremental net-health benefit (INHB) of atogepant at a willingness-to-pay (WTP) threshold of £20,000 and £30,000 compared to the comparators has been included. INHB was selected in line with the preference expressed in the consultation on the NICE methods for health technology evaluations.[268]

At PAS price, atogepant was found to be cost-effective compared to all relevant comparators in EM, yielding INHB for atogepant versus galcanezumab (120 mg), erenumab (140 mg) and fremanezumab (225 mg or 675 mg) of [redacted], [redacted], [redacted] and [redacted], respectively at a willingness-to-pay threshold of £20,000. Similarly, atogepant was cost-effective compared galcanezumab (120 mg), erenumab (140 mg) and fremanezumab (225 mg or 675 mg) in the CM population with a INHB of [redacted], [redacted], [redacted] and [redacted], respectively.

Base case fully incremental analyses were carried out in both the EM and CM populations, as shown in Table 63 and Table 64, respectively. The base case fully incremental analysis in the EM and CM populations showed atogepant to be most cost-effective treatment option at PAS price and were consistent with the pair-wise analysis, with a fully incremental ICER of [redacted] saved per QALY forgone as compared to fremanezumab 225 mg in EM and [redacted] saved per QALY forgone as compared to erenumab 140 mg QM in CM, with all other comparators [redacted]. Fully incremental analyses should however be interpreted with caution given small incremental costs and QALYs between comparators.

The clinical outcomes and disaggregated base case cost-effectiveness results (by cost category, including health states) and QALYs (by health state) are presented in Appendix J.

Table 59: Base-case pair-wise cost-effectiveness results (EM) – atogepant list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER for atogepant vs comparator (£/QALY)	INHB (WTP threshold of £20,000	INHB (WTP threshold of £30,000
Atogepant 60 mg QD	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Galcanezumab 120 mg QM[a]	33,666	21.52	13.69	[redacted]	0.00	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg QM	28,299	21.52	13.68	[redacted]	0.00	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 225 mg Q3M[b]	31,383	21.52	13.74	[redacted]	0.00	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 675 mg Q3M	32,976	21.52	13.75	[redacted]	0.00	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a]Galcanezumab regimen is a 240 mg loading dose followed by 120 mg once a month. [b]Fremanezumab regimen is 675 mg initial dose followed by 225 mg once a month. [c]SW quadrant ICER; costs saved per QALY forgone
Abbreviations: EM: episodic migraine; ICER: incremental cost-effectiveness ratio; Incr.: incremental; INHB: incremental net health benefit; LYG: life years gained; QALYs: quality-adjusted life years; SW: South West.

Table 60: Base-case pair-wise cost-effectiveness results (EM) – atogepant PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER for atogepant vs comparator (£/QALY)	INHB (WTP threshold of £20,000	INHB (WTP threshold of £30,000
Atogepant 60 mg QD	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Galcanezumab 120 mg QM[a]	33,666	21.52	13.69	[redacted]	0.00	[redacted]	-254,998	0.38	0.26
Erenumab 140 mg QM	28,299	21.52	13.68	[redacted]	0.00	[redacted]	-£39,252	0.13	0.10
Fremanezumab 225 mg Q3M[b]	31,383	21.52	13.74	[redacted]	0.00	[redacted]	338,364[c]	0.23	0.15
Fremanezumab 675 mg Q3M	32,976	21.52	13.75	[redacted]	0.00	[redacted]	260,495[c]	0.30	0.19

Footnotes: [a]Galcanezumab regimen is a 240 mg loading dose followed by 120 mg once a month. [b]Fremanezumab regimen is 675 mg initial dose followed by 225 mg once a month. [c]SW quadrant ICER; costs saved per QALY forgone.
Abbreviations: EM: episodic migraine; ICER: incremental cost-effectiveness ratio; Incr.: incremental; INHB: incremental net health benefit; LYG: life years gained; QALYs: quality-adjusted life years; SW: South West.

Table 61: Base-case pair-wise cost-effectiveness results (CM) – atogepant list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER for atogepant vs comparator (£/QALY)	INHB (WTP threshold of £20,000	INHB (WTP threshold of £30,000
Atogepant 60 mg QD	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Galcanezumab 120 mg QM[a]	47,490	21.41	10.86	[redacted]	0.00	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg QM	39,404	21.41	10.87	[redacted]	0.00	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 225 mg Q3M[b]	40,991	21.41	10.86	[redacted]	0.00	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 675 mg Q3M	41,222	21.41	10.86	[redacted]	0.00	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a]Galcanezumab regimen is a 240 mg loading dose followed by 120 mg once a month. [b]Fremanezumab regimen is 675 mg initial dose followed by 225 mg once a month. [c]SW quadrant ICER; costs saved per QALY forgone
Abbreviations: CM: chronic migraine; ICER, incremental cost-effectiveness ratio; Incr.: incremental; INHB: incremental net health benefit; LYG: life years gained; QALYs: quality-adjusted life years; SW: South West.

Table 62: Base-case pair-wise cost-effectiveness results (CM) – atogepant PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER for atogepant vs comparator (£/QALY)	INHB (WTP threshold of £20,000	INHB (WTP threshold of £30,000
Atogepant 60 mg QD	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Galcanezumab 120 mg QM[a]	47,490	21.41	10.86	[redacted]	0.00	[redacted]	1,358,875c	0.65	0.43
Erenumab 140 mg QM	39,404	21.41	10.87	[redacted]	0.00	[redacted]	502,882c	0.25	0.16
Fremanezumab 225 mg Q3M[b]	40,991	21.41	10.86	[redacted]	0.00	[redacted]	1,125,927c	0.33	0.22
Fremanezumab 675 mg Q3M	41,222	21.41	10.86	[redacted]	0.00	[redacted]	82,226,579c	0.35	0.23

Footnotes: [a]Galcanezumab regimen is a 240 mg loading dose followed by 120 mg once a month. [b]Fremanezumab regimen is 675 mg initial dose followed by 225 mg once a month. [c]SW quadrant ICER; costs saved per QALY forgone
Abbreviations: CM: chronic migraine; ICER, incremental cost-effectiveness ratio; Incr.: incremental; INHB: incremental net health benefit; LYG: life years gained; QALYs: quality-adjusted life years; SW: South West.

Table 63: Base-case fully incremental cost-effectiveness results (EM) – atogepant PAS price

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)	Incr. ICER (£/QALY)
Atogepant 60 mg QD	[redacted]	[redacted]	-	-	-	-
Erenumab 140 mg QM	28,299	13.68	-	-	-39,252	Strictly Dominated
Galcanezumab 120 mg QM[a]	31,383	13.74	-	-	338,364	Extendedly Dominated
Fremanezumab 225 mg Q3M[b]	32,976	13.75	[redacted]	[redacted]	260,495	£260,495
Fremanezumab 675 mg Q3M	33,666	13.69	-	-	-254,998	Strictly Dominated

Footnotes: [a]Galcanezumab regimen is a 240 mg loading dose followed by 120 mg once a month. [b]Fremanezumab regimen is 675 mg initial dose followed by 225 mg once a month.
Abbreviations: EM: episodic migraine; ICER, incremental cost-effectiveness ratio; Incr.: incremental; QALYs: quality-adjusted life years.

Table 64: Base-case fully incremental cost-effectiveness results (CM) – atogepant PAS price

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)	Incr. ICER (£/QALY)
Atogepant 60 mg QD	[redacted]	[redacted]	-	-	-	-
Erenumab 140 mg QM	39,404	10.865	[redacted]	[redacted]	502,882	£502,882
Fremanezumab 225 mg Q3M[b]	40,991	10.861	-	-	1,125,927	Strictly Dominated
Fremanezumab 675 mg Q3M	41,222	10.855	-	-	82,226,579	Strictly Dominated
Galcanezumab 120 mg QM[a]	47,490	10.865	-	-	1,358,875	Strictly Dominated

Footnotes: [a]Galcanezumab regimen is a 240 mg loading dose followed by 120 mg once a month. [b]Fremanezumab regimen is 675 mg initial dose followed by 225 mg once a month.
Abbreviations: CM: chronic migraine; ICER, incremental cost-effectiveness ratio; Incr.: incremental; QALYs: quality-adjusted life years.

B.3.11 Exploring uncertainty

Parameter uncertainty in the model was assessed via both probabilistic and deterministic sensitivity analyses the results of which are presented in Sections B.3.11.1 and B.3.11.2, respectively. In addition, key assumptions in the model were explored in several probabilistic scenario analyses, the results of which are presented in Section B.3.11.3. Overall, it is considered that all relevant uncertainties included in the analyses have been adequately accounted for and the base case results were found to be robust to uncertainty in the key model inputs and assumptions.

B.3.11.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted in order to assess the simultaneous effect of uncertainty in the different model parameters and to demonstrate whether the model results are robust to those variations. A Monte-Carlo simulation with 2,000 iterations was performed where model inputs were randomly sampled from the specified probability distributions. The values of the inputs were determined by random variation with statistical distributions described in Appendix N. Note that efficacy inputs derived from the NMA analyses presented in Section B.2.9 were excluded from the PSA due to wide credible intervals for selected analyses introducing substantial bias to the analyses.

EM

A summary of the probabilistic results for EM is presented in Table 65. These results are similar to the base case, with atogepant remaining cost-effective versus all comparators, indicating the results to be robust to uncertainty.

An ICER convergence plot is provided in Figure 26, and probabilistic cost-effectiveness planes for atogepant versus relevant comparators are presented in Figure 27–Figure 30. As shown in the cost-effectiveness curve presented in Figure 31 and in Table 65, the PSA found the probability of atogepant being the most cost-effective treatment option to be [redacted] at a WTP threshold of £30,000 per QALY.

Table 65: Probabilistic results in EM (atogepant with-PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER for atogepant vs comparator (£/QALY)	INHB (WTP threshold of £20,000	INHB (WTP threshold of £30,000	Probability of cost-effectiveness[a]
Atogepant 60 mg QD	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-	[redacted]
Galcanezumab 120 mg QM[b]	33,724	21.52	13.69	[redacted]	0.00	[redacted]	-258,024	0.39	0.27	[redacted]
Erenumab 140 mg QM	28,316	21.52	13.68	[redacted]	0.00	[redacted]	-39,610	0.13	0.10	[redacted]
Fremanezumab 225 mg Q3M[c]	31,462	21.52	13.73	[redacted]	0.00	[redacted]	383,672	0.23	0.15	[redacted]
Fremanezumab 675 mg Q3M	33,040	21.52	13.74	[redacted]	0.00	[redacted]	260,847	0.30	0.19	[redacted]

Footnotes: [a]The probability of the treatment being cost-effective technology at a cost-effectiveness threshold of £30,000/QALY. [b]Galcanezumab regimen is a 240 mg loading dose followed by 120 mg once a month. [c]Fremanezumab regimen is 675 mg initial dose followed by 225 mg once a month. [d]SW quadrant ICER; costs saved per QALY forgone

Abbreviations: EM: episodic migraine; ICER: incremental cost-effectiveness ratio; Incr.: incremental; INHB: incremental net health benefit; LYG: life years gained; QALYs: quality-adjusted life years; SW: South West.

Figure 26: ICER convergence plot (versus galcanezumab; EM)

Abbreviations: ICER: incremental cost-effectiveness ratio.

Figure 27: Probabilistic cost-effectiveness plane for atogepant versus galcanezumab (120 mg) (EM)

Abbreviations: ICER: incremental cost-effectiveness ratio.

Figure 28: Probabilistic cost-effectiveness plane for atogepant versus erenumab (140 mg) (EM)

Abbreviations: ICER: incremental cost-effectiveness ratio.

Figure 29: Probabilistic cost-effectiveness plane for atogepant versus fremanezumab (225 mg) (EM)

Abbreviations: ICER: incremental cost-effectiveness ratio.

Figure 30: Probabilistic cost-effectiveness plane for atogepant versus fremanezumab (675 mg) (EM)

Abbreviations: ICER: incremental cost-effectiveness ratio.

Figure 31: Probabilistic cost-effectiveness acceptability curve for atogepant versus relevant comparators (EM)

Abbreviations: ICER: incremental cost-effectiveness ratio.

CM

A summary of the probabilistic results for CM is presented in Table 66. These results are similar to the base case, with atogepant remaining cost-effective versus all comparators, indicating the results to be robust to uncertainty.

An ICER convergence plot is provided in Figure 32, and probabilistic cost-effectiveness planes for atogepant versus relevant comparators are presented in Figure 33–Figure 36. As shown in

the cost-effectiveness curve presented in Figure 37 and in Table 66, the PSA found the probability of atogepant being the most cost-effective treatment option to be [redacted] at a WTP threshold of £30,000 per QALY.

Table 66: Probabilistic results CM (atogepant with-PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER for atogepant vs comparator (£/QALY)	INHB (WTP threshold of £20,000	INHB (WTP threshold of £30,000	Probability of cost-effectiveness[a]
Atogepant 60 mg QD	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-	[redacted]
Galcanezumab 120 mg QM[b]	47,512	21.412	10.877	[redacted]	0.000	[redacted]	1,384,923	0.658	0.436	[redacted]
Erenumab 140 mg QM	39,349	21.412	10.877	[redacted]	0.000	[redacted]	510,194	0.249	0.163	[redacted]
Fremanezumab 225 mg Q3M[c]	40,961	21.412	10.874	[redacted]	0.000	[redacted]	1,029,840	0.334	0.220	[redacted]
Fremanezumab 675 mg Q3M	41,170	21.412	10.867	[redacted]	0.000	[redacted]	-17,793,429	0.351	0.234	[redacted]

Footnotes: [a]The probability of the treatment being cost-effective technology at a cost-effectiveness threshold of £30,000/QALY. [b]Galcanezumab regimen is a 240 mg loading dose followed by 120 mg once a month. [c]Fremanezumab regimen is 675 mg initial dose followed by 225 mg once a month.
Abbreviations: EM: episodic migraine; ICER: incremental cost-effectiveness ratio; Incr.: incremental; INHB: incremental net health benefit; LYG: life years gained; QALYs: quality-adjusted life years; SW: South West.

Figure 32: ICER convergence plot (versus galcanezumab; CM)

Abbreviations: ICER: incremental cost-effectiveness ratio.

Figure 33: Probabilistic cost-effectiveness plane for atogepant versus galcanezumab (120 mg) (CM)

Abbreviations: ICER: incremental cost-effectiveness ratio.

Figure 34: Probabilistic cost-effectiveness plane for atogepant versus erenumab (140 mg) (CM)

Abbreviations: ICER: incremental cost-effectiveness ratio.

Figure 35: Probabilistic cost-effectiveness plane for atogepant versus fremanezumab (225 mg) (CM)

Abbreviations: ICER: incremental cost-effectiveness ratio.

Figure 36: Probabilistic cost-effectiveness plane for atogepant versus fremanezumab (675 mg) (CM)

Abbreviations: ICER: incremental cost-effectiveness ratio.

Figure 37: Probabilistic cost-effectiveness acceptability curve for atogepant versus relevant comparators (CM)

Abbreviations: ICER: incremental cost-effectiveness ratio.

B.3.11.2 Deterministic sensitivity analysis

In order to assess the robustness of the base case cost-effectiveness results, deterministic sensitivity analyses (DSA) were conducted. The tornado diagrams for atogepant versus relevant comparators are presented in Figures Figure 38–Figure 41 for EM and Figures Figure 42–Figure 45 for CM. The top 25 most influential parameters on the base case are presented in each case.

In both EM and CM, the results of these analyses showed comparator unit drug cost, comparator efficacy and comparator discontinuation rate were commonly influential parameters, with the model being largely robust to uncertainty in the majority of parameters.

EM

Figure 38: DSA tornado diagram for atogepant versus galcanezumab (120 mg) (EM)

Abbreviations: DSA: deterministic sensitivity analysis; EM: episodic migraine.

Figure 39: DSA tornado diagram for atogepant versus erenumab (140 mg) (EM)

Abbreviations: DSA: deterministic sensitivity analysis; EM: episodic migraine.

Figure 40: DSA tornado diagram for atogepant versus fremanezumab (225 mg) (EM)

Abbreviations: DSA: deterministic sensitivity analysis; EM: episodic migraine.

Figure 41: DSA tornado diagram for atogepant versus fremanezumab (675 mg) (EM)

Abbreviations: DSA: deterministic sensitivity analysis; EM: episodic migraine.

CM

Figure 42: DSA tornado diagram for atogepant versus galcanezumab (120 mg) (CM)

Abbreviations: CM: chronic migraine; DSA: deterministic sensitivity analysis.

Figure 43: DSA tornado diagram for atogepant versus erenumab (140 mg) (CM)

Abbreviations: CM: chronic migraine; DSA: deterministic sensitivity analysis.

Figure 44: DSA tornado diagram for atogepant versus fremanezumab (225 mg) (CM)

Abbreviations: CM: chronic migraine; DSA: deterministic sensitivity analysis.

Figure 45: DSA tornado diagram for atogepant versus fremanezumab (675 mg) (CM)

Abbreviations: CM: chronic migraine; DSA: deterministic sensitivity analysis.

B.3.11.3 Scenario analysis

Several scenario analyses were conducted to assess the impact of the uncertainty associated with key inputs and assumptions in the economic model, as detailed in

Table 67. A summary of the scenario analysis results for atogepant versus relevant comparators for the EM, CM and EM+CM populations are presented in Table 68, Table 69 and Table 70, respectively. Key scenario analyses were run probabilistically with others run deterministically, as noted in Table 68.

The majority of scenarios have limited impact on cost-effectiveness results, and atogepant remained consistently cost-effective (i.e. INHB remained positive) versus all relevant comparators (SC CGRP mAbs) across all scenarios tested.

Table 67: Scenario analyses explored in the economic analysis

#	Scenario analysis (probabilistic or deterministic)	Rationale
EM		
1	Missing NMA data equal to average mAb (probabilistic)	In the base case, missing NMA data for treatment response and CFB in MUDs in SC CGRP mAbs are imputed using a conversion factor to convert data describing the proportion of patients that achieve ≥30% reduction in MMDs to a ≥50% threshold, or vice versa, or to convert CFB data available for the full mITT population to the 3+ TF mITT population. This approach is also used for CFB in MUDs data for erenumab in the 3+ mITT population. A scenario analysis has explored an alternative assumption where these missing values are assumed equal to the mean of available SC CGRP mAb data.
2	Consider natural history of migraine (probabilistic)	In the base case, the natural history of migraine is not considered. However, clinical experts have previously indicated that the MMDs that experienced by people with migraine would decline over the course of their lives.[269] Therefore, the natural history of migraine is considered as a scenario analysis, by modelling a reduction in MMDs a patient with migraine experiences over the time horizon. Additionally, in previous appraisals, EAGs have indicated a preference for the natural history of migraine to be captured.[2-4]
3a	Discontinuation before response assessment assumed to be a one-off probability at the response assessment timepoint (deterministic)	In the base case, treatment discontinuation is modelled as a function of all-cause discontinuation rates applied to respective treatments before the response assessment, on a per-cycle basis. A simplified scenario was explored in which all-cause treatment discontinuation was considered as a one-off probability at the response assessment timepoint.
3b	Discontinuation after response assessment informed by alternative value (deterministic)	In the base case, long-term discontinuation after response assessment (3.59% per cycle) is informed by the LTS-302 long-term safety and tolerability study of atogepant, as the most relevant source of evidence. A scenario analysis explored the impact of this parameter by assuming a different discontinuation rate of 0.44% per cycle, informed by the NICE appraisal of erenumab in preventing migraine (TA682).[3]
4	Use of regression model 2 for utilities (deterministic)	In the base case, regression model 1 is used to conduct the mapping of MSQ v2.1 values from relevant clinical trials to EQ-5D-3L data. Regression model 1 considers only the three MSQ dimensions (role preventive, role restrictive, and emotional function). Regression model 2 considers these dimensions and additional covariates for age, sex, race, employment, headache medication use, and comorbidities. In line with previous evaluations, regression model 1 is employed in the base case. However, given that regression model 2 may provide a more comprehensive mapping of MSQ v2.1 values as it takes into consideration patient characteristics and additional covariates, this has been explored as a scenario analysis.

5	Exclusion of disutility associated with SC or IM administration routes (deterministic)	In the base case, separate utility decrements associated with SC or IM routes of treatment administration have been informed by research published by Matza et al. (2019).[135] The exclusion of these disutilities has been explored as a scenario analysis.
6a	Monitoring costs 1 (probabilistic)	In the base case, all SC CGRP mABs are initiated by a headache specialist, whereas 50% of patients treated with atogepant are initiated by a headache specialist and 50% by a general neurologist. Given the routes of administration of atogepant (oral) and its active comparators (SC), clinical follow-ups are expected to be conducted by a general practitioner and a headache specialist, respectively. In practice, the exact distribution of patients being treated by distinct healthcare professionals may be dependent on several factors, such as clinical guidelines, patient preference, and geography. In this scenario analysis, atogepant initiation is conducted by a headache specialist for 100% of patients, while SC CGRP mAbs continue to also be initiated by a headache specialist (100%). Atogepant follow-up is then conducted by a general practitioner (100%), while SC CGRP mAb follow-up is conducted by a specialist (100%).
6b	Monitoring costs 2 (deterministic)	In this scenario analysis, atogepant initiation is conducted by a general practitioner (100%), while SC CGRP mAbs are initiated by a headache specialist (100%). Atogepant follow-up is then conducted by a general practitioner (100%), while SC CGRP mAb follow-up is conducted by a specialist (100%).
7a	EM overall population (deterministic)	In the base case, evidence for atogepant is presented in the 3+ TF mITT patient population, which is the target population of this submission. As a subgroup of the wider license population, the use of overall mITT population trial and NMA data was explored as a scenario analysis (**7a**), given its larger sample size and the broadly consistent results observed between the overall mITT and 3+ TF subgroup. In another scenario analysis (**7b**), baseline-risk adjusted NMA data are explored for the overall mITT population, to control for any potential between-study heterogeneity resulting from differences in placebo effects across trials.
7b	EM overall population (baseline risk-adjusted) (probabilistic)	
CM		
8	Missing NMA data equal to average mAb (deterministic)	Justification for scenario analysis as above for EM
9	Consider natural history of migraine (deterministic)	Justification for scenario analysis as above for EM
10a	Discontinuation before response assessment assumed to be a one-off probability at the response assessment timepoint (deterministic)	Justification for scenario analysis as above for EM

10b	Discontinuation after response assessment informed by alternative value (deterministic)	Justification for scenario analysis as above for EM
11	Use of regression model 2 for utilities (deterministic)	Justification for scenario analysis as above for EM
12	Exclusion of disutility associated with SC or IM administration routes (deterministic)	Justification for scenario analysis as above for EM
13	≥50% response definition (deterministic)	In CM, the base case analysis employs a threshold of ≥30% reduction in MMDs as a definition of treatment response in line with previous NICE appraisals for the prophylaxis of migraine (TA659, TA682, TA764).[2-4] However, at an advisory board, clinicians noted that ≥50% reduction in MMDs was also clinically relevant for CM. As such, a scenario analysis was carried out in which the negative stopping rule for CM was based on a ≥50% response rate.
14a	Monitoring costs 1 (deterministic)	Justification for scenario analysis as above for EM
14b	Monitoring costs 2 (deterministic)	Justification for scenario analysis as above for EM
15	CM overall population (baseline risk-adjusted) (probabilistic)	In the base case, NMA results are based on unadjusted RE models, given the heterogeneity between the trials included in the NMA and in line with clinical and health economic expert opinion at an advisory board. Baseline risk-adjusted models were not considered given regression coefficients were not significant and model fit statistics for these models did not show meaningful improvements over unadjusted models. However, given potential between-study heterogeneity resulting from differences in placebo effects across trials, baseline risk-adjusted models may be theoretically appropriate and thus were explored in a scenario analysis.
EM and CM		
16	Weighted average results across EM and CM	In the base case, results are presented separately for EM and CM. Given that migraine is a disease continuum, a scenario analysis has been conducted to produce a cost-effectiveness estimate across the entire disease spectrum by weighting the average results for EM and CM. In this analysis, an average of the base case incremental costs and QALYs for EM and CM were weighted by the expected spread of atogepant-eligible patients in each of these indications, based on the split of patients eligible to be treated with atogepant or relevant comparators: CM (29.1%) and EM (70.9%) (see Budget Impact Analysis document, Section 7).

Abbreviations: CGRP: calcitonin gene-related peptide; CM: chronic migraine; EM: episodic migraine; mAb: monoclonal antibodies; NMA: network meta-analysis; MMD: monthly migraine day; MSQ: migraine-specific quality-of-life questionnaire; MUDs: medication use days; QALY: quality-adjusted life year; SC: subcutaneous.

Table 68: Scenario analyses (EM) – atogepant PAS price

#	Description	Galcanezumab (120 mg)			Erenumab (140 mg)			Fremanezumab (225 mg)			Fremanezumab (675 mg)		
		Inc. costs (£)	Inc. QALYs	NHB (QALYs)[b]	Inc. costs (£)	Inc. QALYs	NHB (QALYs)[b]	Inc. costs (£)	Inc. QALYs	NHB (QALYs)[b]	Inc. costs (£)	Inc. QALYs	NHB (QALYs)[b]
Base Case		[redacted]	[redacted]	0.264	[redacted]	[redacted]	0.102	[redacted]	[redacted]	0.146	[redacted]	[redacted]	0.189
1	Missing NMA data equal to average mAb[a]	[redacted]	[redacted]	0.265	[redacted]	[redacted]	0.101	[redacted]	[redacted]	0.151	[redacted]	[redacted]	0.190
2	Consider natural history of migraine[a]	[redacted]	[redacted]	0.265	[redacted]	[redacted]	0.101	[redacted]	[redacted]	0.152	[redacted]	[redacted]	0.191
3a	Discontinuation before response assessment assumed to be a one-off probability at the response assessment timepoint	[redacted]	[redacted]	0.268	[redacted]	[redacted]	0.102	[redacted]	[redacted]	0.148	[redacted]	[redacted]	0.191
3b	Discontinuation after response assessment informed by alternative value	[redacted]	[redacted]	0.980	[redacted]	[redacted]	0.372	[redacted]	[redacted]	0.588	[redacted]	[redacted]	0.750
4	Use of regression model 2 for utilities	[redacted]	[redacted]	0.258	[redacted]	[redacted]	0.090	[redacted]	[redacted]	0.156	[redacted]	[redacted]	0.203
5	Exclusion of disutility associated with SC or IM administration routes	[redacted]	[redacted]	0.255	[redacted]	[redacted]	0.094	[redacted]	[redacted]	0.133	[redacted]	[redacted]	0.173
6a	Monitoring costs 1[a]	[redacted]	[redacted]	0.259	[redacted]	[redacted]	0.096	[redacted]	[redacted]	0.143	[redacted]	[redacted]	0.183
6b	Monitoring costs 2	[redacted]	[redacted]	0.271	[redacted]	[redacted]	0.109	[redacted]	[redacted]	0.153	[redacted]	[redacted]	0.196
7a	EM overall population	[redacted]	[redacted]	0.319	[redacted]	[redacted]	0.116	[redacted]	[redacted]	0.136	[redacted]	[redacted]	0.157
7b	EM overall population (baseline risk-adjusted)[a]	[redacted]	[redacted]	0.331	[redacted]	[redacted]	0.117	[redacted]	[redacted]	0.131	[redacted]	[redacted]	0.147

Footnotes: [a]Probabilistic results provided. [b]NHB calculated at a WTP threshold of £30,000.
Abbreviations: CGRP: calcitonin gene-related peptide; EM: episodic migraine; mAbs: monoclonal antibodies; NMA: network meta-analysis; PAS: patient access scheme; SC: subcutaneous; TA: technology appraisal; tx: treatment.

Table 69: Scenario analyses (CM) – atogepant PAS price

#	Description	Galcanezumab (120 mg)			Erenumab (140 mg)			Fremanezumab (225 mg)			Fremanezumab (675 mg)		
		Inc. costs	Inc. QALYs	NHB (QALYs) [b]	Inc. costs	Inc. QALYs	NHB (QALYs) [b]	Inc. costs	Inc. QALYs	NHB (QALYs) [b]	Inc. costs	Inc. QALYs	NHB (QALYs) [b]
Base Case		[redacted]	[redacted]	0.432	[redacted]	[redacted]	0.162	[redacted]	[redacted]	0.219	[redacted]	[redacted]	0.233
8	Missing NMA data equal to average mAb	[redacted]	[redacted]	0.432	[redacted]	[redacted]	0.182	[redacted]	[redacted]	0.219	[redacted]	[redacted]	0.233
9	Consider natural history of migraine	[redacted]	[redacted]	0.433	[redacted]	[redacted]	0.164	[redacted]	[redacted]	0.222	[redacted]	[redacted]	0.235
10a	Discontinuation before response assessment assumed to be a one-off probability at the response assessment timepoint	[redacted]	[redacted]	0.434	[redacted]	[redacted]	0.162	[redacted]	[redacted]	0.221	[redacted]	[redacted]	0.234
10b	Discontinuation after response assessment informed by alternative value	[redacted]	[redacted]	1.851	[redacted]	[redacted]	0.701	[redacted]	[redacted]	0.961	[redacted]	[redacted]	0.967
11	Use of regression model 2 for utilities	[redacted]	[redacted]	0.439	[redacted]	[redacted]	0.170	[redacted]	[redacted]	0.227	[redacted]	[redacted]	0.239
12	Exclusion of disutility associated with	[redacted]	[redacted]	0.416	[redacted]	[redacted]	0.146	[redacted]	[redacted]	0.201	[redacted]	[redacted]	0.215

	SC or IM administration routes												
13	≥50% response definition	[redacted]	[redacted]	0.340	[redacted]	[redacted]	0.110	[redacted]	[redacted]	0.147	[redacted]	[redacted]	0.170
14a	Monitoring costs 1	[redacted]	[redacted]	0.425	[redacted]	[redacted]	0.155	[redacted]	[redacted]	0.212	[redacted]	[redacted]	0.226
14b	Monitoring costs 2	[redacted]	[redacted]	0.439	[redacted]	[redacted]	0.169	[redacted]	[redacted]	0.226	[redacted]	[redacted]	0.240
15	CM overall population (baseline risk-adjusted)[a]	[redacted]	[redacted]	0.289	[redacted]	[redacted]	0.108	[redacted]	[redacted]	0.125	[redacted]	[redacted]	0.141

Footnotes: [a]Probabilistic results provided. [b]NHB calculated at a WTP threshold of £30,000.
Abbreviations: CGRP: calcitonin gene-related peptide; EM: episodic migraine; mAbs: monoclonal antibodies; NMA: network meta-analysis; PAS: patient access scheme; SC: subcutaneous; TA: technology appraisal; tx: treatment.

Table 70: Scenario analyses (EM and CM) – atogepant PAS price

#	Description	Galcanezumab (120 mg)			Erenumab (140 mg)			Fremanezumab (225 mg)			Fremanezumab (675 mg)		
		Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs) [a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs) [a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs) [a]
Base Case (EM)		[redacted]	[redacted]	0.264	[redacted]	[redacted]	0.102	[redacted]	[redacted]	0.146	[redacted]	[redacted]	0.189
Base Case (CM)		[redacted]	[redacted]	0.432	[redacted]	[redacted]	0.162	[redacted]	[redacted]	0.219	[redacted]	[redacted]	0.233
16	Weighted average results across EM (71%) and CM (29%)	[redacted]	[redacted]	0.313	[redacted]	[redacted]	0.119	[redacted]	[redacted]	0.168	[redacted]	[redacted]	0.202

Footnotes: [a] NHB calculated at a WTP threshold of £30,000.
Abbreviations: CM: chronic migraine; EM: episodic migraine; PAS: patient access scheme.

B.3.12 Subgroup analysis

No further subgroup analyses were performed beyond the subpopulations informing the base case analysis: EM and CM patients in whom ≥3 prior preventive treatments have failed.

B.3.13 Benefits not captured in the QALY calculation

Atogepant is a simple, once daily, oral treatment which is fast-acting and effective at reducing the frequency and severity of migraine, providing relief from the severe debilitating impact of migraines. Atogepant efficacy is supported by significant responder rates and clinically meaningful improvements in PRO outcomes across Phase 3 trials, including significant benefits in terms of migraine disability and HRQoL (Section B.2.6.3). Furthermore, improvements versus placebo have been demonstrated in CFB in mean MMDs, monthly acute MUDs, ≥30%/≥50%/≥75% reduction in mean MMDs, HIT-6, MSQ v2.1 and MIDAS in the 3+ TF mITT target patient population (Section B.2.6). Atogepant is well-tolerated with comparable rates of TEAEs leading to treatment discontinuation to placebo, and the short half-life with rapid rate of clearance makes atogepant a particularly useful treatment option for women of childbearing age who may choose to discontinue treatment in order to plan a pregnancy (Section B.2.10).

Due to limited available HRQoL data for CGRP mAbs (EM and CM), the economic model assumes that utility values per MMD are identical between atogepant and SC CGRP mAbs. Given that the results of the NMA are indicative of better and in some cases significantly superior HRQoL for atogepant versus selected comparators (section B.2.9.6), this assumption means that the ICERs associated with base case analyses likely do not capture a potential HRQoL benefit associated with atogepant.

Coupled with similar health benefits and a tolerable safety profile, atogepant employs a more convenient, clinic-sparing route of administration than CGRP mAbs, which are administered via injections that can be viewed as intrusive and inconvenient by patients (Section B.1.3.2), and are not a reasonable option in patients with needle-phobia.[38] As an oral therapy, atogepant is anticipated to alleviate capacity issues associated with the need for in-clinic injections, injectable training, and administrative burden related to the delivery of SC CGRP mAbs via homecare providers (predominantly in the headache specialist setting). The simplicity of administration is therefore expected to introduce efficiencies into the NHS, to give greater prescribing flexibility and alleviate the burden on headache expert specialists. Unlike SC CGRP mAbs, clinical experts have advised that atogepant would not be considered a specialist drug due to the well tolerated, effective nature of the product and simple oral route of administration, reducing the need for patient monitoring. Clinical experts have also indicated that atogepant will not be subject to the same logistical challenges which general neurologists currently face when prescribing CGRP mAbs, as they do not typically have the capacity nor support from specialist nurses to complete the relevant paperwork and train patients in the use of injectable treatments. Clinical expert opinion has been consistent in indicating that unlike CGRP mAbs, atogepant is likely to have high uptake among general neurologists. As such, atogepant is likely to be used more readily by nurses or general neurologists in the secondary care setting and has potential for use by GPs in primary care. Furthermore, it is anticipated that adverse events caused by atogepant could be managed from a pharmacy setting, with the most commonly reported adverse events being nausea, constipation, and fatigue (Section B.2.10). These factors are thought to be particularly relevant given the NHS is still recovering from the after-effects of the SARS-CoV-2 pandemic.

In its Strategy 2021-2026,[270] NICE has made a commitment to take into consideration the environmental impact, alongside the health economic impact, when undertaking its assessments and developing recommendations. In this context, the expected environmental impact of cold storage requirements for the CGRP mAbs and the delivery via homecare providers is an important consideration when comparing the difference in carbon footprint between atogepant and the CGRP mAbs.[120-122]

As migraine attacks are associated with severe headache pain, as well as a range of non-headache disabling and incapacitating symptoms, it is particularly critical for patients with migraine who have experienced three or more treatment failures to have access to novel treatments that empower them to live a normal life. For these reasons, the results of the cost-effectiveness analysis demonstrate that atogepant would provide a valuable and important new treatment option, that is cost-effective for the NHS.

B.3.14 Validation

B.3.14.1 Validation of cost-effectiveness analysis

Overall approach

The model methodology was designed to align with NICE-preferred methods and previous cost-effectiveness analyses presented within previous NICE appraisals for the prevention of migraine, as well as clinical and health economic expert opinion collected during an advisory board and subsequent interviews.

The model was built to align with the NICE reference case, and used an NHS and PSS perspective and discount rates for cost and benefits of 3.5%.[234, 235] The model used a lifetime time horizon in order to capture all costs and QALY gains associated with the interventions.

As introduced in Table 36 and Table 37, the economic model supporting this submission is comparable with those presented in previous NICE appraisals for the prevention of migraine. A semi-Markov model structure was used in which a lifetime time horizon was employed. The modelling of treatment response was based on an initial 12-week treatment period, while a defined utilities were derived in accordance with the number of MMDs experienced by a patient.[2-4]

Validation of economic modelling approach against clinical and health economic expert opinion

Expert clinical input was sought during the development of the cost-effectiveness model to validate the inputs and assumptions used in the analysis were relevant to UK clinical practice and to validate the clinical plausibility of the outcomes predicted by the model. Feedback from UK clinical and health economic experts was obtained at an advisory board and during subsequent interviews with UK clinical experts. As detailed throughout the submission, the approaches and key assumptions used in the economic analyses were validated accordingly. In particular, AbbVie have formally consulted seven migraine specialists in support of this submission.

In an advisory board organised by AbbVie, five migraine specialist clinical experts and two health economic experts were engaged to validate:

- Clinical positioning and proposed use of atogepant in UK clinical practice
- Relevant comparators to atogepant
- The robustness and suitability of NMA results
- The economic model, its inputs and key assumptions, structure, included comparators, and suitability for submission to NICE

Following the advisory board, additional clinical and health economic expert opinion was gathered to further validate key model assumptions and inputs via teleconference calls with two additional migraine specialist clinical experts.

Technical validation and verification

Technical validation was undertaken by a third party, with detailed quality-control procedures followed to ensure that calculations, programming logic and physical implementation of the conceptual model were completed correctly. An independent modelling team undertook a cell-by-cell verification process facilitating a check of all input calculations, formulae and Visual Basic code. Any discrepancies were identified, discussed and corrected as required.

B.3.15 Interpretation and conclusions of economic evidence

Summary of cost-effectiveness evidence

In order to assess the cost-effectiveness of atogepant versus relevant comparators for the prevention of migraine for adult patients in the UK, a de novo cost-effectiveness analysis was conducted from the perspective of the NHS and PSS in England, which followed a similar approach to economic models which informed decision-making in prior NICE migraine appraisals. In line with the licensed indication and anticipated use of atogepant in NHS clinical practice, the model considered the use of atogepant for prophylaxis of migraine in adults who have at least 4 migraine days per month and in whom at least 3 preventive treatments have not worked.

In the base case analysis atogepant (with-PAS price) was found to be cost-effective compared to all relevant comparators across the migraine continuum of EM and CM. In the EM population, the INHB (at a WTP threshold of £20,000) for atogepant versus galcanezumab (120 mg), erenumab (140 mg) and fremanezumab (225 mg or 675 mg) was [redacted], [redacted], [redacted] and [redacted], respectively. In the base case analysis in the CM population the INHB (at a WTP threshold of £20,000) for atogepant versus galcanezumab (120 mg), erenumab (140 mg) and fremanezumab (225 mg or 675 mg) was [redacted], [redacted], [redacted] and [redacted], respectively. The PSA analyses demonstrated that the probability that atogepant is the most cost-effective treatment option is estimated to be [redacted] in both the EM and CM populations at a willingness-to-pay threshold of £30,000 per QALY.

The DSA results identified the comparator unit drug cost, comparator efficacy and comparator discontinuation rate as commonly influential parameters across CM and EM, with the model being largely robust to uncertainty in the majority of parameters. Scenario analyses conducted to address sources of uncertainty in the model showed that the cost-effectiveness conclusions unchanged, with atogepant remaining cost-effective at a willingness-to-pay threshold of £30,000 per QALY across all tested scenarios.

Overall, the base case ICERs for all comparisons demonstrated atogepant to be cost-effective at a willingness-to-pay threshold £30,000 per QALY and thus atogepant can be considered a cost-effective use of NHS resources in both the EM and CM populations.

Strengths and limitations

The key evidence base for this submission is the ELEVATE and PROGRESS trials, which are randomised, double-blind and placebo-controlled and which demonstrate that atogepant is effective in the prevention of EM and CM. Atogepant treatment was associated with reductions in migraine frequency (monthly MMDs, MHDs), acute medication use (acute MUDs), as well as duration (cumulative headache hours) and severity (moderate/severe migraines) of migraine episodes. The lack of statistical powering and stratification of randomised patients by classes of failed prior preventive treatments in this subgroup introduces a potential source of uncertainty, but the use of the PROGRESS overall mITT data, which are a robust and appropriate evidence source to inform the efficacy of atogepant in a CM population, negates the high uncertainty associated with the 3+ TF mITT subgroup and aligns with recent decision-making for another oral CGRP inhibitor, rimegepant.

Furthermore, the lack of head-to-head RCT evidence comparing the efficacy and safety of atogepant and relevant comparators necessitated the conduct of an NMA to obtain comparative evidence. While the feasibility assessment identified heterogeneity between the trials that may increase the uncertainty within the results, the NMA was performed with a robust methodology and made use of trials identified through a comprehensive SLR and evidence sourced from RCTs. Despite this, as outlined in Section B.3.11.1, the wide credible intervals associated with the resulting NMA results for selected analyses necessitated exclusion of these data from sampling in the probabilistic analysis.

Finally, the economic model presented was built to align with the NICE reference case, adopting an NHS and PSS perspective, a time horizon sufficient to capture fully all costs and QALY gains associated with the interventions, and discount rates for costs and benefits of 3.5%. As mentioned in Section B.3.14, the model underwent extensive validation with clinical expert opinion sought to validate the model structure, inputs and assumptions. The economic model is designed to consider all relevant health states for migraine and is detailed to maximise the opportunity to accurately model a patient's MMD distribution over time. A range of sensitivity analyses were conducted that demonstrate that the cost-effectiveness results were robust to an extensive number of scenario analyses.

Conclusions

The clinical results presented demonstrate that atogepant has similar health benefits to technologies recommended in published NICE technology appraisal guidance for the same indication (galcanezumab, erenumab and fremanezumab for the preventive treatment of migraine in adults who have ≥4 migraine days a month and in whom ≥3 prior preventive treatments have failed. The cost-effectiveness analysis further demonstrates that atogepant (PAS discounted) is a cost-effective option when compared to all comparators at list price (comparator PAS discounts are confidential). A series of sensitivity and scenario analyses demonstrates the robustness of the base case analysis, confirming atogepant as a cost-effective option. However, the company acknowledges that results will be dependent on the application of comparator confidential discounts which are not publicly available.

Atogepant is a migraine-specific, fast-acting CGRP inhibitor with proven efficacy, safety, and tolerability in prophylactic migraine treatment.[136-138] Atogepant offers a cost-effective alternative to SC CGRP mAbs, addressing the unmet need for an oral treatment option for patients with ≥3 prior preventive treatment failures, with reduced or minimal budget impact.

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Appendices

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Atogepant for preventing migraine

[ID5090]

Summary of Information for Patients (SIP)

September 2023

File name	Version	Contains confidential information	Date
Atogepant in Migraine_SIP_NoCON	Final	No	29th September 2023

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The Summary of Information for Patients template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article.

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: Atogepant; **brand name**: Aquipta®

1b) Population this treatment will be used by:

Please outline the main patient population that is being appraised by NICE:

The population that this treatment will be used for is adults who have at least four migraine days per month and for whom at least three **preventive*** drug treatments have failed.

*Please note that further explanations for the words and phrases highlighted in **bold** are provided in the glossary (**Section 4b**). Cross-references to other sections are highlighted in **green**.

1c) Authorisation:

Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Marketing authorisation is a licence required to place a medicinal product on the market, that sets out the conditions for use of a drug based on evidence of its safety and clinical effectiveness. Atogepant has received a **marketing authorisation** from the **Medicines**

and Healthcare Product Regulatory Agency (30th August 2023). It is licensed as a preventive treatment for adults who have at least four migraine days per month.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

AbbVie collaborates with a range of stakeholders with an interest in migraine and/or headache. This includes collaboration with patient groups to support improvements in health and care for individuals with migraine.

Where this includes any Transfer of Value, for example to support the development of information for patients and their families, this is declared on an annual basis and is available at: https://www.abbvie.co.uk/our-company/policies-disclosures.html

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Atogepant is intended to treat migraine

What is migraine?

Migraine is a severe and painful long-term health condition. If you have migraine you will have **migraine attacks**, which can be a whole-body experience.[1]

What are the signs and symptoms of migraine?

The main symptom of migraine is a moderate or severe headache felt as a throbbing pain on one side of the head.[2] Other common symptoms of a migraine attack can include:[1, 2]

- Problems with your sight such as seeing flashing lights
- Being very sensitive to light, sounds and smells
- Tiredness
- Feeling sick and being sick

These symptoms can last from four hours to three days.[3] People can also experience symptoms before a migraine attack, such as tiredness and **aura**. Aura includes symptoms such as:[2, 4]

- Visual problems
- Numbness or tingling sensations
- Feeling dizzy
- Difficulty speaking
- Loss of consciousness

Furthermore, people with migraines can experience symptoms after the attacks, such as difficulty concentrating and tiredness.[2, 4]

What causes migraine?

The cause of migraines is uncertain. However, more than half of people with migraine also have a close relative with the condition, suggesting it can be inherited.[1, 2, 5] Migraines are also linked to factors such as changes in hormones, other diseases, tiredness, diet, and stress.[1, 5]

How many people get migraine?

Migraine is one of the most common **neurological** diseases worldwide, affecting around 10 million people in the UK.[2, 6] Usually it begins in adulthood and is more common in women (affecting around 1 in 5 women).[2]

What is the impact of migraine (disease burden)?

Migraines can have a huge impact on people's lives. A survey conducted to explore the impact of migraines on the lives of people with at least four migraine days per month across 16 countries in Europe, South America, Asia and Australia found:[7]

- 69% of people reported that migraine affected their health and wellbeing
- 60% of people reported that it affected their social lives
- 56% of people reported that it affected their work lives
- 39% of people reported that it impacted their relationships with family members

People with migraine frequently experience severe symptoms. Migraines can be extremely painful, and the majority of people experience additional neurological symptoms during a migraine attack such as:[8]

- Feeling or being sick (79%)
- Sensitivity to light (91%)
- Sensitivity to sound (83%)

These symptoms can have a negative impact on people's wellbeing and affects their ability to carry out daily activities. As a result, migraine is a leading cause of disability and severly impacts people's ability to lead a normal life.[5] The impact of migraine is often

underestimated, and there is a misconception of migraine being simply headaches**,** when in reality migraines have been shown to be significantly more painful than other types of headaches.[9]

In addition to the considerable physical impact of migraine symptoms, migraines can have a negative impact on mental health. Roughly 35% of people with migraine experience anxiety and approximately 30% experience depression.[10] Between migraines, people may face concern and anxiety as to when the next painful attack will take place, and whether this will affect future plans or activities.[11]

Migraine can also have a substantial impact on family members, including spouses and children. People with migraine report that they have reduced participation in family activities, miss important events and avoid making commitments. Migraine can also have a negative impact on sex life (see **Section 2d**).[12, 13]

Furthermore**,** migraine is an extremely common condition and it is estimated that the NHS spends around £150 million per year on treating migraines.[14] It is also the most common neurological reason for visiting a general practitioner (**GP**), resulting in around 2.5 million appointments every year.[15] Migraine impacts people throughout their prime working years and therefore can result in significant reductions in work performance, with 5% of people reporting that they can't work and more than 20% of people reported worrying about job loss.[13] Roughly one-third of people with migraine worry about their finances, such as covering household expenses and long-term financial security. It is estimated that:[16]

- The UK loses 43 million days from work or school each year due to migraine
- Migraine / chronic headache is the second most frequently identified cause of short-term absence (for non-manual employees)
- **Absenteeism** from migraine alone costs £2.25 billion per year in the UK

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

How is migraine diagnosed?

There is no specific test to diagnose migraine, however once a GP has ruled out any other underlying causes of a person's symptoms they will usually ask them to keep a **migraine diary**. This is designed to help them keep track of when their migraines take place, how long they last, and what the person was doing at the time of the attack. Depending on the seriousness of their disease, the GP may refer them to a specialist to discuss treatment options such as preventive treatment, which may be prescribed if **acute treatment** (short-term treatment such as pain relief medication) is not working.[17]

How is migraine classified?

People with migraine may differ in terms of the number of headache days experienced per month:[3]

- Those with less than 15 headache days per month are described as having **episodic migraine** (accounting for approximately 90% of people with migraine)[18]
- Those with at least 15 days per month (8 of which having specific migraine features) are described as having **chronic migraine** (accounting for approximately 10% of people with migraine)[18]

However, the severity of disease does not only depend on the frequency of migraine attacks, but also on the severity and duration of migraines.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway is the medicine likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.

Please also consider:

- if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
- are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

What are the current treatment options for migraine?

While there is no cure for migraine, people with migraine may have acute treatment either alone, or alongside preventive treatment if they experience at least four migraine days per month.[19] Acute treatment aims to end an attack and minimise the pain of the headache, while preventive treatment aims to reduce the number of migraines experienced, and how long they last. Preventive treatment is considered when migraines significantly affect daily life and is prescribed for roughly one third of people with migraine.[20] **Figure 1** shows the preventive treatments that are offered to people with migraine.

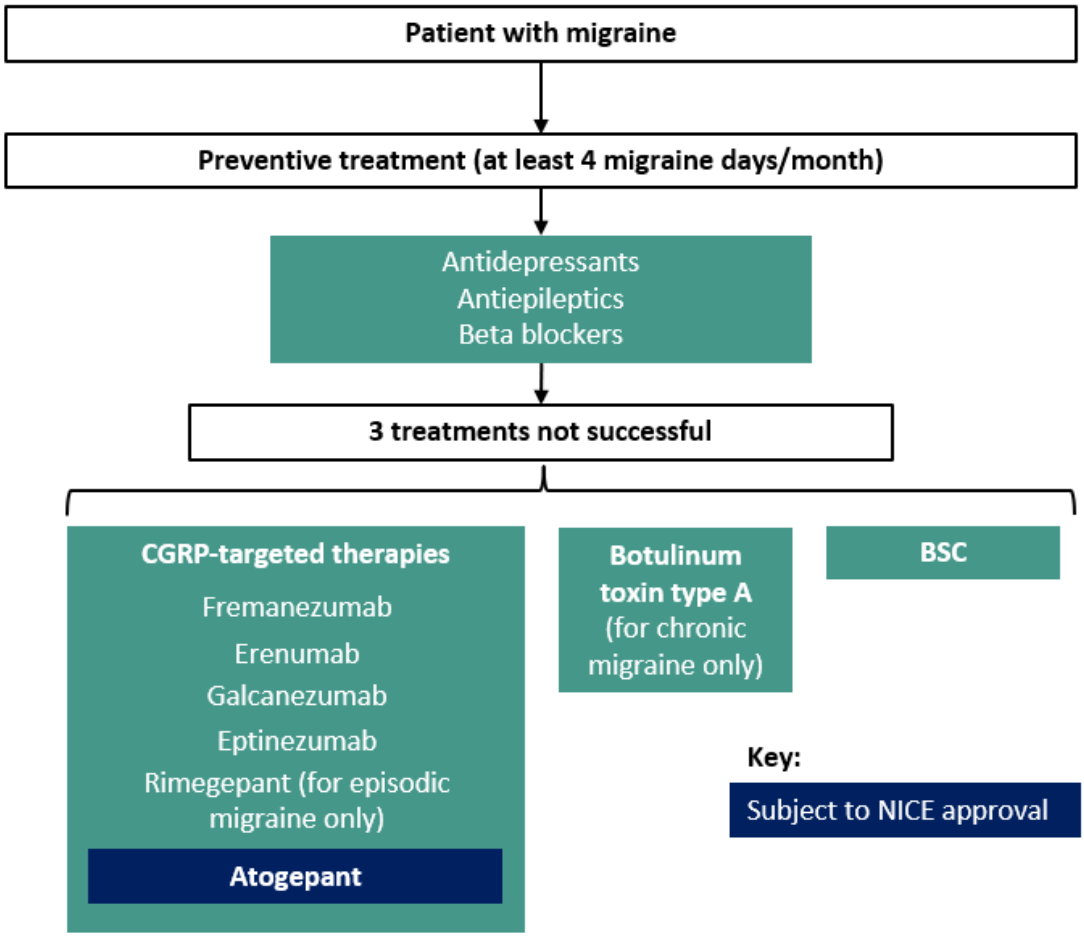
People with migraine are usuallly first prescribed preventive treatments including **antidepressants**, **antiepileptics**, and **beta blockers**, which are all tablets.[19] If at least three of these types of treatments are not successful in treating migraine, people may go on to receive an injectable therapy in the form of either a **monoclonal antibody** (galcanezumab, fremanezumab and erenumab) if they have 4 or more migraine days per month, or **botulinum toxin type A** (also known as BOTOX®) for people with chronic migraine only.[21-24] Monoclonal antibody treatments are either self-administered by the individual or administered by a trained professional approximately once per month, or once every three months (depending on the treatment).[21-23] Botulinum toxin type A is administered as multiple injections approximately 31 to 39 sites in the head and the back. These injections are required once every 12 weeks, and can only be administered by

trained healthcare professional.[24]

Over the course of this NICE submission process, a monoclonal antibody to be delivered by **intravenous infusion** (eptinezumab), and an oral medicine (rimegepant), were recently recommended by NICE for the prevention of migraine.[25, 26] However, these treatments are yet to be used widely, and rimegepant is yet to be made available on the NHS. Therefore, atogepant is likely to be used as an alternative to more established medicines (fremanezumab, erenumab and galcanezumab).

For people with migraine who do not receive monoclonal antibodies or botulinum toxin A, the only remaining treatment option is best supportive care, which is limited to acute treatments that aim to stop symptoms within approximately 2 hours of the attack.[23] In this submission, atogepant is put forward as a new preventive treatment for people with at least four migraine days per month for whom at least 3 treatments have failed. Atogepant is a tablet that is taken once daily and will be offered as an alternative to injectable monoclonal antibodies, as it works in a similar way (Section B.1).

Figure 1: Treatments offered to people with at least four migraine days per month



Abbreviations: NICE: National Institute for Health and Care Excellence.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Migraine from the patient perspective

Migraine attacks have a profound impact on everyday life with roughly three-quarters of people with migraine having a reduced ability to function normally during an attack.[27, 28] Furthermore, a global study of people with migraine found that:[29]

- 74% spend time in darkness due to migraine
- 83% had sleeping difficulties
- 55% lived in fear of the next attack
- 49% felt limited in daily life due to their disease

People with migraine have reported feelings of guilt about the impact of migraine on their family and reduced participation in family activities, a perception that their partners/spouses underestimate their disease and concerns over financial security.[12 13, 29] As a result many people with migraine report hiding their migraine from friends, family and even employers.[7]

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

The monoclonal antibodies used to treat migraine (galcanezumab, fremanezumab and erenumab) are **calcitonin gene-related peptide** monoclonal antibodies (CGRP mAbs). They are the first type of preventive treatments that have been developed specifically for the treatment of migraine. Other preventive treatments such as antidepressants, antiepileptics and beta blockers were all developed for other conditions.

Atogepant works in a similar way to existing CGRP mAbs. Atogepant binds to the **receptor** of a **protein** called CGRP, which is involved in processes in the brain that can cause pain during a migraine attack. CGRP is released by nerves and blood vessels in the brain during a migraine, but atogepant blocks CGRP from binding to CGRP receptor sites in the brain and reduces the migraine effect.[30]

CGRP mAbs that are currently available within the NHS are taken by **subcutaneous injection** (injection under the skin) monthly or every few months.[21-23] Atogepant offers an alternative to these treatments as it comes in a once daily tablet.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Atogepant is not intended to be used with any other preventive treatment. However, in the instance of a migraine attack, acute medication may be used alongside the treatment, including pain relief and anti-sickness medications.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

How is atogepant taken?

60 mg dose of atogepant is taken orally once a day with or without food.[31]

People with migraine can take atogepant at home from day one, reducing the need for repeat appointments which are currently necessary for existing treatments administered by injection. In contrast, monoclonal antibodies can require training to self-inject treatment or a recurring clinic visit to receive an injection by a trained healthcare professional.. Atogepant may also provide improved access to people with **needle-phobia** (see **Section 3f**).

It is important to note that a once daily 10 mg dose is licensed for use in people who have severe **renal impairment** or **end-stage renal disease**, or those currently receiving other treatments in the form of strong CYP3A4 and/or OATP inhibitors.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Studies investigating atogepant as a treatment for migraine

Four key **clinical trials** provide **clinical evidence** for atogepant in people with migraine: ADVANCE, CGP-MD-01, ELEVATE, and PROGRESS.

These trials assessed the ability for atogepant to reduce the frequency and severity of migraine (i.e., its **efficacy**), as well as improve quality of life, compared to a **placebo** (the **comparator**). The trials also assessed the safety and tolerability of atogepant compared to placebo, including frequency of severity of side effects and whether individuals had to stop treatment. A summary of the key information about each trial is provided in **Table 1**.

The main sources of evidence used in this submission are the ELEVATE and PROGRESS studies, which included people for whom at least 3 prior preventive treatments have failed (the target population of this submission). More information on these trials can be found in **Document B** in **Section B.2.2** and is published in the Lancet.[32]

Table 1. Clinical trials investigating atogepant

Trial name and number	Location	Trial design	Population	Treatment	Comparator
ADVANCE (NCT03777059)	US	Phase 3	Adult people with episodic migraine	Atogepant 10 mg, 30 mg, or 60 mg once daily	Placebo

ELEVATE (NCT04740827)	AUS, CA, CZ, DK, FR, DE, HU, IT, NL, PL, RU, ES, SE, UK, US	Phase 3	Adult people with episodic migraine for whom 2–4 types of preventive treatments have failed	Atogepant 60 mg once daily	Placebo
PROGRESS (NCT03855137)	AUS, CA, CN, CZ, DK, FR, DE, IT, JP, KR , PL, RU , ES, SE, TW, UK, US	Phase 3	Adult people with chronic migraine	Atogepant 30 mg twice daily, Atogepant 60 mg once daily	Placebo
CGP-MD-01 (NCT02848326)	US	Phase 2b/3	Adult people with episodic migraine	Atogepant 10 mg once daily, 30 mg (once or twice daily), or 60 mg (once or twice daily)	Placebo

Abbreviations: AUS: Australia; CA: Canada; CN: China; CZ: Czechia; DE: Germany; DK: Denmark; ES: Spain; FR: France; HU: Hungary; IT: Italy; JP: Japan; KR: Korea; NL: Netherlands; PL: Poland; RU: Russia; SE: Sweden; TW: Taiwan; UK: United Kingdom; US: United States.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Trial results

The ELEVATE and PROGRESS clinical trials measured the effectiveness of atogepant for the prevention of migraine. They demonstrated atogepant to be superior to placebo (atogepant was significantly more effective than placebo). The key efficacy results are described below.

- Atogepant reduced the frequency of migraines:
  - Individuals treated with atogepant had a greater average reduction in the number migraine days per month compared to placebo
  - A higher proportion of people treated with atogepant achieved at least a 50% reduction in the average number of migraine days per month compared to people treated with placebo

- Atogepant also reduced the average number of headache days per month (days where individuals experienced any headache, including headaches without specific migraine features), as well as the number of days per month where individuals used acute medication to manage migraine symptoms
- Improvements were also seen in outcomes measuring the duration and severity of migraines as reported through questionnaires (see **Section 3f**)
- Atogepant was shown to act quickly, as early as within the first day of treatment initiation for some people

Full results from the ELEVATE and PROGRESS clinical trials are shown in **Document B Section B.2.3.**

Indirect treatment comparison

No data are available for **direct comparisons** versus existing preventive treatments for migraine, as both the ELEVATE and PROGRESS clinical trials compared atogepant to placebo. Therefore, an analysis called an **indirect comparison** was done to compare atogepant to CGRP mAbs (i.e., treatments available in people with migraine who have experienced three prior preventive treatment failures). This is a common approach in the evaluations of new medicines. This statistical analysis is explained in further detail in **Document B, Section B.2.9.**

Overall, compared to existing treatments, the indirect comparison showed that atogepant was similarly effective in reducing migraine frequency and severity, and is a well-**tolerated** treatment option for the prevention of migraine.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Quality of life impact of atogepant

During the ELEVATE and PROGRESS trials, the quality of life of individuals was assessed through several measures:

- The **MSQ v2.1** questionnaire was used to determine how the individual's life had been affected by their migraines
- The **HIT-6** test was used to understand the impact the migraines had on the individual's ability to go about their daily lives

- The **MIDAS** questionnaire was used to determine headache-related disabilities that people experienced

Overall, across both trials, people treated with atogepant had significantly better quality of life results compared with people treated with placebo. Indirect comparisons indicated that atogepant was similarly effective to existing injectable therapies at improving quality of life.

Patient preferences for preventive treatment

Evidence suggests that people may have a preference for treatments that can be taken orally.

A study investigating the preferences for acute and preventive headache treatment in people with migraine found that the majority (88.1%) preferred oral medication over other treatments. It also found that most people preferred to take a pill once per day (52%) compared to an injection each month (assuming all treatments had the same effect).[33]

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Every medicine has **side effects** and the same medicine can produce different reactions in different people.

In the ELEVATE and PROGRESS trials, atogepant was generally well-tolerated and comparable to currently available monoclonal antibodies that work in a similar way. The most common side effects observed with atogepant included **constipation** and **nausea** and only a few people stopped treatment as a result of side effects. No new side effects were discovered for atogepant compared with the known safety profile of other monoclonal antibody treatments.

Information on other potential side effects will be available in the **Patient Information Leaflet** when published, and results from the ELEVATE and PROGRESS clinical trials are reported in **Document B, Section B.2.10.**

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Atogepant is effective for the prevention of migraine

According to robust clinical trial evidence, atogepant is a fast-acting and effective treatment for the prevention of migraine, reducing the number of days per month that an individual experiences migraines and headaches, and needs to take acute medication. Atogepant also reduces the duration and severity of migraines, improves health-related quality of life, and is a well-tolerated treatment that has comparable safety with existing monoclonal antibody treatments.[32]

Atogepant is an oral treatment which can provide an alternative to current injectable treatments

Established treatment options for people who have received three or more preventive treatments are limited to injectable therapies only in the form of monoclonal antibodies for those with 4 or more migraine days per month. Whilst these treatments are effective, monoclonal antibodies require training to self-inject treatment or a recurring clinic visit to receive an injection by a trained professional.[21-23] In contrast, atogepant is a once daily tablet that can be conveniently taken with minimal interference to day-to-day life, whilst offering similar efficacy and safety to existing treatments.

Furthermore, atogepant may provide improved access to people with needle-phobia, who either face discomfort receiving injectable treatments or avoid treatment altogether.

Atogepant provides a more convenient treatment option for women who are likely to conceive

Injectable monoclonal antibody treatments are not recommended for pregnant women, and it can take considerable time for these drugs to be removed from the body. This means that treatment must be stopped six months prior to pregnancy.[21-23] Given that migraine commonly affects women of child-bearing age, this lack of flexibility presents challenges for those trying to conceive and/or those who become pregnant on these treatments. Atogepant is not recommended in pregnant women; however, it is cleared much more quickly from the body and is not anticipated that women taking it will require such an extensive break from treatment prior to conception.

Atogepant may lead to more equitable and immediate access to treatment across the UK

There are difficulties associated with prescribing and administering injectable therapies due to variations across regions in the availability of the clinicians with the necessary training and/or capacity to administer these treatments. This has led to inconsistent access to treatments as well as the development of extensive waiting lists of up to 18 months. The simple nature of a tablet has the potential to open up opportunities to receive

treatment at an earlier stage of the NHS referrals pathway, which may lead to more equitable and immediate access to treatment across the UK.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Atogepant is generally well-tolerated and effective. However, like all existing migraine treatments, atogepant does not work for everyone and some people might not experience any improvement in their migraines.

Additionally, like all active treatments for migraines, some people may experience side effects while they are taking the treatment. The most common side effects include constipation and nausea, which are usually manageable, and most people do not need to stop treatment because of side effects.

There may also be a perceived disadvantage related to how atogepant is taken (oral medication) as people are trusted to take the tablets as **prescribed**. However, given migraine is a severe disease, people may be more motivated to take the treatment correctly. For example, across the ELEVATE and PROGRESS clinical trials, almost all treatments were taken as prescribed, and no one discontinued due to non-compliance.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)

- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Healthcare services need to get the best value from their limited budgets. To do this, they want to know whether a new medicine provides 'good value for money' compared to existing medicines. They will look at the costs of the new medicine and how the health of people with migraine is likely to improve if they take it. The pharmaceutical company that develops the medicines provides this information to healthcare teams using a **health economic model**. The pharmaceutical company uses the health economic model to perform an analysis, which compares the benefits and costs of the new treatment (atogepant) with the existing treatment or comparator (CGRP mAbs).

How the model reflects migraine

The economic model was designed to reflect the key features of migraine and **clinical practice** in the UK. In order to compare the clinical benefits, costs and quality of life associated with people treated with atogepant and comparators, a similar approach was taken to prior NICE appraisals of CGRP mAbs to calculate the duration of time in which an individual remains on treatment across a pre-specified number of years (i.e. time horizon).[21-23]

Modelling migraine prevention provided by a treatment

A number of migraine-related outcomes were used to assess whether atogepant was effective in preventing migraines compared to placebo, including:

- Number of migraine days per month
- Number headache days per month
- Duration and severity of migraines experienced

The information gathered across the duration of the trial was then used to estimate how effective treatments would be over a longer period through modelling. In this model, atogepant was found to be similarly effective to comparators at reducing migraines and migraine symptoms.

Modelling how much a treatment improves quality of life

Migraine-related **quality of life** measures were used to assess how atogepant affected an individual's quality of life (**Section 3f**; MSQ v2.1, HIT-6, MIDAS). These were collected by asking people to complete questionnaires about their migraines and migraine symptoms.

Modelling how the costs of treatment differ with the new treatment

Various different costs are included in the model for the different migraine treatments. These costs include:

- The cost to purchase the medicine itself and how much it costs to administer the medicine (e.g., healthcare professional time dedicated to injections in clinic)
- The costs of clinician time, covering both initial consultation on treatment initiation and subsequent check-ups

Model results indicated that atogepant may reduce costs for the NHS compared with CGRP mAbs as a preventive treatment for migraine. The key reasons for this include:

- As atogepant is an oral medicine, it does not have any administration costs. Therefore, atogepant reduces in-clinic administration costs compared with 10% of people treated with CGRP mAbs who require assistance with administration in-clinic[23]
- Atogepant reduces the duration of headache specialist time required for administration and follow-up consultation

Several assumptions were made in the model that were validated by clinicians. Information on these assumptions can be found in **Document B, Section B.3.9.2**.

Variations of other inputs in the model were also tested and the results of these tests are explained in **Document B, Section B.3.11.**

Cost effectiveness results

The model indicated that treatment with atogepant was associated with reduced costs alongside similar benefits compared with the relevant comparators. The economic model estimated that this resulted in **net health benefits** for atogepant versus all relevant comparators in both EM and CM populations. However, it should be noted that these results are based on company-preferred assumptions and do not account for confidential discounts applied to existing treatments. A positive net health benefit would be considered cost-effective for the NHS.

Benefits of atogepant not captured in the economic analysis

Compared to some other medicines used for the treatment of migraine, atogepant does not require any uncomfortable procedures as it is given as a tablet. This may improve an individual's experience by reducing any discomfort associated with injections and by being a more convenient option that does not require a visit to hospital for treatment administration. The oral route of administration may also be beneficial for a subset of people with migraine who prefer to receive their treatment in tablet form, especially in those who are needle-phobic.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Atogepant would represent an important advancement in the treatment of migraine

Migraine is a condition that can have a significant impact on an individual's mental health, emotional wellbeing, and quality of life. Despite this, there is no cure for migraine and current treatments are only available as injections. Available treatments are effective in reducing the likelihood of experiencing a migraine, but are associated with declining effectiveness during the period between injections.[34, 35] Given their injectable form and the need to be administered/supervised by healthcare professionals who are both comfortable and have sufficient capacity to administer injectable therapies; access is limited and many people who have experienced three or more treatment failures are not actively treated with a preventive medication.

Atogepant works in a similar way to available monoclonal antibodies and is similarly effective in reducing migraine frequency and severity. Monoclonal antibodies have been established as a market-leading treatment with over four years of clinical experience since the regulatory approval of galcanezumab.[36] However, as atogepant is a once daily tablet, it has the potential to offer additional benefits to people with migraine and may resolve access issues associated with injectable therapies.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues here

It is not anticipated that the provision (or non-provision) of atogepant would exclude any people protected by equality legislation, lead to a recommendation that has a different impact on people protected by equality legislation than on the wider population, or lead to recommendations that have an negative impact on people with a particular disability or disabilities.

However, there may be geographical inequity in access to current treatments, given that CGRP mAbs and botulinum toxin type A are only available as injections, which may require hospital visits and administration by specialists. Introduction of orally-administered atogepant may therefore help reduce inequity in access.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Further information on migraine:

- What is migraine? What is migraine? - The Migraine Trust
- Overview Migraine. Migraine - NHS (www.nhs.uk)
- Calcitonin Gene-Related Peptide (CGRP) monoclonal antibodies. Calcitonin Gene-Related Peptide (CGRP) monoclonal antibodies - The Migraine Trust
- What we currently know about migraine. What we currently know about migraine - The Migraine Trust
- State of the Migraine Nation Dismissed for too long: Recommendations to improve migraine care in the UK. Dismissed-for-too-long_Recommendations-to-improve-migraine-care-in-the-UK.pdf (migrainetrust.org)
- What is migraine? What is migraine? - National Migraine Centre
- What Is Migraine? Symptoms, Treatments & Causes. What Is Migraine? Symptoms, Treatments & Causes

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

This glossary explains terms highlighted in **black bold text** in this summary of information for patients. At times, an explanation for a term might mean you need to read other terms to understand the original terms.

Absenteeism	Absence from work for lengths beyond what is considered usual.
Acute treatment	Active, short-term treatment for a condition that manages the symptoms but does not reduce the risk of symptom occurrence.
Antidepressants	Medication used to treat depression.
Antiepileptics	Medication used to treat epilepsy.
Aura	Sensory symptoms that happen before a migraine e.g., visual problems (such as seeing flashing lights, zig-zag patterns or blind spots), numbness or tingling sensation (e.g., pins and needles), feeling dizzy or off balance, difficulty speaking, or loss of consciousness
Beta blockers	Medication commonly used to manage heart conditions.
Botulinum toxin type A	Also referred to as Botox, it is a treatment that can be used for the prevention of migraines. It is injected into the skin and works by reducing the number of pain signals that reach the brain.
Calcitonin gene-related peptide monoclonal antibodies	A type of treatment used for the prevention of migraine that works by blocking CGRP or CGRP receptors. CGRP is a protein that is known to be involved in the brain processes which cause pain during a migraine attack.

Chronic migraine	A classification of migraine that includes people who experience headache on at least 15 days per month.
Clinical evidence	The results provided by a clinical trial/ clinical study.
Comparator	Another treatment that can be used as a standard for comparison.
Constipation	Infrequent bowel movements or difficult passage of stool
Clinical trial/clinical study	A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis or treatment of a disease. Also called a clinical study.
Clinical practice	The agreed-upon and customary means of delivering healthcare by doctors, nurses and other healthcare professionals.
Direct comparisons	An analysis that compares medicines directly in a head-to-head, randomised clinical trial.
Efficacy	The ability of a drug to produce the desired beneficial effect on your disease or illness in a clinical trial.
End-stage renal disease	Also called kidney failure, it occurs when loss of kidney function reaches an advanced state.
Episodic migraine	A classification of migraine that includes people who experience headache less than 15 days per month.

GP	A general health practitioner, which is a doctor based in the community that treats people with minor or chronic illnesses and refers those with serious conditions to a hospital.
Health economic model	A way to predict the costs and effects of a technology over time or in patient groups not covered in a clinical trial.
HIT-6	A 6-question questionnaire used to measure the impact that headaches have on an individual's ability to function.
Indirect comparisons	An analysis that compares medicines that have not been compared directly in a head-to-head, randomised clinical trial.
Intravenous infusion (IV)	An IV infusion is a way of putting medicine directly into an individual's bloodstream over a longer time period than having an injection.
Marketing authorisation	The legal approval by a regulatory body that allows a medicine to be given to people in a particular country.
Medicines and Healthcare products Regulatory Agency (MHRA)	The regulatory body that evaluates, approves and supervises medicines throughout the United Kingdom.
MIDAS	A 7-item questionnaire designed to understand headache-related disability over a three-month period.
Migraine attack	A moderate or severe headache felt as a throbbing pain on one side of the head.
Migraine diary	A diary that can be kept to learn more about people's migraines and what triggers them.

MSQ v2.1	A 14-item questionnaire designed to measure health-related quality-of-life impact of migraines on the individual over a period of four weeks.
Multicentre	A trial involving several hospitals, clinics, or research institutions.
Needle-phobic	A fear of needles.
Nausea	Sickness in the stomach with an urge to vomit.
Neurological	Relates to diseases of the nervous system, which is the part of the body that controls actions and senses.
Oral medication	Medication that is taken through the mouth.
Patient Information Leaflet	A document included in the package of a medication that provides information about that drug and its use.
Phase 3 clinical trial	This type of clinical trial that tests how well a new treatment works and its safety compared with a standard treatment. For example, it evaluates which group of patients has better survival rates or fewer side effects.
Placebo	A substance that appears to be a medicine, but has no actual therapeutic benefit. It is used in clinical trials to compare against the new treatment that is being developed.
Preventive	Designed to keep the condition’s symptoms from occurring.

Protein	These are structures inside all cells of our body that are important for many activities including growth, repair and signalling.
Quality of life	An individual's physical, emotional, and social wellbeing. Many clinical trials assess the effects of a disease and its treatment on the quality of life of individuals. These studies measure aspects of an individual's sense of well-being and their ability to carry out activities of daily living.
Real-world evidence	Evidence that has come from routine clinical practice and not a clinical trial.
Receptors	A group of specialised cells within the body that can detect a change in the environment and produce responses.
Regulatory bodies	These are legal bodies that review and certify the quality, safety and efficacy of medicines and medical technologies.
Renal impairment	The inability for the kidney to function properly.
Side effect (also called adverse event)	An unexpected medical problem that arises during treatment. Side effects may be mild, moderate or severe.
Subcutaneous injection	A type of injection in which a short needle is used to inject a drug into tissue layer between the skin and the muscle.
Time horizon	The time horizon used for an economic evaluation is the duration over which health outcomes and costs are calculated

Tolerated	The ability of an individual to persist a treatment, despite the treatment's side effects.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Atogepant for preventing migraine [ID5090]

Clarification questions

October 2023

File name	Version	Contains confidential information	Date
ID5090_Atogepant Clarification Question_ Responses_Redacted	V1.0	Yes	3rd November 2023

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

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Section A: Clarification on effectiveness data

Comparators

A1. Priority Question. Given that rimegepant (EM only) and eptinezumab (EM and CM) have now received final NICE guidance as part of TA906 and TA871, respectively, with recommendations for these treatments in those in whom three prior oral treatments have failed, the EAG has confirmed with NICE that these two treatments are relevant to the current UK migraine prevention pathway:

a) **Please update all NMAs provided to also include these two treatments, ensuring that updated results, updated NMA files (to allow them to be validated by the EAG) and updated model fit statistics are provided for all NMAs currently presented;**
b) **Please include rimegepant and eptinezumab as comparators in the economic model, including base case and scenario analyses.**

As detailed in Section B.1.1 of the Company Submission (CS), AbbVie maintain the position that rimegepant and eptinezumab are not relevant comparators for this submission as they are not established practice in the NHS, nor are they expected to become established practice within the NHS at point of committee decision. Both treatments are currently associated with very low market share, while rimegepant was not reimbursed on the NHS at the point of CS in September 2023.[1, 2] Looking forward, clinical experts have highlighted challenges in local implementation of each treatment, meaning that market shares are anticipated to remain low for rimegepant and eptinezumab for the foreseeable future, with Clarivate™ forecast data estimating market shares

of [redacted] for rimegepant and [redacted] for eptinezumab among patients with migraine eligible for NICE-recommended fourth-line preventive therapies in 2024 (after adjustment to account for patients receiving BSC).

Eptinezumab uptake is expected to be particularly slow, given the need to set up services capable of infusing the treatment in-clinic. In line with this, clinical expert opinion obtained at NICE committee meeting (TA871) indicated that its use is likely to be reserved for patients with severe migraine attacks or those who are unable to use the subcutaneously administered CGRP mAbs. Therefore, it is unlikely that this would represent a relevant comparator even if the intervention were considered to be established practice within the NHS, given the difference in positioning versus atogepant. Clinical experts consulted by AbbVie further suggested that it is highly unlikely that services would prioritise an infusion-based treatment administered in-clinic over a home-administered treatment. Therefore, atogepant would typically be positioned ahead of eptinezumab, alongside the subcutaneous CGRP mAbs.

While neither rimegepant nor eptinezumab are considered relevant comparators for this submission, currently available evidence indicates that including neither treatment would impact the outcome of the cost-effectiveness analysis.

Results of a matching-adjusted indirect comparison (MAIC) of rimegepant and atogepant published at AHS 2023 demonstrate that atogepant was more effective in reducing the frequency of migraine (CFB in MMDs) and in improving HRQoL (MSQ-RFR) compared with rimegepant.[3] Clinical experts noted that the results of the MAIC were in line with their expectations based on their understanding of available trial data for atogepant and rimegepant and given that atogepant is a once daily tablet, versus rimegepant which is taken once every other day. Given that rimegepant is [redacted], the inclusion of rimegepant is not anticipated to impact the outcome of a cost-effectiveness analysis for atogepant.

While no indirect treatment comparisons exploring the comparative efficacy of atogepant and eptinezumab have been published and it was not possible to conduct this comparison within the timeframe of the clarification question responses, a naïve comparison of the two treatments is presented in Table 1 (EM) and Table 2 (CM). These results indicate that the efficacy of the two treatments is likely comparable, while clinical experts noted that efficacy of atogepant may be similar to eptinezumab based on their understanding of available trial evidence. In addition, [redacted]costs are anticipated for eptinezumab versus atogepant due to the differing routes of administration, with eptinezumab administration costs estimated to be £8,090 over a model lifetime horizon in the CS for TA871. Therefore, it is not anticipated that its inclusion in the cost-effectiveness analysis would have an impact on the conclusions. With respect to safety, clinical experts did not raise any reasons that they would expect safety profile of atogepant to be markedly different to that of rimegepant or eptinezumab.

For these reasons, the NMA and cost-effectiveness analysis have not been updated to include rimegepant and eptinezumab.

Table 1: Naive comparison of key efficacy outcomes (EM)

Study	Treatment	Primary Time Point (weeks)	Endpoint			
			CFB in MMD		50% response in MMD	
			Point estimate (95% CI)	Treatment effect vs. Placebo (95% CI)	Number of responders (%)	Treatment effect vs. placebo
ADVANCE[4]	Atogepant 60 mg	1 – 12 weeks	−4.2 (−4.6 to −2.8)	−1.7 (−2.3 to −1.2)	135/222 (60.8%)	31.8%
	Placebo		−2.5 (−2.9 to −2.1)		62/214 (29.0%)	
PROMISE-1[5]	Eptinezumab 100 mg	1 – 12 weeks	−3.9 (−4.3 to −3.5)	−0.7 (−1.3 to −0.1)	110/221 (49.8%)	12.4%
	Placebo		−3.2 (−3.6 to −2.8)		83/222 (37.4%)	N/A

Footnote: Point estimates, CIs and treatment effects rounded to 1 decimal place.
Abbreviations: CFB: change from baseline; CI: confidence interval; MMDs: monthly migraine days; SE: standard error;

Table 2: Naive comparison of key efficacy outcomes (CM)

Study	Treatment	Primary Time Point (weeks)	Endpoint					
			CFB in MMD		50% response in MMD		30% response in MMD	
			Point estimate (95% CI)	Treatment effect vs. placebo	Number of responders (%)	Treatment effect vs. placebo	Number of responders (%)	Treatment effect vs. placebo
PROGRESS[6]	Atogepant 60 mg	1 – 12 weeks	−6.9 (-7.7 to -6.1)	−1.8 (-2.9 to -0.8)	105/256 (41.0%)	15.0%	[redacted]	[redacted]
	Placebo		−5.1 (-5.9 to -4.3)		64/246 (26.0%)		[redacted]	
PROMISE-2[7]	Eptinezumab 100 mg	1 – 12 weeks	−7.7 (NR)	−2.0 (−2.9 to −1.2)	205/356 (57.6%)	18.3%	NR	NR
	Placebo		−5.6 (NR)		144/366 (39.3%)			NR

Footnote: Point estimates, CIs and treatment effects rounded to 1 decimal place.
Abbreviations: CFB: change from baseline; CI: confidence interval; MMDs: monthly migraine days; NR = not reported; SE: standard error

Atogepant clinical trials

A2. For the overall mITT population and 3+ subgroup for ELEVATE and PROGRESS trials, please provide the number and proportion of patients at baseline for each treatment arm with:

a) 4-7 and ≥8 baseline MMDs (ELEVATE only);

The proportion of patients with 4–7 and ≥8 MMDs at baseline in the ELEVATE trial is presented in Table 3.

Table 3: Proportion of patients with 4–7 and ≥8 baseline MMDs in ELEVATE

Baseline MMDs group, n (%)	Placebo	Atogepant 60 mg QD
Overall mITT population	[redacted]	[redacted]
4–7 MMDs at baseline	[redacted]	[redacted]
≥8 MMDs at baseline	[redacted]	[redacted]
3+ TF mITT population	[redacted]	[redacted]
4–7 MMDs at baseline	[redacted]	[redacted]
≥8 MMDs at baseline	[redacted]	[redacted]

Abbreviations: 3+ TF: patients in whom ≥3 prior preventive treatments have failed; mITT: modified intent-to-treat; MMDs: monthly migraine days; QD: once daily.

b) <18 and ≥18 baseline MMDs (PROGRESS only).

The proportion of patients with <18 and ≥18 MMDs at baseline in the overall modified intent-to-treat (mITT) population of the PROGRESS trial is presented in Table 4. As described further in response to Question A9 below, no robust subgroup analyses can be provided for the 3+ TF mITT population. As such, data specific to this patient subgroup are not provided here.

Table 4: Proportion of patients with <18 and ≥18 baseline MMDs in PROGRESS (overall mITT population)

Baseline MMDs group, n (%)	Placebo (N=246)	Atogepant 60 mg QD (N=256)
<18 MMDs at baseline	[redacted]	[redacted]
≥18 MMDs at baseline	[redacted]	[redacted]

Abbreviations: mITT: modified intent-to-treat; MMDs: monthly migraine days; QD: once daily.

A3. Please provide an overview of any missing data for the 3+ failure subgroups and overall populations of ELEVATE and PROGRESS, including proportions in each arm with missing data for outcomes at 12 weeks and any assumptions that were made for missing data in the analyses.

As it is unlikely that missing data are “missing at random”, if there are missing data, please consider a scenario analysis making the conservative assumption of reversion to baseline for any missing data.

The EAG notes that the information on missing data was already provided as part of the CCE process (CQ A7) but would appreciate this being provided again in case the EAG wishes to cite any figures provided in its report. However, analyses using the reversion to baseline assumption were not provided by the company as part of the CCE; it acknowledges that a copy-reference approach was performed as a scenario for one outcome but does not consider this to be as robust an assumption as the reversion to baseline approach suggested by the EAG.

Multiple measures were taken to reduce the drop-out rate in the ADVANCE, PROGRESS and ELEVATE studies, including the following:

- Efficacy data was collected for participants with premature-treatment discontinuation up to 12 weeks for PROGRESS and up to 4 weeks for ADVANCE and ELEVATE.
- The completers of placebo-controlled study were allowed to roll over to the long-term extension studies.
- The double-blind treatment period was relatively short, only 12 weeks
- Participants were allowed to use acute migraine relief medications to stay in the study.

Despite this, the company acknowledges the need to assess any potential impact of missing data and therefore present below information on these data, as provided previously.

A summary of missing data is presented by 4-Week interval for the primary efficacy outcome, CFB in MMDs (Table 5 and Table 6) and at Week 12 for PRO outcomes across ELEVATE and PROGRESS studies (Table 7: Missing data for HRQoL endpoints in ELEVATE

Endpoint	Placebo		Atogepant 60 mg	
	Missing	Percentage	Missing	Percentage
ELEVATE (overall mITT)				
CFB in MSQ-RFR domain score at Week 12	[redacted]	[redacted]	[redacted]	[redacted]
CFB in MSQ-RFP domain score at Week 12	[redacted]	[redacted]	[redacted]	[redacted]
CFB in MSQ-EF domain score at Week 12	[redacted]	[redacted]	[redacted]	[redacted]
CFB in HIT-6 domain score at Week 12	[redacted]	[redacted]	[redacted]	[redacted]
CFB in MIDAS domain score at Week 12	[redacted]	[redacted]	[redacted]	[redacted]
ELEVATE (3+ TF mITT)				
CFB in MSQ-RFR domain score at Week 12	[redacted]	[redacted]	[redacted]	[redacted]
CFB in MSQ-RFP domain score at Week 12	[redacted]	[redacted]	[redacted]	[redacted]
CFB in MSQ-EF domain score at Week 12	[redacted]	[redacted]	[redacted]	[redacted]

CFB in HIT-6 domain score at Week 12	[redacted]	[redacted]	[redacted]	[redacted]
CFB in MIDAS domain score at Week 12	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 3+ TF: patients in whom ≥3 prior preventive treatments have failed; HIT-6: headache impact test-6; mITT: modified intent-to-treat; MIDAS: migraine disability assessment; MSQ-EF: migraine specific quality of life emotional function; MSQ

Table 8 and Table 7).

Table 5: Missing data for CFB in MMDs by 4-Week intervals for ELEVATE

Derived Visit	Placebo	Atogepant 60 mg QD
Overall mITT population	N=[redacted]	N=[redacted]
Weeks 1–4	[redacted]	[redacted]
Weeks 5–8	[redacted]	[redacted]
Weeks 9–12	[redacted]	[redacted]
3+ TF mITT population	N=[redacted]	N=[redacted]
Weeks 1–4	[redacted]	[redacted]
Weeks 5–8	[redacted]	[redacted]
Weeks 9–12	[redacted]	[redacted]

Abbreviations: 3+ TF: patients in whom ≥3 prior preventive treatments have failed; mITT: modified intent-to-treat; QD: every day.

Table 6: Missing data for CFB in MMDs by 4-Week intervals for PROGRESS

Derived Visit	Placebo	Atogepant 60 mg QD
Overall mITT population	N=246	N=256
Weeks 1–4	[redacted]	[redacted]
Weeks 5–8	[redacted]	[redacted]
Weeks 9–12	[redacted]	[redacted]

Abbreviations: mITT: modified intent-to-treat; QD: every day.

Table 7: Missing data for HRQoL endpoints in ELEVATE

Endpoint	Placebo		Atogepant 60 mg	
	Missing	Percentage	Missing	Percentage
ELEVATE (overall mITT)				
CFB in MSQ-RFR domain score at Week 12	[redacted]	[redacted]	[redacted]	[redacted]
CFB in MSQ-RFP domain score at Week 12	[redacted]	[redacted]	[redacted]	[redacted]
CFB in MSQ-EF domain score at Week 12	[redacted]	[redacted]	[redacted]	[redacted]
CFB in HIT-6 domain score at Week 12	[redacted]	[redacted]	[redacted]	[redacted]
CFB in MIDAS domain score at Week 12	[redacted]	[redacted]	[redacted]	[redacted]
ELEVATE (3+ TF mITT)				

CFB in MSQ-RFR domain score at Week 12	[redacted]	[redacted]	[redacted]	[redacted]
CFB in MSQ-RFP domain score at Week 12	[redacted]	[redacted]	[redacted]	[redacted]
CFB in MSQ-EF domain score at Week 12	[redacted]	[redacted]	[redacted]	[redacted]
CFB in HIT-6 domain score at Week 12	[redacted]	[redacted]	[redacted]	[redacted]
CFB in MIDAS domain score at Week 12	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 3+ TF: patients in whom ≥3 prior preventive treatments have failed; HIT-6: headache impact test-6; mITT: modified intent-to-treat; MIDAS: migraine disability assessment; MSQ-EF: migraine specific quality of life emotional function; MSQ

Table 8: Missing data for HRQoL endpoints at Week 12 in PROGRESS

Endpoint	Placebo		Atogepant 60 mg	
	Missing	Percentage	Missing	Percentage
PROGRESS (overall mITT)				
CFB in MSQ-RFR domain score at Week 12	[redacted]	[redacted]	[redacted]	[redacted]
CFB in MSQ-RFP domain score at Week 12	[redacted]	[redacted]	[redacted]	[redacted]
CFB in MSQ-EF domain score at Week 12	[redacted]	[redacted]	[redacted]	[redacted]
CFB in HIT-6 domain score at Week 12	[redacted]	[redacted]	[redacted]	[redacted]
CFB in MIDAS domain score at Week 12	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HIT-6: headache impact test-6; mITT: modified intent-to-treat; MIDAS: migraine disability assessment; MSQ-EF: migraine specific quality of life emotional function; MSQ-RFP: migraine specific quality of life role function-preventive; QD: once daily; SD: standard deviation.

However, AbbVie note that the mechanism of missing (especially for Missing Not at Random) is not testable and not verifiable since these data are missing. Therefore, the recommended approach of conducting several sensitivity analyses in the structured approach to evaluate whether results are consistent under the assumptions was followed, in line with EMA guidance (ICH E9 R1).[8] To this end, multiple sensitivity analyses for missing data handling were prespecified in study Statistical Analysis Plans (SAPs) for ADVANCE, PROGRESS and ELEVATE, and additional sensitivity analyses were conducted in EMA clinical responses. All of these analyses demonstrated consistent results and confirmed the robust finding from the primary analyses.

Carpenter *et al*., (2013) introduced the reference-based imputation methods including copy-reference (CR) approach and jump-to-reference (J2R).[9] The J2R approach can be interpreted as participants in the active treatment arms having the same profile as in the treatment arm up to study withdrawal. In the ADVANCE, PROGRESS and ELEVATE trials, study withdrawal was the end of eDiary collection (end of study) for participants who were on or off treatment, instead of treatment discontinuation, but after withdrawal the profile jumps to the estimated profile for the reference arm (i.e., placebo arm). To understand CR approach for participants who withdraw, their profiles including both before and after withdrawal follow the whole profile estimated for the

control arm for missing data imputation, i.e., missing data are imputed as if the participants were on reference (i.e., the placebo group) throughout the study.

Analyses results for CR and J2R approaches are presented in Table 9 and

Table 10 for the primary endpoint. All sensitivity analyses confirmed the robustness of the study results and justification of missing data handling in the data analyses.

Table 9: Change from baseline in mean MMDs across the initial 12-week treatment period in ADVANCE (EM)

		ADVANCE			
	Statistic	Placebo	Atogepant 10 mg QD	Atogepant 30 mg QD	Atogepant 60 mg QD
Primary Analysis Approach (MMRM)					
Baseline number of days	N	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant vs. placebo	LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
	LSMD		[redacted]	[redacted]	[redacted]
	95% CI		[redacted]	[redacted]	[redacted]
	Nominal p-value		[redacted]	[redacted]	[redacted]
	Adjusted p-value		[redacted]	[redacted]	[redacted]
Copy-Reference Approach					
Change from baseline	LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant vs. placebo	LSMD		[redacted]	[redacted]	[redacted]
	95% CI		[redacted]	[redacted]	[redacted]
	Nominal p-value		[redacted]	[redacted]	[redacted]
Jump-to-Reference Approach					
Change from baseline	LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant vs. placebo	LSMD		[redacted]	[redacted]	[redacted]
	95% CI		[redacted]	[redacted]	[redacted]
	Nominal p-value		[redacted]	[redacted]	[redacted]

Abbreviations: BID: twice daily; CI: confidence interval; EM: episodic migraine; LS: least squares; LSMD: least squares mean difference; MMD: monthly migraine day; MMRM: mixed model for repeated measures; QD: once daily; SD: standard deviation; SE: standard error.

Table 10: Change from baseline in mean MMDs across the initial 12-week treatment period in PROGRESS and ELEVATE (CM and EM)

	Statistic	PROGRESS			ELEVATE	
		Placebo	Atogepant 30 mg BID	Atogepant 60 mg QD	Placebo	Atogepant 60 mg QD
Primary Analysis Approach (MMRM)						
Baseline number of days	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant vs. placebo	LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	LSMD		[redacted]	[redacted]		[redacted]
	95% CI		[redacted]	[redacted]		[redacted]
	Nominal p-value		[redacted]	[redacted]		[redacted]
	Adjusted p-value		[redacted]	[redacted]		[redacted]
Copy-Reference Approach						
Change from baseline	LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant vs. placebo	LSMD		[redacted]	[redacted]		[redacted]
	95% CI		[redacted]	[redacted]		[redacted]
	Nominal p-value		[redacted]	[redacted]		[redacted]
Jump-to-Reference Approach						
Change from baseline	LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant vs. placebo	LSMD		[redacted]	[redacted]		
	95% CI		[redacted]	[redacted]		
	Nominal p-value		[redacted]	[redacted]		

Footnote: *Copy-Reference Approach and Jump-to-Reference Approach yielded similar results in analyses for the ADVANCE and PROGRESS studies; therefore, the Jump-to-Reference approach was not required for the ELEVATE study

Abbreviations: BID: twice daily; CI: confidence interval; EM: episodic migraine; LS: least squares; LSMD: least squares mean difference; MMD: monthly migraine day; MMRM: mixed model for repeated measures; QD: once daily; SD: standard deviation; SE: standard error.

In addition to the statistical appropriateness of the approach used, clinical experts indicated that the reversion to baseline approach suggested by the EAG is not considered appropriate given the uncertainty in the reasons for missing data across each patient. Therefore, a scenario analysis making the assumption of reversion to baseline for any missing data has not been conducted, on the grounds that such an analysis would be overly conservative.

AbbVie maintain that the mixed model for repeated measures (MMRM) methodology for continuous variables is appropriate; this approach to data analysis has been accepted by the EMA and MHRA in informing the regulatory approval for atogepant, and has been deemed sufficiently robust for peer-reviewed publication.[10, 11] In addition, similar approaches to missing data handling have been taken in NICE prior appraisals for treatments in the prevention of migraine; for example, repeated measures analyses where missing data were assumed to be missing-at-random and last-observation-carried forward (LOCF) approaches were used to handle missing data for the CONQUER study in the NICE appraisal of galcanezumab (TA659).[12] Similarly, a reversion to baseline assumption was not applied for patients with missing data in studies informing the prior NICE appraisals for fremanezumab (TA764) and rimegepant (TA906).[13]

NMAs

A4. Priority question. Regarding NMAs performed with baseline risk adjustment, for each type of outcome (i.e. those presented as ORs, CFB and cloglog HR NMAs), please provide the code used for baseline risk adjusted NMA so that it can be validated against that outlined in NICE DSU TSD 3. The EAG has seen that it was run in R in the document already provided but the equivalent code used in WinBUGS would be useful.

Equivalent code in WinBUGS was not available for inclusion as part of this response. However, a set of complete R scripts for a representative selection of endpoints for the unadjusted and adjusted models is provided in the reference pack. These go from specific input data used through to high level reporting and include high level outputs that should be directly reproducible by the EAG. Please note that these are not the exact scripts used to generate the submitted analysis given that additional complexities have been removed, and due to random sampling, the outputs from these scripts will not completely match those submitted in the CS.

For the baseline risk adjusted models for discontinuation, the methods used were based on derived hazard ratios using a slight difference from the non-risk-adjusted analyses previously submitted. This alternative approach was to derive a hazard ratio from the reported binomial data following a published method (https://doi.org/10.1002/jrsm.1301) and then use this log hazard ratio as an input into a contrast NMA assuming log hazard ratios are normally distributed. The non-risk-adjusted models following this method is also provided in the reference pack and show similar results to the cloglog approach previously included despite this minor change in approach.

A5. Priority question. The company does not present results in Table 30 of the CS appendices for the ≥30% MMD reduction outcome in CM when using the RE NMA with baseline adjustment, given it considers the results to be unreliable. Given this model did converge, please provide these results and comment on why they are considered to be unreliable.

AbbVie wish to emphasise that although the RE model converged for the ≥30% reduction in MMDs outcome, the model produced implausible results with credible intervals spanning from 0.00 towards infinity for treatment effects and a wide credible interval for beta (–72.21, 67.53). These data are therefore considered unreliable and inappropriate for use in the model. To provide further context around this assessment, the relevant model fit statistics, convergence statistics and model results are presented in Table 11, Table 12 and Table 13, respectively.

Table 11: Model fit statistics – ≥30% reduction in MMDs in CM (Overall mITT)

Endpoints	Model	DIC	Beta			Residual Deviance	SD
			Median	LB	UB		
≥30% reduction in MMDs	Baseline risk-adj. FE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Baseline risk-adj. RE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CM: chronic migraine; DIC: deviance information criterion; FE: fixed effect; LB: lower bound; mITT: modified intent-to-treat; MMDs: monthly migraine days; RE: random effect; SD: standard deviation; UB: upper bound.

Table 12: Model convergence statistics – ≥30% reduction in MMDs in CM (Overall mITT)

Gelman-Rubin statistics			
Endpoints	**Model**	**Max-Gelman statistic**	**Converged?**
≥30% reduction in MMDs	Baseline risk-adj. FE	[redacted]	[redacted]
	Baseline risk-adj. RE	[redacted]	[redacted]

Note: A model converged if the associated Max-Gelman statistic <1.05.
Abbreviations: CM: chronic migraine; DIC: deviance information criterion; FE: fixed effect; mITT: modified intent-to-treat; MMDs: monthly migraine days; RE: random effect.

Table 13: Relative effect of atogepant 60 mg QD compared to all treatments for ≥30% reduction in MMDs in CM (Overall mITT)

	Baseline risk-adjusted FE	Baseline risk-adjusted RE
Atogepant 60 mg QD vs all treatments, odds ratio (95% credible intervals)		
Placebo	Model did not converge	[redacted]
Erenumab 140 mg QM		[redacted]
Fremanezumab 225mg Q3M[a]		[redacted]
Fremanezumab 675mg Q3M		[redacted]
Galcanezumab 120 mg QM[b]		[redacted]
Botulinum toxin type A 155–195 units Q3M		[redacted]

Footnotes: [a]Fremanezumab regimen is 675 mg initial dose followed by 225 mg once a month. [b]Galcanezumab regimen is a 240 mg loading dose followed by 120 mg once a month.
Abbreviations: CM: chronic migraine; FE: fixed effect; mITT: modified intent-to-treat; MMDs: monthly migraine days; Q3M: once every three months; QD: every day; QM: once monthly; RE: random effect.

A6. Priority question. Regarding cloglog analyses performed for TEAEs and all-cause discontinuation, please can the company:

a) Explain why cloglog models were considered useful for these outcomes in particular (and not others) and why they were preferred over ORs for use in the economic model for all-cause discontinuation, including any references from the literature or other appraisals to support the rationale;

In the analysis of safety and tolerability outcomes, the cloglog model was preferred over ORs due to the underlying assumptions in each of these approaches. For the outcomes of TEAE and discontinuation due to AEs, the cumulative probability of an individual having experienced the outcome of interest can only increase over time. For this reason, these outcomes can be described as survival analysis problems: once an individual has experienced at least one TEAE or discontinues, they must necessarily fall into the category of having experienced the event at any future time point. As such, use of the cloglog NMA models, which are survival analysis models that assume a constant hazard and estimate the hazard based on the time period, the number of participants who experience the event, and the total number of participants, is methodologically appropriate.

In contrast, the dichotomous efficacy outcomes of ≥50% or ≥30% reduction in MMDs are not survival analysis problems, as it is possible that a given participant may be a responder at month 4 yet revert to a non-responder at Month 5. This fundamental difference is the justification for using a logit link odds ratio model for these outcomes, since this model type does not maintain any innate relationship to time.

While methodologically appropriate to apply these models dependent on outcome type, the safety and tolerability results presented in Appendix D, which include both OR and HR models, show that comparisons between treatments are similar regardless of the model and thus demonstrate that this distinction has little to no effect for treatment comparisons within the presented data.

b) Explain where the truncation step in the code provided was sourced from, the rationale for this and whether/when it was considered applicable to use for any of the cloglog analyses performed.

Sampling a probability estimate too close to 0 or 1 in the analysis results in numerical overflow and causes WinBUGS to crash and thus provide no usable outputs. Given that the cloglog models are numerically volatile, it was possible that at least one of the treatment probabilities would sample a value too high or too low during the extensive burn-in process (50k burn-ins with 10 thins is effectively 500k iterations, with 3 chains starting at distinct values) prior to the chains converging on a stationary distribution. In the case that the unconstrained model crashed for this reason, a constrained model was used instead. This was performed using a truncation step directly to the probability p with theoretical bounds of [0, 1], sourced from the publication

"Bayesian Modeling Using WinBUGS".[14] The code is provided directly on Page 266 and uses the WinBUGS function 'step' to place artificial boundaries on the probability estimate such that values too close to 0 or 1 cannot be sampled to prevent sampling a value too close to 0 or 1.

In this analysis, the use of a constrained model was found to be necessary in every outcome. The constrained model should not have any practical effect on the estimation of probabilities for models which converge, as the artificially constrained values are unrealistically extreme and will likely not be sampled after burn-in has moved the chains to the stationary distribution.

A numerically simpler but conceptually similar truncation was applied on the hazard ratio nodes when the constrained model was used. The hazard ratio can also cause overflow when converted from the log hazard ratio. The code constrains the acceptable values to [e^-10, e^10], which while unrealistic for any real-world hazard ratio in this context, are not so extreme as to cause numerical overflow when used by a computer with finite precision.

A7. Priority question. In terms of studies included in NMAs, please address the following points that the EAG has noted:

a) **Please ensure that all supplementary references required for the EAG to validate all data included in NMAs (with a breakdown for each study, similar to that provided in response to CQs as part of the CCE process) is provided, as the EAG has been unable to validate some data, for example:**

   i. **for efficacy outcomes in the EM overall mITT population, the EAG could not validate the numbers presented in the NMA Excel sheets compared to the STRIVE [Goadsby 2017] publication provided;**
   ii. **for change from baseline in MMD in the EM overall mITT population, the EAG could not validate the numbers presented in the NMA Excel sheets compared to the EVOLVE-1 and EVOLVE-2 publications (Stauffer 2018 and Skljarevski 2018);**
   iii. **for the 50% MMD reduction data provided for PREEMPT-1 in CM, the EAG could not validate data in the NMA Excel sheet against the data in the excerpt that was provided in response to CQ A13 as part of the CCE;**
   iv. **for the 30% MMD reduction outcome in CM, the EAG could not validate data included for FOCUS and REGAIN in the NMA Excel sheet;**

v. **the EAG could not validate MUD data for PREEMPT-1 in Aurora 2010 – should change from baseline values be -10.4 and -10.3 rather than -5.80 and -5.70, for placebo and botulinum toxin groups, respectively (Table 2 of the publication)? Please ensure this is updated in the relevant NMA and updated NMA files provided.**

As requested, additional detail on the studies used in the NMA are provided in Table 14, with all references provided in the accompanying reference pack.

Table 14: Additional NMA source information

Study	Endpoint	Reference	Specific location within the reference
STRIVE	CFB in MMDs:	Diener *et al.* (2021)[15]	Table 1, Page 3
	≥50% reduction in MMDs:	Goadsby *et al.* (2017)[16]	Table 2, Page 2,127
	CFB in monthly acute MUDs:	Reuter *et al.* (2017)[17]	Figure 1, Page 2
EVOLVE-1	CFB in MMDs:	CADTH Reimbursement Review: Galcanezumab[18]	Table 18, Page 101
EVOLVE-2	CFB in MMDs:	CADTH Reimbursement Review: Galcanezumab[18]	Table 18, Page 101
PREEMPT 1	≥50% reduction in MMDs (Overall):	AbbVie Data on File: PREEMPT 1 CSR Excerpt[19]	Table 14.2-29, Page 513
FOCUS (CM)	≥30% reduction in MMDs:	Ashina *et al.* (2020) [20]	Lines 1-3 of the Results section
REGAIN	≥30% reduction in MMDs (Overall):	Emgality (galcanezumab) EPAR[21]	Table 12, Page 86
PREEMPT 1	CFB in monthly acute MUDs (Overall):	AbbVie Data on File: PREEMPT 1 CSR Excerpt[22, a]	Table 14.2-32, Page 517

Footnote: [a]Aurora *et al.* (2010) refers to "change from baseline in frequency of acute headache pain medication intakes" rather than "acute medication use days".
Abbreviations: CADTH: Canadian Agency for Drugs and Technologies in Health; CM: chronic migraine; CSR: clinical study report; EPAR: European Public Assessment Report; MMD = monthly migraine day;

A8. In the EAG's CCE report, the EAG favoured the FE analysis in the 3+ TF patient population as there was insufficient data in the analyses to appropriately inform the between-study heterogeneity. Could the company explain why it maintains a preference for the RE analysis for the 3+ EM population?

While AbbVie accept that there were insufficient data in the 3+ TF mITT population to inform between-study heterogeneity, this lack of data also makes it unfeasible to determine whether the use of FE or RE would result in better model fit. In light of a lack of sufficient data to assess between-study heterogeneity fully, the use of FE could result in an underestimation of uncertainty associated with treatment comparisons. Additionally, there are notable differences in baseline characteristics across the studies included in the EM 3+ TF mITT analysis, particularly age. This heterogeneity, discussed in further detail in Appendix D.2.4.2 of the CS, justifies a RE approach.

As presented in Appendix D.2.5.3 of the CS, results for the EM 3+ TF population were similar between the RE and FE analyses, supporting that use of RE data as compared with FE data is likely to have minimal impact on the resulting economic analyses.

A9. Please provide the NMA results for CM efficacy outcomes in the 3+ treatment failure subgroup and compare to the overall mITT NMA results in its report. The company previously provided the same analyses as part of the CCE submission earlier this year. Please update the NMAs if any eptinezumab studies are eligible for inclusion. Please provide the NMA files so that they can be validated in addition to details on model fit.

As outlined in Section B.2.2 of the CS, the PROGRESS study did not include a pre-specified 3+ TF subgroup analysis. While the overall mITT population of this study did include a small number of patients with 3+ TF, PROGRESS was not powered to assess efficacy in these patients. Furthermore, this patient subgroup did not feature in the stratification of randomised patients by classes of failed prior preventive treatments, leading to imbalances in key baseline characteristics between treatment arms. While data from the CM 3+TF mITT population were provided as supportive supplementary information during the previous cost-comparison submission, the limitations of this analysis were clearly highlighted within the submission. Therefore, use of data from this post-hoc analysis within an NMA is associated with considerable uncertainty and the results would not be sufficient or appropriate to inform a cost-utility analysis.

Instead, analyses are presented using the larger, overall mITT population which avoids risk of bias associated with post-hoc analyses and allows for all available trial data to be included within the NMA. This analysis provides the most robust estimate of comparative efficacy in terms of strength and balance of evidence in the network and avoids risk of bias while accounting for appropriate study power/stratification. This approach is in line with that taken in the recent NICE appraisal of rimegepant (TA906), in which the overall mITT population from a study that excluded patients with non-response to >2 classes of preventive medication, was considered generalisable to the subgroup with at least three prior preventive treatment failures, and was therefore employed to provide evidence to assess the comparative efficacy of the treatments in the 3+ TF mITT population.[13]

As discussed in further detail in the response to CQ A1 above, eptinezumab is not considered an appropriate comparator as it is not anticipated to be established practice in the NHS at the point of NICE committee decision-making in this appraisal, and given that atogepant is anticipated to be positioned

ahead of eptinezumab within the treatment pathway in typical practice. Therefore, updated NMAs have not been presented in this response.

A10. The EAG notes that the systematic literature review was last updated in September 2022. Given the search is now over a year old, please consider running update searches to assess whether any new studies eligible for inclusion in the NMAs have been published since September 2022. If any new studies are identified, please update NMAs (and provide results, updated NMA files and model fit statistics) and model inputs as appropriate.

A targeted literature review (TLR) has highlighted that no relevant new evidence has been published for the comparators of interest to this submission since the original systematic literature review (SLR) was conducted in September 2022, as outlined below.

Methodology

Electronic database searches for clinical trials and randomised clinical trials in '*migraine'* were conducted on 23rd October 2023 in PubMed. The date range for the search was limited to 1st September 2022 (date of the previous SLR update) to 29th March 2023 (within 6 months of submission, in order to meet the standard requirements for undertaking a literature review per NICE guidance within the available timeframe of the clarification question response period[23]).

Records were screened for inclusion in the TLR through title/abstract screening using the pre-defined Population, Intervention, Comparator, Outcomes, and Study Design (PICOS) eligibility criteria presented in Table 15. The PICOS criteria are largely aligned with the criteria utilised in the SLR detailed in the CS.

Table 15: Inclusion and exclusion criteria

Category	Inclusion criteria	Exclusion criteria
Population	Adult (age ≥18 years) patients with migraine	• Paediatric patients • Healthy volunteers • Primary disease other than EM
Interventions	The following interventions either alone or in combination with other pharmacological intervention used for the preventive treatment of migraine: • CGRP inhibitor therapies: atogepant, eptinezumab, erenumab, fremanezumab, galcanezumab, rimegepant • Botulinum toxin type A	Interventions not on the list
Comparators	• Placebo • BSC (author defined) • Any of the interventions listed above • Any other pharmacological/non-pharmacological interventions	None
Outcomes	• Migraine frequency/migraine day • Headache day • Responder rate (e.g. 50%) • Acute medication use • HRQoL	Studies assessing outcomes not relevant to the review

Category	Inclusion criteria	Exclusion criteria
	• Treatment-related adverse events • Treatment-emergent adverse event • Serious adverse event • Study/treatment discontinuation • Mortality • Subgroup extractions – prior treatments	
Study design	RCTs	• Preclinical studies • Reviews, letters, comments and editorials • Non-RCTs and observational studies • Systematic reviews based on non-RCTs and observational studies
Language	No limit	None

Abbreviations: BSC: best supportive care; CGRP: Calcitonin gene-related peptide; HRQoL: health-related quality of life; RCT: randomised controlled trial.

Results

The electronic database search identified 77 records. Following review of the titles and abstracts, 68 were excluded due to irrelevant population, intervention, outcomes or study design, as detailed in Table 16.

Table 16: Summary of studies excluded from TLR

#	Citation	Reason for exclusion
1	Croop R, Madonia J, Stock DA, Thiry A, Forshaw M, Murphy A, Coric V, Lipton RB. Zavegepant nasal spray for the acute treatment of migraine: A Phase 2/3 double-blind, randomized, placebo-controlled, dose-ranging trial. Headache. 2022 Oct;62(9):1153-1163. doi: 10.1111/head.14389. Epub 2022 Oct 14.	Population
2	Lipton RB, Croop R, Stock DA, Madonia J, Forshaw M, Lovegren M, Mosher L, Coric V, Goadsby PJ. Safety, tolerability, and efficacy of zavegepant 10 mg nasal spray for the acute treatment of migraine in the USA: a phase 3, double-blind, randomised, placebo-controlled multicentre trial. Lancet Neurol. 2023 Mar;22(3):209-217. doi: 10.1016/S1474-4422(22)00517-8.	Population
3	Balci B, Akdal G. Outcome of vestibular rehabilitation in vestibular migraine. J Neurol. 2022 Dec;269(12):6246-6253. doi: 10.1007/s00415-022-11250-4. Epub 2022 Jul 8.	Intervention
4	MacGregor EA, Komori M, Krege JH, Baygani S, Vincent M, Pavlovic J, Igarashi H. Efficacy of lasmiditan for the acute treatment of perimenstrual migraine. Cephalalgia. 2022 Dec;42(14):1467-1475. doi: 10.1177/03331024221118929. Epub 2022 Aug 18.	Population
5	Görür K, Gür H, İsmi O, Özcan C, Vayisoğlu Y. The effectiveness of propranolol, flunarizine, amitriptyline and botulinum toxin in vestibular migraine complaints and prophylaxis: a non-randomized controlled study. Braz J Otorhinolaryngol. 2022 Nov-Dec;88(6):975-981. doi: 10.1016/j.bjorl.2021.02.005. Epub 2021 Mar 7.	Study design
6	Lipton RB, Dodick DW, Goadsby PJ, Burstein R, Adams AM, Lai J, Yu SY, Finnegan M, Kuang AW, Trugman JM. Efficacy of Ubrogepant in the Acute Treatment of Migraine With Mild Pain vs Moderate or Severe Pain. Neurology. 2022 Oct 25;99(17):e1905-e1915. doi: 10.1212/WNL.0000000000201031. Epub 2022 Aug 17.	Population
7	Ailani J, Andrews JS, Tockhorn-Heidenreich A, Wenzel R, Rettiganti M. Effect of Galcanezumab on Total Pain Burden in Patients Who Had Previously Not Benefited from Migraine Preventive Medication (CONQUER Trial): A Post Hoc Analysis. Adv Ther. 2022 Oct;39(10):4544-4555. doi: 10.1007/s12325-022-02233-y. Epub 2022 Aug 5.	Outcome
8	Tepper SJ, Grosberg B, Daniel O, Kuruvilla DE, Vainstein G, Deutsch L, Sharon R. Migraine treatment with external concurrent occipital and trigeminal neurostimulation-A randomized controlled trial. Headache. 2022 Sep;62(8):989-1001. doi: 10.1111/head.14350. Epub 2022 Jun 24.	Intervention
9	Simshäuser K, Pohl R, Behrens P, Schultz C, Lahmann C, Schmidt S. Mindfulness-Based Cognitive Therapy as Migraine Intervention: a Randomized Waitlist Controlled Trial. Int J Behav Med. 2022 Oct;29(5):597-609. doi: 10.1007/s12529-021-10044-8. Epub 2021 Dec 21.	Intervention
10	Ashina H, Iljazi A, Al-Khazali HM, Do TP, Eigenbrodt AK, Larsen EL, Andersen AM, Hansen KJ, Bräuner KB, Chaudhry BA, Christensen CE, Amin FM, Schytz HW. CGRP-induced migraine-like headache in persistent post-traumatic headache attributed to mild traumatic brain injury. J Headache Pain. 2022 Oct 17;23(1):135. doi: 10.1186/s10194-022-01499-5.	Intervention
11	Lovati C, d'Alessandro CM, Ventura SD, Muzio F, Pantoni L. Ketogenic diet in refractory migraine: possible efficacy and role of ketone bodies-a pilot experience. Neurol Sci. 2022 Nov;43(11):6479-6485. doi: 10.1007/s10072-022-06311-5. Epub 2022 Aug 11.	Intervention
12	Butt JH, S Eddelien H, Kruuse C. The headache and aura-inducing effects of sildenafil in patients with migraine with aura. Cephalalgia. 2022 Sep;42(10):984-992. doi: 10.1177/03331024221088998. Epub 2022 Mar 25.	Intervention
13	Feng WX, Tang C, Zhang JP, Li XY, Zhang H. [Heat-sensitive moxibustion for migraine without aura: a randomized controlled trial]. Zhongguo Zhen Jiu. 2023 Aug 12;43(8):921-4. doi: 10.13703/j.0255-2930.20220910-0002.	Intervention
14	Kurt A, Turhan B. Physiotherapy Management of Migraine Pain: Facial Proprioceptive Neuromuscular Facilitation Technique Versus	Intervention

	Connective Tissue Massage. J Craniofac Surg. 2022 Nov-Dec 01;33(8):2328-2332. doi: 10.1097/SCS.0000000000008638. Epub 2022 Mar 10.	
15	Hashimoto Y, Komori M, Tanji Y, Ozeki A, Hirata K. Lasmiditan for single migraine attack in Japanese patients with cardiovascular risk factors: subgroup analysis of a phase 2 randomized placebo-controlled trial. Expert Opin Drug Saf. 2022 Dec;21(12):1495-1503. doi: 10.1080/14740338.2022.2078302. Epub 2022 Jun 24.	Population
16	Schott Andersen AS, Maarbjerg S, Noory N, Heinskou TB, Forman JL, Cruccu G, Ashina M, Bendtsen L. Safety and efficacy of erenumab in patients with trigeminal neuralgia in Denmark: a double-blind, randomised, placebo-controlled, proof-of-concept study. Lancet Neurol. 2022 Nov;21(11):994-1003. doi: 10.1016/S1474-4422(22)00294-0. Epub 2022 Sep 13.	Population
17	Tepper SJ, Rabany L, Cowan RP, Smith TR, Grosberg BM, Torphy BD, Harris D, Vizel M, Ironi A, Stark-Inbar A, Blumenfeld AM. Remote electrical neuromodulation for migraine prevention: A double-blind, randomized, placebo-controlled clinical trial. Headache. 2023 Mar;63(3):377-389. doi: 10.1111/head.14469. Epub 2023 Jan 27.	Intervention
18	Gross EC, Putananickal N, Orsini AL, Schoenen J, Fischer D, Soto-Mota A. Defining metabolic migraine with a distinct subgroup of patients with suboptimal inflammatory and metabolic markers. Sci Rep. 2023 Mar 7;13(1):3787. doi: 10.1038/s41598-023-28499-y.	Intervention
19	Dawood Rahimi M, Taghi Kheirkhah M, Salehi Fadardi J. Efficacy of tDCS in chronic migraine: A multiprotocol randomized controlled trial. Clin Neurophysiol. 2023 Jun;150:119-130. doi: 10.1016/j.clinph.2023.03.013. Epub 2023 Mar 31.	Intervention
20	Klan T, Gaul C, Liesering-Latta E, Witthöft M, Hennemann S. Behavioral treatment for migraine prophylaxis in adults: Moderator analysis of a randomized controlled trial. Cephalalgia. 2023 Jun;43(6):3331024231178237. doi: 10.1177/03331024231178237.	Intervention
21	Kudrow D, Nguyen L, Semler J, Stroud C, Samaan K, Hoban DB, Wietecha L, Hsu HA, Pearlman E. A phase IV clinical trial of gastrointestinal motility in adult patients with migraine before and after initiation of a calcitonin gene-related peptide ligand (galcanezumab) or receptor (erenumab) antagonist. Headache. 2022 Oct;62(9):1164-1176. doi: 10.1111/head.14390. Epub 2022 Sep 16.	Outcome
22	De Icco R, Vaghi G, Allena M, Ghiotto N, Guaschino E, Martinelli D, Ahmad L, Corrado M, Bighiani F, Tanganelli F, Bottiroli S, Cammarota F, Sances G, Tassorelli C. Does MIDAS reduction at 3 months predict the outcome of erenumab treatment? A real-world, open-label trial. J Headache Pain. 2022 Sep 17;23(1):123. doi: 10.1186/s10194-022-01480-2.	Study design
23	Absher JR. In migraine with previous treatment failures, eptinezumab safely reduced migraine days at 1 to 12 wk. Ann Intern Med. 2022 Oct;175(10):JC117. doi: 10.7326/J22-0077. Epub 2022 Oct 4.	Study design
24	Takeshima T, Komori M, Tanji Y, Ozeki A, Tatsuoka Y. Efficacy of Lasmiditan Across Patient and Migraine Characteristics in Japanese Patients with Migraine: A Secondary Analysis of the MONONOFU Trial. Adv Ther. 2022 Nov;39(11):5274-5288. doi: 10.1007/s12325-022-02304-0. Epub 2022 Sep 22.	Population
25	Mahon R, Vo P, Pannagl K, Tiwari S, Heemstra H, Ferraris M, Zhao J, Betts KA, Proot P. Assessment of the relative effectiveness of erenumab compared with onabotulinumtoxinA for the prevention of chronic migraine. Curr Med Res Opin. 2023 Jan;39(1):105-112. doi: 10.1080/03007995.2022.2131299. Epub 2022 Oct 13.	Study design
26	Yan C, Li H, Wang C, Yu H, Guo T, Wan L, Yundan P, Wang L, Fang W. Frequency and Size of In Situ Thrombus Within Patent Foramen Ovale. Stroke. 2023 May;54(5):1205-1213. doi: 10.1161/STROKEAHA.122.041524. Epub 2023 Mar 9.	Intervention
27	Bernar B, Gande N, Stock AK, Staudt A, Pechlaner R, Hochmayr C, Kaltseis K, Winder B, Kiechl SJJ, Broessner G, Geiger R, Kiechl S; Early Vascular Ageing (EVA) Tyrol Study Group; Kiechl-Kohlendorfer U, Knoflach M. Early Vascular Ageing in adolescents with migraine with aura: a community-based study. BMC Cardiovasc Disord. 2023 Aug 1;23(1):384. doi: 10.1186/s12872-023-03409-2.	Intervention
28	Li W, Liu R, Liu W, Li G, Chen C. The effect of topiramate versus flunarizine on the non-headache symptoms of migraine. Int J Neurosci. 2023 Jan;133(1):19-25. doi: 10.1080/00207454.2021.1881091. Epub 2021 Feb 10.	Intervention

29	Mo H, Kim BK, Moon HS, Cho SJ. Real-world experience with 240 mg of galcanezumab for the preventive treatment of cluster headache. J Headache Pain. 2022 Oct 8;23(1):132. doi: 10.1186/s10194-022-01505-w.	Population
30	Pozo-Rosich P, Dodick DW, Ettrup A, Hirman J, Cady R. Shift in diagnostic classification of migraine after initiation of preventive treatment with eptinezumab: post hoc analysis of the PROMISE studies. BMC Neurol. 2022 Oct 25;22(1):394. doi: 10.1186/s12883-022-02914-9.	Study design
31	Hirata K, Matsumori Y, Tanji Y, Khanna R, Ozeki A, Komori M. Safety profile of lasmiditan in patients with migraine in an Asian population. Expert Opin Drug Saf. 2023 Jan;22(1):91-101. doi: 10.1080/14740338.2022.2087630. Epub 2022 Jul 12.	Population
32	Geng B, Clark K, Evangelista M, Wolford E. Low rates of headache and migraine associated with intravenous immunoglobulin infusion using a 15-minute rate escalation protocol in 123 patients with primary immunodeficiency. Front Immunol. 2023 Feb 2;13:1075527. doi: 10.3389/fimmu.2022.1075527. eCollection 2022.	Intervention
33	Pohl H, Sandor PS, Moisa M, Ruff CC, Schoenen J, Luechinger R, O'Gorman R, Riederer F, Gantenbein AR, Michels L. Occipital transcranial direct current stimulation in episodic migraine patients: effect on cerebral perfusion. Sci Rep. 2023 Aug 25;13(1):13944. doi: 10.1038/s41598-023-39659-5.	Intervention
34	Geppetti P, De Cesaris F, Benemei S, Cortelli P, Cevoli S, Pierangeli G, Favoni V, Lisotto C, Usai S, Frediani F, Di Fiore P, D'Arrigo G, Tassorelli C, Sances G, Cainazzo MM, Baraldi C, Sarchielli P, Corbelli I, De Vanna G, Tedeschi G, Russo A; Italian 17I-DCsc09 Study Team. Self-administered subcutaneous diclofenac sodium in acute migraine attack: A randomized, double-blind, placebo-controlled dose-finding pilot study. Cephalalgia. 2022 Sep;42(10):1058-1070. doi: 10.1177/03331024221093712. Epub 2022 Apr 26.	Population
35	Adeeb Sheet D, Bibani RH, Kheder AH. Comparison of the Effect of Propranolol Combination with Cinnarizine and Propranolol in the Prevention of Acute Migraine Attacks. Cell Mol Biol (Noisy-le-grand). 2022 Nov 30;68(11):37-42. doi: 10.14715/cmb/2022.68.11.7.	Intervention
36	Xu X, Zhou M, Wu X, Zhao F, Luo X, Li K, Zeng Q, He J, Cheng H, Guan X, Huang P, Zhang M, Liu K. Increased iron deposition in nucleus accumbens associated with disease progression and chronicity in migraine. BMC Med. 2023 Apr 7;21(1):136. doi: 10.1186/s12916-023-02855-1.	Intervention
37	Ehrlich M, Hentschke C, Sieder C, Maier-Peuschel M, Reuter U. Erenumab versus topiramate: post hoc efficacy analysis from the HER-MES study. J Headache Pain. 2022 Nov 15;23(1):141. doi: 10.1186/s10194-022-01511-y.	Intervention not relevant
38	Gibler RC, Peugh JL, Coffey CS, Chamberlin LA, Ecklund D, Klingner E, Yankey J, Korbee LL, Kabbouche M, Kacperski J, Porter LL, Reidy BL, Hershey AD, Powers SW. Impact of preventive pill-based treatment on migraine days: A secondary outcome study of the Childhood and Adolescent Migraine Prevention (CHAMP) trial and a comparison of self-report to nosology-derived assessments. Headache. 2023 Jun;63(6):805-812. doi: 10.1111/head.14474. Epub 2023 Feb 9.	Population
39	Pijpers JA, Kies DA, van Zwet EW, de Boer I, Terwindt GM. Cutaneous allodynia as predictor for treatment response in chronic migraine: a cohort study. J Headache Pain. 2023 Aug 30;24(1):118. doi: 10.1186/s10194-023-01651-9.	Intervention
40	Aksu S, Şirin TC, Hasırcı Bayır BR, Ulukan Ç, Soyata AZ, Kurt A, Karamürsel S, Baykan B. Long-Term Prophylactic Transcranial Direct Current Stimulation Ameliorates Allodynia and Improves Clinical Outcomes in Individuals With Migraine. Neuromodulation. 2023 Jun;26(4):778-787. doi: 10.1016/j.neurom.2022.06.007. Epub 2022 Aug 12.	Intervention
41	Mykland MS, Uglem M, Stovner LJ, Brenner E, Snoen MS, Gravdahl GB, Sand T, Omland PM. Insufficient sleep may alter cortical excitability near the migraine attack: A blinded TMS crossover study. Cephalalgia. 2023 Mar;43(3):3331024221148391. doi: 10.1177/03331024221148391.	Intervention
42	Vandenbussche N, Van Hee C, Hoste V, Paemeleire K. Using natural language processing to automatically classify written self-reported narratives by patients with migraine or cluster headache. J Headache Pain. 2022 Sep 30;23(1):129. doi: 10.1186/s10194-022-01490-0.	Intervention

43	Barbanti P, Goadsby PJ, Lambru G, Ettrup A, Christoffersen CL, Josiassen MK, Phul R, Sperling B. Effects of eptinezumab on self-reported work productivity in adults with migraine and prior preventive treatment failure in the randomized, double-blind, placebo-controlled DELIVER study. J Headache Pain. 2022 Dec 2;23(1):153. doi: 10.1186/s10194-022-01521-w.	Outcome
44	Schwedt TJ, Nikolova S, Dumkrieger G, Li J, Wu T, Chong CD. Longitudinal changes in functional connectivity and pain-induced brain activations in patients with migraine: a functional MRI study pre- and post- treatment with Erenumab. J Headache Pain. 2022 Dec 14;23(1):159. doi: 10.1186/s10194-022-01526-5.	Study design
45	Cowan R, Stark-Inbar A, Rabany L, Harris D, Vizel M, Ironi A, Vieira JR, Galen M, Treppendahl C. Clinical benefits and economic cost-savings of remote electrical neuromodulation (REN) for migraine prevention. J Med Econ. 2023 Jan-Dec;26(1):656-664. doi: 10.1080/13696998.2023.2205751.	Intervention
46	Xie YJ, Tian L, Hui SS, Qin J, Gao Y, Zhang D, Ma T, Suen LKP, Wang HH, Liu ZM, Hao C, Yang L, Loke AY. Efficacy and feasibility of a 12-week Tai Chi training for the prophylaxis of episodic migraine in Hong Kong Chinese women: A randomized controlled trial. Front Public Health. 2022 Dec 13;10:1000594. doi: 10.3389/fpubh.2022.1000594. eCollection 2022.	Intervention
47	Arab A, Khorvash F, Kazemi M, Heidari Z, Askari G. Effects of the Dietary Approaches to Stop Hypertension (DASH) diet on clinical, quality of life and mental health outcomes in women with migraine: a randomised controlled trial. Br J Nutr. 2022 Oct 28;128(8):1535-1544. doi: 10.1017/S000711452100444X. Epub 2021 Nov 12.	Intervention
48	Thuraiaiyah J, Al-Karagholi MA, Elbahi FA, Zhuang ZA, Ashina M. Adenosine causes short-lasting vasodilation and headache but not migraine attacks in migraine patients: a randomized clinical trial. Pain. 2023 May 1;164(5):1118-1127. doi: 10.1097/j.pain.0000000000002804. Epub 2022 Oct 17.	Intervention
49	Sedighiyan M, Jafari E, Athar SS, Yekaninejad MS, Alvandi E, Abdolahi M, Djalali M. The Effects of Nano-curcumin Supplementation on Leptin and Adiponectin in Migraine Patients: A Double-blind Clinical Trial Study from Gene Expression to Clinical Symptoms. Endocr Metab Immune Disord Drug Targets. 2023;23(5):711-720. doi: 10.2174/1871530322666220701100817.	Intervention
50	Arab A, Khorvash F, Karimi E, Heidari Z, Askari G. The effects of the dietary approaches to stop hypertension (DASH) diet on oxidative stress and clinical indices of migraine patients: a randomized controlled trial. Nutr Neurosci. 2022 Nov;25(11):2259-2268. doi: 10.1080/1028415X.2021.1954294. Epub 2021 Jul 16.	Intervention
51	Ashina M, Roos C, Li LQ, Komori M, Ayer D, Ruff D, Krege JH. Long-term treatment with lasmiditan in patients with migraine: Results from the open-label extension of the CENTURION randomized trial. Cephalalgia. 2023 Apr;43(4):3331024231161745. doi: 10.1177/03331024231161745.	Population
52	Grazzi L, Raggi A, Guastafierro E, Passavanti M, Marcassoli A, Montisano DA, D'Amico D. A Preliminary Analysis on the Feasibility and Short-Term Efficacy of a Phase-III RCT on Mindfulness Added to Treatment as Usual for Patients with Chronic Migraine and Medication Overuse Headache. Int J Environ Res Public Health. 2022 Oct 29;19(21):14116. doi: 10.3390/ijerph192114116.	Intervention
53	Toprak Celenay S, Coban O, Mete O, Karahan N. An investigation of the effects of connective tissue massage in women with migraine: A controlled clinical trial. J Bodyw Mov Ther. 2023 Jan;33:112-119. doi: 10.1016/j.jbmt.2022.09.008. Epub 2022 Sep 23.	Intervention
54	Blumenfeld AM, Boinpally R, De Abreu Ferreira R, Trugman JM, Dabruzzo B, Ailani J, Lipton RB. Phase Ib, open-label, fixed-sequence, drug-drug interaction, safety, and tolerability study between atogepant and ubrogepant in participants with a history of migraine. Headache. 2023 Mar;63(3):322-332. doi: 10.1111/head.14433. Epub 2023 Jan 5.	Study design
55	Malek EM, Navalta JW, McGinnis GR. Time of Day and Chronotype-Dependent Synchrony Effects Exercise-Induced Reduction in Migraine Load: A Pilot Cross-Over Randomized Trial. Int J Environ Res Public Health. 2023 Jan 23;20(3):2083. doi: 10.3390/ijerph20032083.	Intervention
56	Viganò A, Toscano M, Petolicchio B, Bianchi A, Cabrini DM, Di Piero V. Letter to the editor regarding "Efficacy and tolerability of	Study Design

	combination treatment of topiramate and greater occipital nerve block versus topiramate monotherapy for the preventive treatment of chronic migraine: A randomized controlled trial". Cephalalgia. 2022 Nov;42(13):1443-1444. doi: 10.1177/03331024221111528. Epub 2022 Jul 3.	
57	Chowdhury D, Tomar A, Deorari V, Duggal A, Krishnan A, Koul A. Greater occipital nerve blockade for the preventive treatment of chronic migraine: A randomized double-blind placebo-controlled study. Cephalalgia. 2023 Feb;43(2):3331024221143541. doi: 10.1177/03331024221143541.	Intervention
58	Ford JH, Ye W, Ayer DW, Mi X, Bhandari S, Buse DC, Lipton RB. Validation and meaningful within-patient change in work productivity and activity impairment questionnaire (WPAI) for episodic or chronic migraine. J Patient Rep Outcomes. 2023 Apr 4;7(1):34. doi: 10.1186/s41687-023-00552-4.	Intervention
59	Varnado OJ, Ye W, Mi X, Burge R, Hall J. Annual indirect costs savings in patients with episodic or chronic migraine: a post-hoc analysis of phase 3 galcanezumab clinical trials in the United States. J Med Econ. 2023 Jan-Dec;26(1):149-157. doi: 10.1080/13696998.2023.2165365.	Study design
60	Keerthana D, Mishra D, Chauhan MK, Juneja M. Effect of Propranolol Prophylaxis on Headache Frequency in Children with Migraine Without Aura: A Randomized, Double-Blind, Placebo-Controlled Trial. Indian J Pediatr. 2023 Sep;90(9):880-885. doi: 10.1007/s12098-022-04279-w. Epub 2022 Jul 22.	Intervention
61	Yonker ME, McVige J, Zeitlin L, Visser H. A multicenter, randomized, double-blind, placebo-controlled, crossover trial to evaluate the efficacy and safety of zolmitriptan nasal spray for the acute treatment of migraine in patients aged 6 to 11 years, with an open-label extension. Headache. 2022 Oct;62(9):1207-1217. doi: 10.1111/head.14391.	Intervention
62	Mykland MS, Uglem M, Bjørk MH, Matre D, Sand T, Omland PM. Effects of insufficient sleep on sensorimotor processing in migraine: A randomised, blinded crossover study of event related beta oscillations. Cephalalgia. 2023 Mar;43(3):3331024221148398. doi: 10.1177/03331024221148398.	Intervention
63	Ashina S, Melo-Carrillo A, Szabo E, Borsook D, Burstein R. Pre-treatment non-ictal cephalic allodynia identifies responders to prophylactic treatment of chronic and episodic migraine patients with galcanezumab: A prospective quantitative sensory testing study (NCT04271202). Cephalalgia. 2023 Mar;43(3):3331024221147881. doi: 10.1177/03331024221147881.	Outcome
64	Meise R, Carvalho GF, Thiel C, Luedtke K. Additional effects of pain neuroscience education combined with physiotherapy on the headache frequency of adult patients with migraine: A randomized controlled trial. Cephalalgia. 2023 Feb;43(2):3331024221144781. doi: 10.1177/03331024221144781.	Intervention
65	Alipouri M, Amiri E, Hoseini R, Hezarkhani LA. Effects of eight weeks of aerobic exercise and vitamin D supplementation on psychiatric comorbidities in men with migraine and vitamin D insufficiency: A randomized controlled clinical trial. J Affect Disord. 2023 Aug 1;334:12-20. doi: 10.1016/j.jad.2023.04.108. Epub 2023 May 3.	Intervention
66	Djalali M, Abdolahi M, Hosseini R, Miraghajani M, Mohammadi H, Djalali M. The effects of nano-curcumin supplementation on Th2/tregulatory axis in migraine patients: a randomized, double-blind, placebo-controlled trial. Int J Neurosci. 2023 Feb;133(2):169-175. doi: 10.1080/00207454.2021.1897587. Epub 2021 Mar 16.	Intervention
67	Lipton RB, Buse DC, Sandoe CH, Ford JH, Hand AL, Jedynak JP, Port MD, Detke HC. Changes in migraine interictal burden following treatment with galcanezumab: Results from a phase III randomized, placebo-controlled study. Headache. 2023 May;63(5):683-691. doi: 10.1111/head.14460. Epub 2023 Feb 16.	Outcome
68	Kudrow D, Dafer R, Dodick DW, Starling A, Ailani J, Dougherty C, Kalidas K, Zhang F, Jeswani R, Patel N, Khodavirdi AC. Evaluation of vascular risk in patients with migraine with and without aura treated with erenumab: Post hoc analysis of pooled long-term clinical trial data. Headache. 2023 Mar;63(3):418-428. doi: 10.1111/head.14485.	Outcome

Following these exclusions, nine studies remained:

- McAllister P, Kudrow D, Cady R, Hirman J, Ettrup A. Reduction in migraine-associated burden after eptinezumab treatment in patients with chronic migraine. Cephalalgia. 2022 Sep;42(10):1005-1012. doi: 10.1177/03331024221089567. Epub 2022 Mar 25.
- Cowan RP, Marmura MJ, Diener HC, Starling AJ, Schim J, Hirman J, Brevig T, Cady R. Quantity changes in acute headache medication use among patients with chronic migraine treated with eptinezumab: subanalysis of the PROMISE-2 study. J Headache Pain. 2022 Sep 6;23(1):115. doi: 10.1186/s10194-022-01482-0.
- Lipton RB, Pozo-Rosich P, Blumenfeld AM, Li Y, Severt L, Stokes JT, Creutz L, Gandhi P, Dodick D. Effect of Atogepant for Preventive Migraine Treatment on Patient-Reported Outcomes in the Randomized, Double-blind, Phase 3 ADVANCE Trial. Neurology. 2023 Feb 21;100(8):e764-e777. doi: 10.1212/WNL.0000000000201568. Epub 2022 Nov 17.
- Yu S, Kim BK, Wang H, Zhou J, Wan Q, Yu T, Lian Y, Arkuszewski M, Ecochard L, Wen S, Yin F, Li Z, Su W, Wang SJ. A phase 3, randomised, placebo-controlled study of erenumab for the prevention of chronic migraine in patients from Asia: the DRAGON study. J Headache Pain. 2022 Nov 21;23(1):146. doi: 10.1186/s10194-022-01514-9.
- Powell LC, L'Italien G, Popoff E, Johnston K, O'Sullivan F, Harris L, Croop R, Coric V, Lipton RB. Health State Utility Mapping of Rimegepant for the Preventive Treatment of Migraine: Double-Blind Treatment Phase and Open Label Extension (BHV3000-305). Adv Ther. 2023 Feb;40(2):585-600. doi: 10.1007/s12325-022-02369-x. Epub 2022 Nov 22.
- Goadsby PJ, Barbanti P, Lambru G, Ettrup A, Christoffersen CL, Josiassen MK, Phul R, Sperling B. Eptinezumab improved patient-reported outcomes and quality of life in patients with migraine and prior preventive treatment failures. Eur J Neurol. 2023 Apr;30(4):1089-1098. doi: 10.1111/ene.15670. Epub 2023 Jan 21.
- Starling AJ, Cowan RP, Buse DC, Diener HC, Marmura MJ, Hirman J, Brevig T, Cady R. Eptinezumab improved patient-reported outcomes in patients with migraine and medication-overuse headache: Subgroup analysis of the randomized PROMISE-2 trial. Headache. 2023 Feb;63(2):264-274. doi: 10.1111/head.14434. Epub 2023 Jan 12.
- Ashina M, Tepper SJ, Reuter U, Blumenfeld AM, Hutchinson S, Xia J, Miceli R, Severt L, Finnegan M, Trugman JM. Once-daily oral atogepant for the long-term preventive treatment of migraine: Findings from a multicenter, randomized, open-label, phase 3 trial. Headache. 2023 Jan;63(1):79-88. doi: 10.1111/head.14439. Epub 2023 Jan 18.
- Li Y, Wang X, Ballesteros-Perez A, Bertz R, Lu Z. Pharmacokinetics and Safety of Single and Multiple Daily Dosing of 75-mg Rimegepant Orally Disintegrating Tablets in Healthy Chinese Adults: A Randomized Placebo-Controlled Trial. Clin Pharmacol Drug Dev. 2023 Jun;12(6):594-601. doi: 10.1002/cpdd.1230. Epub 2023 Feb 20.

These studies were further considered, but none were deemed to be relevant for inclusion within the NMAs, for the following reasons:

- All atogepant data that has been published since the last SLR update was captured within the unpublished CSRs for ADVANCE, ELEVATE, PROGRESS and CGP-MD-01 that were included within the previous SLR update. As such, Lipton *et al.* (2022) and Ashina *et al.* (2023) were excluded as the data they present are already included within the reported evidence base.

- In line with the reasoning detailed in the response to Question A1, rimegepant and eptinezumab are not considered relevant comparators for this appraisal. Studies investigating the efficacy and safety of rimegepant and eptinezumab (Li *et al.* [2023], Starling *et al.* [2023], Goadsby *et al.* [2023], Powell *et al.* [2022], Cowan *et al.* [2022] and McAllister *et al.* [2022]) were therefore not considered relevant for inclusion.
- The DRAGON study detailed in Yu *et al.* (2022) investigated the efficacy and safety of the 70 mg dose of erenumab among patients with chronic migraine. As this dose is not recommended by NICE, the study was not considered relevant for inclusion within the NMA.

Additionally, the AbbVie Medical team are not aware of any additional relevant data in outcomes informing the NMAs and the economic model that have been presented at headache and migraine conferences since 2022.

Overall, the TLR demonstrates that there no relevant studies that have been published since the last SLR update was run and as such, the NMA has not been updated.

A11. Please confirm that model fit statistics for the NMAs that include botulinum toxin (Section O.1 of the CS appendices) are those presented in Table 24 of the CS and Table 25 of the CS appendices.

The company can confirm that the model fit statistics for the NMA results for botulinum toxin type A are those presented in Table 24 of Document B of the CS (for NMAs without baseline-risk adjustment) and Table 25 of the appendices of the CS (for NMAs with baseline-risk adjustment).

A12. Regarding the various types of NMAs performed, please can the company confirm:

a) Why no baseline risk adjusted analyses were performed for HRQoL NMAs?

b) Why no baseline risk adjusted analyses of cloglog models for TEAE NMAs were performed?

c) Why baseline risk adjusted analyses of logit analyses for TEAE NMAs were not performed?

NMA data for these endpoints were not included within the cost-effectiveness model, so any additional analyses would not have an impact on the cost-effectiveness results. Therefore, baseline-risk adjusted analyses were not run for these endpoints. However, baseline risk adjusted analyses were conducted for efficacy measures of MMDs because efficacy outcomes such as MMDs are more heterogeneous in definition and investigator assessment, as already mentioned above and as acknowledged by the EAG in the rimegepant appraisal (TA906).[13] Therefore, these outcomes are more likely to be affected by baseline risk than TEAEs and standardised HRQoL measures, which are generally consistently defined across RCTs.

Other analyses

A13. Priority question. The EAG notes that page 82 of the CS describes placebo meta-analyses performed, with some suggestion of their use in the economic model for calculating atogepant absolute effects. However, there is limited further mention of this in the CS. Please can the company:

a) **Clarify exactly how they were used (e.g. were the absolute probability of response values presented in Tables 41 and 42 of the CS calculated using these)?**

b) **Provide the relevant meta-analysis results, files (so that they can be validated) and a description of the methods, including studies included and model fit statistics.**

AbbVie confirm that any suggestion of the use of placebo meta-analyses in the economic model for calculating atogepant absolute effects in the CS was inadvertent. The placebo meta-analyses performed were ultimately not required to produce the NMA data that informed the economic model: the modelling approach used in the CS employed trial results for the reference treatment (atogepant 60 mg), while applying contrasts from the NMA.

Absolute probabilities of response as presented in Table 41 and 42 of the CS were calculated as follows. First, the absolute odds of response (≥50%/≥30% reduction in mean MMDs) for atogepant was derived from the trial based on the absolute probabilities of responders and non-responders, according to the following formula:

$$\text{odds}_{ATO} = \frac{p_{ATO}}{1 - p_{ATO}}$$

The log odds of response for each treatment were then derived from the sum of the estimates derived from the relevant atogepant trials and relative treatment effects from the NMA (i.e., ORs for each treatment versus atogepant):

$$\log(\text{odds}_{TRT}) = \log(\text{odds}_{ATO}) + \log(\text{OR}_{\text{TRT}})$$

This formula may then be rearranged to give the probability of experiencing response for each treatment, which was applied in the model:

$$p_{TRT} = \frac{\text{odds}_{TRT}}{1 + \text{odds}_{TRT}}$$

As their relevance to the economic model is limited, AbbVie have presented a set of R scripts and NMA inputs for a representative selection of endpoints in the accompanying reference pack ('CQ 4&13_NMA Input and Code' and 'CQ 13_ HRQoL NMA Input').

Section B: Clarification on cost-effectiveness data

Treatment pathway

B1. The company states, “patients with CM receiving botulinum toxin type A is expected to decline considerably following the introduction of CGRP mAbs and oral CGRP inhibitors”. However, the company have access to market share data and CGRP mAbs have been approved since 2018, is there any evidence available in the company data showing a pronounced decline in use?

Botulinum toxin type A is undergoing a pronounced decline in usage for the preventive treatment of chronic migraine following the introduction of CGRP mAbs

In line with extensive waiting lists and NHS capacity issues which limit access to botulinum toxin type A, a pronounced decline in the use of botulinum toxin type A for the prevention of migraine is evident following the introduction of self-administered CGRP mAbs. Clarivate™ migraine prophylaxis forecast data (2020–2030) indicates that botulinum toxin type A usage has been decreasing among patients eligible for NICE-recommended fourth-line treatments (i.e. in whom ≥3 preventive treatments has failed). After adjustment to account for patients receiving best supportive care (BSC), botulinum toxin type A market share is forecast to fall from [redacted]% of fourth-line eligible chronic migraine patients in 2020, to [redacted]% in 2023, to [redacted]% by 2025, and [redacted]% by 2030 (inclusive of both incident and prevalent fourth-line patients with chronic migraine, assuming that 70% are receiving BSC in line with assumptions made within the fremanezumab resource impact template).[1, 24]

Most new patients entering the fourth-line preventive setting are initiated on a CGRP mAb

Clinical experts have further confirmed that there has been a pronounced decline in the use of botulinum toxin type A within the NHS; with most new patients entering the fourth-line setting now receiving a CGRP mAb. Headache specialists consulted by AbbVie estimated that between 70–80% of new fourth-line patients are receiving a CGRP mAb in their respective centres. Furthermore, these observations are supported by in-hospital pharmacy dispensing data collected by IQVIA™; which indicates that between H2 2022 and H1 2023, erenumab, fremanezumab, and galcanezumab accounted for [redacted]% of new (i.e. incident) fourth-line patients receiving treatment with a subcutaneous CGRP mAb or botulinum toxin type A across the UK.[1]

NMA data used in the economic model

B2. Priority question. Please could the equivalent response rates in Table 41 of the CS be provided when the ORs from the overall mITT population for EM (Table 27 of the CS appendices - RE without baseline adjustment) are considered.

The probability of 50% response for each treatment, based on NMA data for the overall mITT population in EM (unadjusted; random-effects model applied) is presented in Table 17.

Table 17: Probability of ≥50% response in MMDs across the 12-week treatment period for atogepant and relevant comparators in EM (overall mITT population, unadjusted; RE model)

	RE (without baseline-risk adjustment)	
	OR (95% CrI)	Probability response
Atogepant 60 mg QD (reference)	[redacted]	[redacted]
Galcanezumab 120 mg QM[a]	[redacted]	[redacted]
Erenumab 140 mg QM	[redacted]	[redacted]
Fremanezumab 225 mg Q3M[b]	[redacted]	[redacted]
Fremanezumab 675 mg Q3M	[redacted]	[redacted]

Footnotes: [a]Galcanezumab regimen is a 240 mg loading dose followed by 120 mg once a month.
[b]Fremanezumab regimen is 675 mg initial dose followed by 225 mg once a month.
Abbreviations: CrI: credible interval; EM: episodic migraine; MMDs: monthly migraine days; OR: odds ratio; QD: every day; QM: every month; Q3M: every three months; RE: random effects.

B3. Priority question. The EAG notes that the HRs presented in Table 40 of the CS for discontinuation do not align (when inverted) with the RE NMA results presented in Table 27 of the CS for EM and CM, which the EAG understands presents the company's preferred NMAs for this outcome. Please ensure that this is corrected where required or clarify where the inverted HRs in Table 40 were obtained from.

The EAG are correct in noting a discrepancy between Table 27 and Table 40 of the CS. AbbVie can confirm that Table 27 in the CS presents the correct values, whereas the values presented in CS Table 40 are incorrect.

In addition, a small number of input errors elsewhere in the NMA data that informed the economic model have been identified. These errors relate to the upper and lower bounds associated with point estimates informing the model; it is important to note that while the point estimates inform the model, the upper and lower bounds do not and so these errors will not have affected the cost-effectiveness results. For completeness, these have been amended in the updated version of the model, with all changes from the version accompanying the CS highlighted in green.

AbbVie apologise for these errors and present a corrected version of CS Table 40 below (Table 18). The corrected NMA inputs and code are provided within the reference pack.

Table 18: Probability of discontinuation before response assessment for atogepant and relevant comparators in EM and CM

	EM		CM	
	HR (95% CrI)	Probability of disc.	HR (95% CrI)	Probability of disc.
Atogepant 60 mg QD (reference)	-	[redacted]	-	[redacted]
Galcanezumab 120 mg QM[a]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg QM	[redacted]	[redacted]	[redacted]	[redacted]

Fremanezumab 225 mg Q3M[b]	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 675 mg Q3M	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a]Galcanezumab regimen is a 240 mg loading dose followed by 120 mg once a month. [b]Fremanezumab regimen is 675 mg initial dose followed by 225 mg once a month.
Abbreviations: CM: chronic migraine; CrI: credible interval; disc.: discontinuation; EM: episodic migraine; HR: hazard ratio; QD: every day; QM: every month; Q3M: every three months;

Given that incorrect values previously presented in CS Table 40 were included within the cost-effectiveness model (CEM), their correction to align with CS Table 27 means all base case and scenario results previously presented need to be updated. The corrected results for base case and scenario analyses previously presented in Section B.3.11.3 of the CS are presented in Appendix A and Appendix B below. These results demonstrate that this error had a minimal impact on cost-effectiveness results and no impact on the conclusions of the analysis.

B4. Priority question. The EAG notes that the data presented in Table 44 of the CS does not appear aligned with Table 26 of the appendix: 95% credible intervals (CrI) for median CFB for EM appears to have been converted incorrectly, resulting in certain CFB values lying outside of the upper and lower CrI. Please ensure that this is corrected where required or clarify how the values were obtained.

The values shown in Table 44 of the CS reflect the data used in the model. However, the lower bounds of the credible intervals associated with median CFB values presented for EM (RE) were incorrectly converted, and therefore were not aligned with the correct values presented in Table 26 of the CS appendices.

A corrected version of CS Table 44 is provided below (Table 19). AbbVie apologise for this error, and can confirm that when incorporated into the CEM, this change does not have any impact on the cost-effectiveness results presented in the CS. Similarly, as NMA data were not varied in the probabilistic sensitivity analysis, these amended credible intervals would not affect associated probabilistic results.

Table 19: Change from baseline in mean MMDs across the 12-week treatment period to atogepant and relevant comparators in EM and CM

	EM (RE; unadjusted)		CM (RE; unadjusted)	
	Median CFB (95% CrI)	Mean MMDs	Median CFB (95% CrI)	Mean MMDs
Atogepant 60 mg QD (reference)	[redacted]	[redacted]	[redacted]	[redacted]
Galcanezumab 120 mg QM[a]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg QM	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 225 mg Q3M[b]	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 675 mg Q3M	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a]Galcanezumab regimen is a 240 mg loading dose followed by 120 mg once a month. [b]Fremanezumab regimen is 675 mg initial dose followed by 225 mg once a month.
Abbreviations: EM: episodic migraine; CM: chronic migraine; CFB: change from baseline; CrI: credible interval; EM: episodic migraine; MMDs: monthly migraine days; QD: once daily; QM: every month; Q3M: every three months; RE: random effects.

B5. Priority question. The EAG notes that data for some outcomes were not available for erenumab (i.e. ≥30% MMD reduction in CM overall and change from baseline in acute MUDs in EM 3+) and botulinum toxin (i.e. ≥30% MMD reduction in CM overall), but that inputs for the economic model have been obtained (e.g. in Tables 42 and 46 of the CS). The EAG notes that a conversion factor is described in Table 67 of the CS. Please can the company:

a) Confirm if these were the only three cases where a conversion factor was required for inclusion in the economic model;

The company can confirm that the three cases noted were the only instances in which a conversion factor was required.

b) Provide more details about the conversion factor used in each case, including the rationale, methodology and calculation.

In the absence of available data informing the proportion of patients who achieved a given reduction in MMDs (e.g., erenumab for ≥30% MMD reduction in CM overall), a conversion factor was used to convert available data for one threshold (e.g., erenumab for ≥50% MMD reduction in CM overall) to the other based on the relative treatment effect of the intervention compared to all other comparators. This methodology is in line with that employed in the prior NICE appraisal of fremanezumab (TA764) and eptinezumab (TA871), respectively.[25, 26]

For each case in which a conversion factor was used, the methodology and calculation was as follows:

- Ratios between the treatment in question and other treatments were calculated for the outcome in which data were available
- These ratios were applied to the known values in other treatments for the outcome in which data were not available for the treatment in question to produce a series of values
- The average of these values was used as a proxy input for the missing value of the treatment in question

For example, ratios of the response achieved by patients in the CM overall population treated with erenumab for ≥50% MMD reduction as compared to other treatments would be calculated. These ratios would then be applied to the respective responses achieved for ≥30% MMD reduction for each treatment, producing a series of values, the average of which was used as a proxy input for response achieved by patients in the CM overall population treated with erenumab for ≥30% MMD reduction.

Response and discontinuation

B6. Priority question. Discontinuation due to non-response and discontinuation prior to the assessment timepoint is higher in EM. Clinical experts have advised this is likely to be due to the higher severity of CM, resulting in patients being less likely to discontinue a treatment that is improving their condition, even if they experience adverse events. Given this, the assumption that long term discontinuation is the same in CM and EM would appear to be unlikely. Please can the company provide a scenario analysis assuming a lower rate of long-term discontinuation for CM.

While in agreement that long-term discontinuation is an important consideration, applying an equivalent long-term discontinuation rate across EM and CM is consistent with previous NICE appraisals in migraine and with migraine being considered a disease continuum by clinical experts.[27-32] Furthermore, AbbVie are not aware of publicly available data to demonstrate that long-term discontinuation rates differ between EM and CM.

Available RCT evidence shows that discontinuation rates can be similar between patients with EM and patients with CM, with similar ranges of all-cause discontinuation rates reported for patients on active treatment across each sub-indication (EM: 2.2–19.5% vs CM: 2.1–18.2%; CS appendices Table 17 and Table 23, respectively]). In particular, all-cause discontinuation rates have been reported for EM and CM subgroups across Phase 2/3 RCTs for atogepant, fremanezumab, and erenumab (Table 20). In line with this, clinical experts indicated that there is not a strong rationale to assume different long-term discontinuation rates for EM versus CM, and agreed there is a lack of publicly available evidence to support such a scenario analysis.

Table 20: Naive comparison of all-cause discontinuation rates for EM and CM

Treatment	All-cause discontinuation rate	
	EM	CM
Atogepant 60mg[4, 6]	ADVANCE: [redacted]%	PROGRESS: [redacted]%
Fremanezumab 225 mg[33, 34]	HALO EM: 9.7%	HALO CM: 9.5%
Erenumab 140 mg[35, 36]	LIBERTY: 2.5%	Tepper: 2.1%

The primary timepoint in all trials was 12 weeks, except Tepper where the primary timepoint was 24 weeks.
Abbreviations: CM: chronic migraine; EM: episodic migraine.

In the absence of long-term discontinuation data for patients with EM and CM separately, it is not possible to provide a scenario analysis in which a lower rate of discontinuation is assumed for CM than EM without introducing substantial uncertainty. Therefore, clinical experts have indicated that the most appropriate approach would be as implemented in the base case: application of a single long-term discontinuation rate collected from LTS-302 across EM and CM (3.59%). The application of the same constant per-cycle long-term discontinuation rate to both EM and CM is also consistent with the approach taken in previous NICE appraisals of relevant comparators.[30-32]

However, in order to account for uncertainty, a highly conservative scenario was conducted and presented in the original CS in which a per-cycle long-term discontinuation rate of 0.44% was

applied to both EM and CM, in line with the NICE appraisal for erenumab (TA682) (submitted scenarios 3b and 10b, Section B.3.11.3 of Document B, with updated results presented below in Table 21).[30] Further scenarios implementing long-term discontinuation rates reported in other previous TAs have also now been explored (Table 21). In these scenarios, atogepant remained cost-effective (i.e. INHB remained positive) versus all relevant comparators in EM and CM, and the conservative discontinuation rates had minimal impact on the cost-effectiveness results.

Table 21: Scenario analyses (atogepant PAS price) – long term discontinuation rates (deterministic results)

#	Description	Galcanezumab (120 mg)			Erenumab (140 mg)			Fremanezumab (225 mg)			Fremanezumab (675 mg)		
		Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]
EM													
Base Case		[redacted]	[redacted]	0.26	[redacted]	[redacted]	0.10	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.19
1a	Long-term discontinuation based on fremanezumab (1.95% per cycle)	[redacted]	[redacted]	0.39	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.22	[redacted]	[redacted]	0.29
1b	Long-term discontinuation based on galcanezumab (0.79% per cycle)	[redacted]	[redacted]	0.70	[redacted]	[redacted]	0.27	[redacted]	[redacted]	0.42	[redacted]	[redacted]	0.53
1c	Long-term discontinuation based on erenumab (0.44% per cycle)	[redacted]	[redacted]	0.98	[redacted]	[redacted]	0.37	[redacted]	[redacted]	0.59	[redacted]	[redacted]	0.75
CM													
Base Case		[redacted]	[redacted]	0.43	[redacted]	[redacted]	0.16	[redacted]	[redacted]	0.22	[redacted]	[redacted]	0.23
2a	Long-term discontinuation based on fremanezumab (1.95% per cycle)	[redacted]	[redacted]	0.68	[redacted]	[redacted]	0.26	[redacted]	[redacted]	0.35	[redacted]	[redacted]	0.36
2a	Long-term discontinuation based on galcanezumab (0.79% per cycle)	[redacted]	[redacted]	1.30	[redacted]	[redacted]	0.49	[redacted]	[redacted]	0.67	[redacted]	[redacted]	0.68
2c	Long-term discontinuation based on erenumab (0.44% per cycle)	[redacted]	[redacted]	1.85	[redacted]	[redacted]	0.70	[redacted]	[redacted]	0.96	[redacted]	[redacted]	0.97

Footnotes: [a]NHB calculated at a WTP threshold of £30,000.
Abbreviations: CM: chronic migraine; EM: episodic migraine; Inc.: incremental; MMD: monthly migraine days; NHB: net health benefit; PAS: patient access scheme; QALY, quality-adjusted life year; WTP: willingness-to-pay.
Sources: NICE appraisal of galcanezumab (TA659);[32] NICE appraisal of erenumab (TA682);[30] NICE appraisal of fremanezumab (TA764).[31]

B7. Priority question. The company states that the long-term all-cause discontinuation rate of 3.59% is based on mean treatment duration of 291.6 days for atogepant. Please can the company provide explicit details of how this long-term discontinuation rate was calculated?

In addition to the mean treatment duration during the LTS-302 long-term safety and tolerability study of atogepant in EM (291.6 days), the calculation of the long-term discontinuation rate was informed by the number of randomised patients (N=546) and the number of patients who discontinued due to any cause (n=173) during the study, as per the below formulae (also accounting for the model cycle length of 28 days).

$$Rate\ per\ day = {-\ln\left(1-\frac{173}{546}\right)}/{291.6}$$

$$Rate\ per\ cycle = 1 - e^{(-Rate\ per\ day \times 28)} = 3.59\%$$

B8. Priority question. Table 901.1-01.02.04 from the MAAP ELEVATE study appears to show a discontinuation rate for atogepant of [redacted]% and yet the rate listed in table 40 of the CS is [redacted]%. Is there a reason for this discrepancy? Please clarify the source of the [redacted]%, if it is not derived from what's reported in Table 901.1-01.02.04?

The discontinuation rate of [redacted] (sourced from Table 901.1-01.02.04) refers to the discontinuation rate of patients with high-frequency EM in whom 3 or more classes of preventive medications have failed, whereas the discontinuation rate of [redacted]% is reflective of the population of interest (patients with EM in whom 3 or more classes of preventive medications have failed). This value is sourced from Table 901.1–01.02.02 from the MAAP ELEVATE study report and represents the proportion of patients who received atogepant (N=[redacted]) in the atogepant 60 mg QD treatment arm who discontinued (N=[redacted]).

B9. Table 901.3-02.02.04 from the MAAP ELEVATE study appears to list the probability of ≥50% response in MMDs at 3 months as [redacted]% and yet table 41 of the CS lists this as [redacted]%. Is there a reason for this discrepancy? Please clarify the source of the [redacted]%, if it is not derived from what is reported in Table 901.3-02.02.04?

As above, Table 901.3-02.02.04 ([redacted]) refers to patients with high-frequency EM in whom 3 or more classes of preventive medications have failed. However, the population of interest is patients with EM in whom 3 or more classes of preventive medications have failed. As such, the company can confirm that Table 41 of Document B of the CS presents the correct value for consideration ([redacted]). This has been sourced from Table 901.3-02.02.02 from the MAAP ELEVATE file included within the reference pack.

MMDs

B10. Priority question. In the model responder MMDs were restricted to a "clinically plausible" minimum 1 MMD:

a) **Please can the company provide the justification for 1 MMD being a clinically plausible minimum?**
b) **If the model is specified appropriately, and if the results of the NMAs are robust, the EAG cannot see a plausible rationale for this restriction. Please can the company explain why this limitation needs to be included in the model?**

The minimum MMD cap was introduced into the model to avoid negative responder MMDs while splitting out responder and non-responder MMDs from the combined NMA data for change from baseline in MMDs. The minimum of 1 MMD was selected as this was deemed the most clinically plausible.

It was necessary to implement a minimum MMD cap into the model due to a paucity of data relating to comparator treatments; pooled responder and non-responder MMD were used in the relevant NMA, signifying that any NMA results describing a CFB in MMDs apply to a combined responder and non-responder patient population.

In turn, the cost-effectiveness model calculates MMDs for both the responder and non-responder patient populations from pooled CFB in MMD data from the NMA. In the absence of any relevant comparator data, a simplifying assumption was made that any CFB in MMDs is driven by the change in MMDs seen in patients who are treatment responders, and that MMDs experienced by patients who are non-responders are equivalent for all treatments, based on the pooled baseline MMDs across the ELEVATE and PROGRESS trials.

However, in a small number of cases (EM 3+ TF population – atogepant versus galcanezumab; EM overall population – atogepant versus galcanezumab; EM overall population – atogepant versus fremanezumab 225 mg; EM overall population – atogepant versus fremanezumab 675 mg), the maintenance of the correct CFB in MMD value between treatment responders and non-responders led to negative responder MMDs, which is not clinically plausible. Therefore, a minimum cap was introduced for responder MMDs (1 MMD).

B11. Priority question. A Poisson distribution is currently used to represent MMD distribution:

a) **Please can the company justify why the distribution was this chosen and why it was felt necessary to model MMDs rather than using the observed data?**

A parametric distribution was chosen over observed data in order to align with the approach taken in previous appraisals.[30-32] However, as per EAG request, a scenario using the observed MMDs by health state has been provided in Question B11 part b.

b) Please can the company provide a scenario using the observed MMDs by health state?

A scenario analysis in which MMD distributions observed for atogepant in the respective clinical trials were applied to all CGRP mAb comparators (as well as atogepant itself) has been conducted as requested, with results presented in Table 22. This assumption results in negligible changes to the model outcomes, with no change in the conclusion that atogepant is cost-effective versus all relevant comparators in EM and CM.

Table 22: Scenario analyses (atogepant PAS price) – using observed MMDs by health state (deterministic results)

#	Description	Galcanezumab (120 mg)			Erenumab (140 mg)			Fremanezumab (225 mg)			Fremanezumab (675 mg)		
		Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]
EM													
Base Case		[redacted]	[redacted]	0.26	[redacted]	[redacted]	0.10	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.19
1	Use of trial-observed MMD distributions	[redacted]	[redacted]	0.27	[redacted]	[redacted]	0.10	[redacted]	[redacted]	0.16	[redacted]	[redacted]	0.19
CM													
Base Case		[redacted]	[redacted]	0.43	[redacted]	[redacted]	0.16	[redacted]	[redacted]	0.22	[redacted]	[redacted]	0.23
2	Use of trial-observed MMD distributions	[redacted]	[redacted]	0.44	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.18	[redacted]	[redacted]	0.20

Footnotes: [a]NHB calculated at a WTP threshold of £30,000.
Abbreviations: CM: chronic migraine; EM: episodic migraine; Inc.: incremental; MMD: monthly migraine days; NHB: net health benefit; PAS: patient access scheme; QALY, quality-adjusted life year; WTP: willingness-to-pay

c) Please can the company explore the fit of alternative distributions: beta-binomial, zero-inflated negative binomial, negative binomial, in line with the work done in the previous submissions for erenumab, galcanezumab and rimegepant (TA682, TA659 and TA906)?

Parametric distributions were fitted to the observed data in order to represent the MMD distribution, and different options were explored. However, these required several inputs which made it very challenging to apply the NMA results to get the MMD distribution for the indirect comparators. Given the large number of indirect comparators, this approach was simplified to consider Poisson and Negative Binomial only, since these options require only the mean MMD (and dispersion parameter for Negative Binomial) as inputs. Poisson distribution was chosen over Negative Binomial because the measure of dispersion can only be calculated through the use of patient-level data, a relatively fixed and narrow range of possible MMD values was evident, and there was minimal overdispersion (Table 23).

Table 23: Parametric estimates of baseline MMDs using Negative Binomial and Poisson distributions

Study (population)	Statistic	Negative binomial distribution		Poisson distribution	
		Placebo	Atogepant 60 mg QD	Placebo	Atogepant 60 mg QD
ELEVATE (3+TF)	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Mu (SE)	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI of Mu	[redacted]	[redacted]	[redacted]	[redacted]
	Dispersion (SE)	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI of Dispersion	[redacted]	[redacted]	[redacted]	[redacted]
ELEVATE (overall mITT)	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Mu (SE)	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI of Mu	[redacted]	[redacted]	[redacted]	[redacted]
	Dispersion (SE)	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI of Dispersion	[redacted]	[redacted]	[redacted]	[redacted]
PROGRESS (overall mITT)	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Mu (SE)	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI of Mu	[redacted]	[redacted]	[redacted]	[redacted]
	Dispersion (SE)	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI of Dispersion	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: Distribution parameters and 95% CIs are estimated using maximum likelihood estimation method. Numbers of migraine days have been rounded to the nearest integers in fitting the parametric distribution.
Abbreviations: CI: confidence interval; mITT: modified intent-to-treat; QD: once daily; SD: standard deviation: SE: standard error; TF: treatment failure

As outlined above and by the EAG in the recent TA906 appraisal, Poisson was deemed the most appropriate model distribution for MMDs. Given the minimal impact of changing MMD inputs demonstrated in Part b) above, AbbVie maintain that use of the Poisson distribution is appropriate.

B12. Priority question. Patients who are non-responders have the MMDs for treatment-specific non-responders before resorting to pooled baseline MMDs after one cycle. The company states that this is in line with NICE appraisal of rimegepant (TA906); however, this is not accurate, as the rimegepant submission modelled a reversion to baseline occurring over a 1 year period (12 cycles).

a) **Please can the company provide a scenario which applies a gradual loss of benefit over a year period, applying the same assumption as TA906?**
b) **Please can the company confirm that the reversion to baseline MMDs is assumed to be due to the loss of placebo response? If this is not the case, please can the company inform the EAG of their alternative rationale?**

AbbVie understands that loss of placebo effect has been modelled in prior fremanezumab (TA764) and rimegepant appraisals (TA906)[13], whereby the treatment effect for people who responded to BSC diminished to baseline over 1 year.

However, AbbVie can confirm that the reversion to baseline MMDs is not due to loss of placebo response. As discussed in the prior NICE appraisal of fremanezumab (TA764), there is no strong evidence available to show the time period over which a placebo effect persists following treatment discontinuation in patients with migraine.[31] Therefore, modelling an immediate reversion to baseline MMDs in this situation is appropriate. As shown within the economic model ("MMDs" sheet), there is no loss of placebo effect applied for placebo responders and in the absence of data describing change in MMDs following treatment discontinuation, the appropriate and conservative assumption is to assume immediate reversion to baseline MMDs following discontinuation of active treatments due to any reason. This assumption is conservative, given that the placebo response observed in the clinical trial is extrapolated for the lifetime horizon of the model.

Despite this, a scenario analysis has been conducted which applies a gradual loss of benefit over a year to patients who discontinue treatment (placebo or any active treatment) following response assessment due to any reason (i.e. patients in the "Off Tx non-responder" and "Off Tx after response assessment" health states), as shown in Table 24. This assumption of a gradual loss of benefit results in negligible changes to the model outcomes, with no change in the conclusion that atogepant is cost-effective versus all relevant comparators in EM and CM.

Table 24: Scenario analyses (atogepant PAS price) – assuming a gradual loss of treatment benefit over a 1-year period following discontinuation (deterministic results)

#	Description	Galcanezumab (120 mg)			Erenumab (140 mg)			Fremanezumab (225 mg)			Fremanezumab (675 mg)		
		Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]
EM													
Base Case		[redacted]	[redacted]	0.26	[redacted]	[redacted]	0.10	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.19
1	Assuming a gradual loss of benefit over 1 year	[redacted]	[redacted]	0.26	[redacted]	[redacted]	0.10	[redacted]	[redacted]	0.14	[redacted]	[redacted]	0.19
CM													
Base Case		[redacted]	[redacted]	0.43	[redacted]	[redacted]	0.16	[redacted]	[redacted]	0.22	[redacted]	[redacted]	0.23
2	Assuming a gradual loss of benefit over 1 year	[redacted]	[redacted]	0.43	[redacted]	[redacted]	0.16	[redacted]	[redacted]	0.22	[redacted]	[redacted]	0.23

Footnotes: [a]NHB calculated at a WTP threshold of £30,000.
Abbreviations: CM: chronic migraine; EM: episodic migraine; Inc.: incremental; NHB: net health benefit; PAS: patient access scheme; QALY, quality-adjusted life year; WTP: willingness-to-pay.

a) **If it is considered to occur due to the loss of the "placebo effect" from clinical trials, please can the company explain why this trial specific effect (potentially due to the additional care patients receive within a trial) would not also impact patients on active treatments?**

As discussed in Question 12 part a and b above, AbbVie did not include a loss of placebo effect in the model and therefore it is not necessary to adjust for loss of placebo effect for patients in the active treatment arms.

B13. The company uses CFB in MMDs across non-responders and responders, along with the response rate, to derive MMDs for responders in comparator treatments. This means that the difference in the MMDs of responders and non-responders, between treatments, is entirely assigned to responders and the company assumes MMDs for non-responders to any treatment is equivalent. Please can the company provide justification for this assumption?

As outlined in the response to clarification question B10 part b), due to a lack of data relating to comparator treatments, pooled responder and non-responder MMD were used in the relevant NMA. As previously stated, a simplifying assumption was therefore made that any CFB in MMDs is driven by the change in MMDs seen in patients who are treatment responders, and that MMDs experienced by patients who are non-responders are equivalent for all treatments, based on the pooled baseline MMDs across the ELEVATE and PROGRESS trials. This is in line with the assumption made in the rimegepant NICE appraisal (TA906).[13]

B14. Please can the company provide a scenario that assumes all treatments have equal MMD distributions for responders, consistent with the recent submission to NICE for migraine (TA906).

The results of a scenario analysis based on the assumption of equal MMD distributions for responders across all treatments (based on applying the atogepant-specific distribution equally for all comparators) are presented in Table 25; this scenario results in overall minimal changes to the model outcomes.

Table 25: Scenario analyses (atogepant PAS price) – same MMD distribution for responders across all treatments (deterministic results)

#	Description	Galcanezumab (120 mg)			Erenumab (140 mg)			Fremanezumab (225 mg)			Fremanezumab (675 mg)		
		Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]
EM													
Base Case		[redacted]	[redacted]	0.26	[redacted]	[redacted]	0.10	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.19
1	All treatments have equal MMD distributions for responders (based on atogepant data)	[redacted]	[redacted]	0.27	[redacted]	[redacted]	0.10	[redacted]	[redacted]	0.16	[redacted]	[redacted]	0.19
CM													
Base Case		[redacted]	[redacted]	0.43	[redacted]	[redacted]	0.16	[redacted]	[redacted]	0.22	[redacted]	[redacted]	0.23
2	All treatments have equal MMD distributions for responders (based on atogepant data)	[redacted]	[redacted]	0.44	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.18	[redacted]	[redacted]	0.20

Footnotes: [a]NHB calculated at a WTP threshold of £30,000.
Abbreviations: CM: chronic migraine; EM: episodic migraine; Inc.: incremental; MMD: monthly migraine days; NHB: net health benefit; PAS: patient access scheme; QALY, quality-adjusted life year; WTP: willingness-to-pay.

HRQoL

B15. Priority question. The HRQoL regression contains MMD and "responder" yet responder is defined by MMD change. Please can the company rerun this regression using:

a) MMD alone;

Table 26 presents the results of a scenario analysis wherein the HRQoL regression contains MMD alone; this scenario results in overall minimal changes to the model outcomes.

b) MMD and "on treatment", consistent with the recent submission to NICE for migraine (TA906).

AbbVie did not run the HRQoL regression using MMD and "on treatment" as covariates, as it would require treatments to be defined whereby patients are dynamically assigned based on whether they were still on study medication at the end of each model cycle and therefore is not feasible within the functionality of the model.

Table 26: Scenario analyses (atogepant PAS price) – HRQoL regression with MMD alone (deterministic results)

#	Description	Galcanezumab (120 mg)			Erenumab (140 mg)			Fremanezumab (225 mg)			Fremanezumab (675 mg)		
		Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]
EM													
Base Case		[redacted]	[redacted]	0.26	[redacted]	[redacted]	0.10	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.19
1a	HRQoL regression based on MMDs alone	[redacted]	[redacted]	0.25	[redacted]	[redacted]	0.09	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.21
CM													
Base Case		[redacted]	[redacted]	0.43	[redacted]	[redacted]	0.16	[redacted]	[redacted]	0.22	[redacted]	[redacted]	0.23
2a	HRQoL regression based on MMDs alone	[redacted]	[redacted]	0.44	[redacted]	[redacted]	0.17	[redacted]	[redacted]	0.24	[redacted]	[redacted]	0.25

Footnotes: [a]NHB calculated at a WTP threshold of £30,000.
Abbreviations: CM: chronic migraine; EM: episodic migraine; HRQoL: health-related quality-of-life; Inc.: incremental; MMD: monthly migraine days; NHB: net health benefit; PAS: patient access scheme; QALY, quality-adjusted life year; WTP: willingness-to-pay.

Section C: Textual clarification and additional points

Clinical effectiveness

C1. In Table 12 of the CS, for the 3+ TF subgroup results, should the upper confidence interval for the treatment effect (TE) of the change from baseline in mean monthly acute MUDs be [redacted] rather than [redacted]?

The company can confirm that a typographical error was made in the reporting of these data. This cell in Table 12 should read [redacted]

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Appendix A: Updated base case results

In line with the error identified in response to Question B3, AbbVie has updated the base case results and presented these below. Apart from the corrected error, these results were generated using the same settings as those presented in Document B, and results are consistent with those presented in the CS.

The probabilistic base case pairwise results of the economic evaluation for the EM and CM populations are presented for atogepant at list price in Table 27 and Table 30, respectively, and for atogepant at with-PAS price in Table 29 and Table 32, respectively. At PAS price, atogepant was found to be cost-effective compared to all relevant comparators in EM, yielding INHBs for atogepant versus galcanezumab (120 mg), erenumab (140 mg) and fremanezumab (225 mg or 675 mg) of 0.38, 0.13, 0.23 and 0.30, respectively at a willingness-to-pay threshold of £20,000. Similarly, atogepant was cost-effective compared galcanezumab (120 mg), erenumab (140 mg) and fremanezumab (225 mg or 675 mg) in the CM population with a INHB of 0.66, 0.25, 0.33 and 0.35, respectively. Deterministic base case pairwise results are presented in Table 28 (EM, atogepant with-PAS price) and Table 31 (CM, atogepant with-PAS price).

Base case fully incremental analyses were carried out in both the EM and CM populations, as shown in **Error! Reference source not found.** and Table 34, respectively. The base case fully incremental analysis in the EM and CM populations showed atogepant to be the most cost-effective treatment option at PAS price and were consistent with the pair-wise analysis, with a fully incremental ICER of £256,112 saved per QALY forgone as compared to fremanezumab 675 mg in EM and £420,750 saved per QALY forgone as compared to erenumab 140 mg QM in CM, with all other comparators strictly dominated or extendedly dominated. Fully incremental analyses should however be interpreted with caution given small incremental costs and QALYs between comparators.

Table 27: Base-case pair-wise cost-effectiveness results (EM) – atogepant list price (probabilistic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER for atogepant vs comparator (£/QALY)	INHB (WTP threshold of £20,000)	INHB (WTP threshold of £30,000)
Atogepant 60 mg QD	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Galcanezumab 120 mg QM[a]	33,683	21.52	13.70	[redacted]	0.00	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg QM	28,245	21.52	13.69	[redacted]	0.00	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 225 mg Q3M[c]	31,431	21.52	13.75	[redacted]	0.00	[redacted]	[redacted][c]	[redacted]	[redacted]

Fremanezumab 675 mg Q3M	33,001	21.52	13.76	[redacted]	0.00	[redacted]	[redacted][c]	[redacted]	[redacted]

Footnotes: [a]Galcanezumab regimen is a 240 mg loading dose followed by 120 mg once a month. [b]Fremanezumab regimen is 675 mg initial dose followed by 225 mg once a month. [c]SW quadrant ICER; costs saved per QALY forgone
Abbreviations: EM: episodic migraine; ICER: incremental cost-effectiveness ratio; Incr.: incremental; INHB: incremental net health benefit; LYG: life years gained; QALYs: quality-adjusted life years; SW: South West.

Table 28: Base-case pair-wise cost-effectiveness results (EM) – atogepant PAS price (deterministic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER for atogepant vs comparator (£/QALY)	INHB (WTP threshold of £20,000)	INHB (WTP threshold of £30,000)
Atogepant 60 mg QD	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Galcanezumab 120 mg QM[a]	33,647	21.52	13.69	[redacted]	0.00	[redacted]	-£252,877	0.38	0.26
Erenumab 140 mg QM	28,260	21.52	13.68	[redacted]	0.00	[redacted]	-£37,856	0.13	0.10
Fremanezumab 225 mg Q3M[b]	31,394	21.52	13.74	[redacted]	0.00	[redacted]	334,719[c]	0.23	0.15
Fremanezumab 675 mg Q3M	32,980	21.52	13.75	[redacted]	0.00	[redacted]	259,951[c]	0.30	0.19

Footnotes: [a]Galcanezumab regimen is a 240 mg loading dose followed by 120 mg once a month. [b]Fremanezumab regimen is 675 mg initial dose followed by 225 mg once a month. [c]SW quadrant ICER; costs saved per QALY forgone.
Abbreviations: EM: episodic migraine; ICER: incremental cost-effectiveness ratio; Incr.: incremental; INHB: incremental net health benefit; LYG: life years gained; QALYs: quality-adjusted life years; SW: South West.

Table 29: Base-case pair-wise cost-effectiveness results (EM) – atogepant PAS price (probabilistic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER for atogepant vs comparator (£/QALY)	INHB (WTP threshold of £20,000)	INHB (WTP threshold of £30,000)
Atogepant 60 mg QD	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Galcanezumab 120 mg QM[a]	33,714	21.52	13.69	[redacted]	0.00	[redacted]	-258,391	0.38	0.27
Erenumab 140 mg QM	28,277	21.52	13.67	[redacted]	0.00	[redacted]	-38,116	0.13	0.10

Fremanezumab 225 mg Q3M[b]	31,466	21.52	13.73	[redacted]	0.00	[redacted]	377,997[c]	0.23	0.15
Fremanezumab 675 mg Q3M	33,047	21.52	13.74	[redacted]	0.00	[redacted]	256,112[c]	0.30	0.19

Footnotes: [a]Galcanezumab regimen is a 240 mg loading dose followed by 120 mg once a month. [b]Fremanezumab regimen is 675 mg initial dose followed by 225 mg once a month. [c]SW quadrant ICER; costs saved per QALY forgone.
Abbreviations: EM: episodic migraine; ICER: incremental cost-effectiveness ratio; Incr.: incremental; INHB: incremental net health benefit; LYG: life years gained; QALYs: quality-adjusted life years; SW: South West.

Table 30: Base-case pair-wise cost-effectiveness results (CM) – atogepant list price (probabilistic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER for atogepant vs comparator (£/QALY)	INHB (WTP threshold of £20,000)	INHB (WTP threshold of £30,000)
Atogepant 60 mg QD	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Galcanezumab 120 mg QM[a]	47,577	21.41	10.87	[redacted]	0.00	[redacted]	[redacted][c]	[redacted]	[redacted]
Erenumab 140 mg QM	39,476	21.41	10.88	[redacted]	0.00	[redacted]	[redacted][c]	[redacted]	[redacted]
Fremanezumab 225 mg Q3M[b]	40,988	21.41	10.87	[redacted]	0.00	[redacted]	[redacted][c]	[redacted]	[redacted]
Fremanezumab 675 mg Q3M	41,192	21.41	10.86	[redacted]	0.00	[redacted]	[redacted][c]	[redacted]	[redacted]

Footnotes: [a]Galcanezumab regimen is a 240 mg loading dose followed by 120 mg once a month. [b]Fremanezumab regimen is 675 mg initial dose followed by 225 mg once a month. [c]SW quadrant ICER; costs saved per QALY forgone.
Abbreviations: CM: chronic migraine; ICER, incremental cost-effectiveness ratio; Incr.: incremental; INHB: incremental net health benefit; LYG: life years gained; QALYs: quality-adjusted life years; SW: South West.

Table 31: Base-case pair-wise cost-effectiveness results (CM) – atogepant PAS price (deterministic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER for atogepant vs comparator (£/QALY)	INHB (WTP threshold of £20,000)	INHB (WTP threshold of £30,000)
Atogepant 60 mg QD	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Galcanezumab 120 mg QM[a]	47,530	21.41	10.87	[redacted]	0.00	[redacted]	1,293,516[c]	0.65	0.43

Erenumab 140 mg QM	39,510	21.41	10.87	[redacted]	0.00	[redacted]	402,679[c]	0.25	0.16
Fremanezumab 225 mg Q3M[b]	40,993	21.41	10.86	[redacted]	0.00	[redacted]	1,116,173[c]	0.33	0.22
Fremanezumab 675 mg Q3M	41,220	21.41	10.86	[redacted]	0.00	[redacted]	128,711,462[c]	0.35	0.23

Footnotes: [a]Galcanezumab regimen is a 240 mg loading dose followed by 120 mg once a month. [b]Fremanezumab regimen is 675 mg initial dose followed by 225 mg once a month. [c]SW quadrant ICER; costs saved per QALY forgone.
Abbreviations: CM: chronic migraine; ICER, incremental cost-effectiveness ratio; Incr.: incremental; INHB: incremental net health benefit; LYG: life years gained; QALYs: quality-adjusted life years; SW: South West.

Table 32: Base-case pair-wise cost-effectiveness results (CM) – atogepant PAS price (probabilistic results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER for atogepant vs comparator (£/QALY)	INHB (WTP threshold of £20,000)	INHB (WTP threshold of £30,000)
Atogepant 60 mg QD	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Galcanezumab 120 mg QM[b]	47,569	21.41	10.87	[redacted]	0.00	[redacted]	1,314,438[c]	0.66	0.44
Erenumab 140 mg QM	39,452	21.41	10.88	[redacted]	0.00	[redacted]	420,750[c]	0.25	0.16
Fremanezumab 225 mg Q3M[c]	40,919	21.41	10.87	[redacted]	0.00	[redacted]	1,255,618[c]	0.33	0.22
Fremanezumab 675 mg Q3M	41,180	21.41	10.86	[redacted]	0.00	[redacted]	-50,434,768	0.35	0.23

Footnotes: [a]Galcanezumab regimen is a 240 mg loading dose followed by 120 mg once a month. [b]Fremanezumab regimen is 675 mg initial dose followed by 225 mg once a month. [c]SW quadrant ICER; costs saved per QALY forgone
Abbreviations: CM: chronic migraine; ICER, incremental cost-effectiveness ratio; Incr.: incremental; INHB: incremental net health benefit; LYG: life years gained; QALYs: quality-adjusted life years; SW: South West.

Table 33: Base-case fully incremental cost-effectiveness results (EM) – atogepant PAS price (probabilistic results)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)	Incr. ICER (£/QALY)
Atogepant 60 mg QD	[redacted]	[redacted]	-	-	-	-
Erenumab 140 mg QM	28,277	13.67	-	-	-38,116	Strictly Dominated
Fremanezumab 225 mg Q3M[b]	31,466	13.73	-	-	377,997	Extendedly Dominated
Fremanezumab 675 mg Q3M	33,047	13.74	[redacted]	[redacted]	256,112	256,112
Galcanezumab 120 mg QM[a]	33,714	13.69	-	-	-258,391	Strictly Dominated

Footnotes: [a]Galcanezumab regimen is a 240 mg loading dose followed by 120 mg once a month. [b]Fremanezumab regimen is 675 mg initial dose followed by 225 mg once a month.
Abbreviations: EM: episodic migraine; ICER, incremental cost-effectiveness ratio; Incr.: incremental; QALYs: quality-adjusted life years.

Table 34: Base-case fully incremental cost-effectiveness results (CM) – atogepant PAS price (probabilistic results)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)	Incr. ICER (£/QALY)
Atogepant 60 mg QD	[redacted]	[redacted]	-	-	-	-
Erenumab 140 mg QM	39,452	10.88	[redacted]	[redacted]	420,749.86	420,750
Fremanezumab 225 mg Q3M[b]	40,919	10.87	-	-	1,255,617.94	Strictly Dominated
Fremanezumab 675 mg Q3M	41,180	10.86	-	-	-50,434,767.94	Strictly Dominated
Galcanezumab 120 mg QM[a]	47,569	10.88	-	-	1,314,437.78	Strictly Dominated

Footnotes: [a]Galcanezumab regimen is a 240 mg loading dose followed by 120 mg once a month. [b]Fremanezumab regimen is 675 mg initial dose followed by 225 mg once a month.
Abbreviations: CM: chronic migraine; ICER, incremental cost-effectiveness ratio; Incr.: incremental; QALYs: quality-adjusted life years.

Appendix B: Updated scenario results

In line with the error identified in response to Question B3, AbbVie have also updated the scenario analyses and presented these below. Apart from the corrected error, these results were generated using the same settings as those presented in Document B. Results generated are consistent with those presented in Document B.

Table 35: Scenario analyses (EM) – atogepant PAS price (deterministic results)

#	Description	Galcanezumab (120 mg)			Erenumab (140 mg)			Fremanezumab (225 mg)			Fremanezumab (675 mg)		
		Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs) [a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs) [a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs) [a]
Base Case		[redacted]	[redacted]	0.26	[redacted]	[redacted]	0.10	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.19
1	Missing NMA data equal to average mAb	[redacted]	[redacted]	0.26	[redacted]	[redacted]	0.10	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.19
2	Consider natural history of migraine	[redacted]	[redacted]	0.26	[redacted]	[redacted]	0.10	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.19
3a	Discontinuation before response assessment assumed to be a one-off probability at the response assessment timepoint	[redacted]	[redacted]	0.27	[redacted]	[redacted]	0.10	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.19
3b	Discontinuation after response assessment informed by alternative value	[redacted]	[redacted]	0.98	[redacted]	[redacted]	0.37	[redacted]	[redacted]	0.59	[redacted]	[redacted]	0.75
4	Use of regression model 2 for utilities	[redacted]	[redacted]	0.26	[redacted]	[redacted]	0.09	[redacted]	[redacted]	0.16	[redacted]	[redacted]	0.20
5	Exclusion of disutility associated with SC or IM administration routes	[redacted]	[redacted]	0.26	[redacted]	[redacted]	0.09	[redacted]	[redacted]	0.13	[redacted]	[redacted]	0.17
6a	Monitoring costs 1	[redacted]	[redacted]	0.26	[redacted]	[redacted]	0.09	[redacted]	[redacted]	0.14	[redacted]	[redacted]	0.18
6b	Monitoring costs 2	[redacted]	[redacted]	0.27	[redacted]	[redacted]	0.11	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.20
7	EM overall population	[redacted]	[redacted]	0.42	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.18	[redacted]	[redacted]	0.20

Footnotes: [a]NHB calculated at a WTP threshold of £30,000. Note: Baseline risk-adjusted analyses were removed given that the NMA exploring ≥50% reduction in MMDs following baseline risk-adjustment did not converge (per CS appendices Table 26).
Abbreviations: CGRP: calcitonin gene-related peptide; EM: episodic migraine; mAbs: monoclonal antibodies; NMA: network meta-analysis; PAS: patient access scheme; SC: subcutaneous; TA: technology appraisal; tx: treatment.

Table 36: Scenario analyses (CM) – atogepant PAS price (deterministic results)

#	Description	Galcanezumab (120 mg)			Erenumab (140 mg)			Fremanezumab (225 mg)			Fremanezumab (675 mg)		
		Inc. costs (£)	Inc. QALYs	NHB (QALYs) [a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs) [a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs) [a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs) [a]
Base Case		[redacted]	[redacted]	0.43	[redacted]	[redacted]	0.16	[redacted]	[redacted]	0.22	[redacted]	[redacted]	0.23
8	Missing NMA data equal to average mAb	[redacted]	[redacted]	0.43	[redacted]	[redacted]	0.18	[redacted]	[redacted]	0.22	[redacted]	[redacted]	0.23
9	Consider natural history of migraine	[redacted]	[redacted]	0.43	[redacted]	[redacted]	0.16	[redacted]	[redacted]	0.22	[redacted]	[redacted]	0.24
10a	Discontinuation before response assessment assumed to be a one-off probability at the response assessment timepoint	[redacted]	[redacted]	0.43	[redacted]	[redacted]	0.16	[redacted]	[redacted]	0.22	[redacted]	[redacted]	0.23
10b	Discontinuation after response assessment informed by alternative value	[redacted]	[redacted]	1.85	[redacted]	[redacted]	0.70	[redacted]	[redacted]	0.96	[redacted]	[redacted]	0.97
11	Use of regression model 2 for utilities	[redacted]	[redacted]	0.44	[redacted]	[redacted]	0.17	[redacted]	[redacted]	0.23	[redacted]	[redacted]	0.24
12	Exclusion of disutility associated with SC or IM administration routes	[redacted]	[redacted]	0.42	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.20	[redacted]	[redacted]	0.22
13	≥50% response definition	[redacted]	[redacted]	0.34	[redacted]	[redacted]	0.11	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.17

14a	Monitoring costs 1	[redacted]	[redacted]	0.43	[redacted]	[redacted]	0.16	[redacted]	[redacted]	0.21	[redacted]	[redacted]	0.23
14b	Monitoring costs 2	[redacted]	[redacted]	0.44	[redacted]	[redacted]	0.17	[redacted]	[redacted]	0.23	[redacted]	[redacted]	0.24

Footnotes: [a]NHB calculated at a WTP threshold of £30,000. Note: Baseline risk-adjusted analyses were removed as per the response to clarification question A5.
Abbreviations: CGRP: calcitonin gene-related peptide; EM: episodic migraine; mAbs: monoclonal antibodies; NMA: network meta-analysis; PAS: patient access scheme; SC: subcutaneous; TA: technology appraisal; tx: treatment.

Table 37: Scenario analyses (EM and CM) – atogepant PAS price (deterministic results)

#	Description	Galcanezumab (120 mg)			Erenumab (140 mg)			Fremanezumab (225 mg)			Fremanezumab (675 mg)		
		Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]
Base Case (EM)		[redacted]	[redacted]	0.26	[redacted]	[redacted]	0.10	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.19
Base Case (CM)		[redacted]	[redacted]	0.43	[redacted]	[redacted]	0.16	[redacted]	[redacted]	0.22	[redacted]	[redacted]	0.23
15	Weighted average results across EM (71%) and CM (29%)	[redacted]	[redacted]	0.31	[redacted]	[redacted]	0.12	[redacted]	[redacted]	0.17	[redacted]	[redacted]	0.20

Footnotes: [a]NHB calculated at a WTP threshold of £30,000.
Abbreviations: CM: chronic migraine; EM: episodic migraine; PAS: patient access scheme.

1. The B10 response makes clear why a minimum was required to avoid negative MMDs but it is still not clear why 1 is the most clinically plausible minimum MMD and not 0. Can the company clarify why 1 was deemed the most clinically plausible value?

As AbbVie do not have access to individual patient-level data nor data indicating the decrease in MMD for responder and non-responders separately for each comparator treatment, the model allows for the calculation of responder MMD based on NMA results for CFB in MMDs pooled across both responders and non-responders. This approach more accurately captures potential differences in treatment efficacy and conservatively assumes greater reduction in MMDs for galcanezumab vs atogepant despite the absence of data; whereas in the fremanezumab appraisal (TA764),[1] MMD reductions for responders and non-responders were assumed to be equivalent across treatments in the absence of data.

In order to prevent negative/nonsensical MMDs, a minimum MMD threshold has been implemented. Responder minimum MMD reflects the minimum mean MMD of the patient cohort and does not imply that individual patients cannot have 0 MMDs within the model. The mean is used to calculate the distribution of patients over the range of MMDs, as described in Section B.3.3.5 of the company submission. If a minimum MMD of 0 was implemented, this leads to a non-realistic Poisson distribution for galcanezumab responders in EM (in that 100% of patients have 0 MMDs). Therefore, a value of 1 was chosen as a more realistic threshold. Although it is not logical to reduce the minimum mean MMDs to 0, the results of a scenario in which the responder minimum MMDs are set to 0 shows only a negligible impact on the cost-effectiveness results in the comparison vs galcanezumab in EM (and no impact on any other comparison across EM and CM; Table 1).

Table 1: Scenario analyses (atogepant PAS price) – minimum MMDs for responders

#	Description	Galcanezumab (120 mg)			Erenumab (140 mg)			Fremanezumab (225 mg)			Fremanezumab (675 mg)		
		Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]
EM													
Base Case		[redacted]	[redacted]	0.26	[redacted]	[redacted]	0.10	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.19
1	Responder minimum MMDs set to zero	[redacted]	[redacted]	0.26	[redacted]	[redacted]	0.10	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.19
CM													
Base Case		[redacted]	[redacted]	0.43	[redacted]	[redacted]	0.16	[redacted]	[redacted]	0.22	[redacted]	[redacted]	0.23
2	Responder minimum MMDs set to zero	[redacted]	[redacted]	0.43	[redacted]	[redacted]	0.16	[redacted]	[redacted]	0.22	[redacted]	[redacted]	0.23

Footnotes: [a]NHB calculated at a WTP threshold of £30,000.

Abbreviations: CM: chronic migraine; EM: episodic migraine; Inc.: incremental; MMD: monthly migraine days; NHB: net health benefit; PAS: patient access scheme; QALY, quality-adjusted life year; WTP: willingness-to-pay.

2. The B15 response justifies not including an 'on treatment' variable in the HRQoL regression by stating "AbbVie did not run the HRQoL regression using MMD and “on treatment” as covariates, as it would require treatments to be defined whereby patients are dynamically assigned based on whether they were still on study medication at the end of each model cycle and therefore is not feasible within the functionality of the model". Can the company further elaborate on why this is not possible, given that, in the model, patients are assigned to health states based on whether they were still "On Tx" or "Off Tx" at the end of each model cycle and each health state has an independent utility?

When the utility regression models were fitted to the trial data, the treatment covariate was based on randomisation. This approach is consistent with the modified intent-to-treat analyses of the primary and secondary endpoints of the atogepant trials. It is also consistent with the approach to regression models of utilities based on “treatment arm” used in the rimegepant economic model (see Section B.3.4.5, TA906).[2]

During the model fitting process, the treatment covariate was not recalculated dynamically from the trial data based on whether each trial participant was still taking the study drug at each time point, which would be required to reflect the "On Tx" or "Off Tx" health states as defined in the economic model. Attempting to dynamically define treatment status this way would require recalculating mean monthly migraine days separately for time periods when participants were still taking the study drug versus after they discontinued the study drug. In addition, the only observations that would have different values for treatment status compared with treatment assignment would be observations collected from participants who had discontinued the study drug but continued to fill in the daily migraine diary, and so it is expected that limited data would be available to truly capture treatment status dynamically.

Given the way the cost-effectiveness model is structured, it is more appropriate to use the utility regressions with a response covariate than the utility regressions with a treatment covariate, as differences in treatment efficacy in the economic model are primarily based on differences in response rates (which then translate into continued treatment due to the negative stopping rule for non-responders). Thus, the regression models with the response covariate are likely to produce more reliable estimates of the relative value of different treatments than the regression models with the treatment covariate, which are based on trial data for both responders and non-responders (i.e. does not differentiate between responders and non-responders for each treatment respectively). Furthermore, a response-based regression accounts for an added utility benefit for responders beyond a lower number of MMDs, for example caused by reducing the severity of MMDs or by reducing non-migraine headache days.

3. In addition to our request for further clarification on the company's response to B15, please can the company provide the coefficients and SE from the regression requested in B15 a and b?

The requested values (coefficient and standard error [SE]) are available in the economic model on worksheet 'Utilities'. Rows 31–43 detail the active values used in the model (repeated below for clarity; Table 2 for EM, Table 3 for CM). Rows 46–128 within the 'Utilities' tab present values for all regressions run.

Table 2: HRQoL regression coefficients and SE in EM (3+ TF population)

	Coefficient	SE
Response-based		
Intercept	[redacted]	[redacted]
MMD	[redacted]	[redacted]
Response	[redacted]	[redacted]
MMD only		
Intercept	[redacted]	[redacted]
MMD	[redacted]	[redacted]
Treatment-based		
Intercept	[redacted]	[redacted]
MMD	[redacted]	[redacted]
Treatment	[redacted]	[redacted]

Abbreviations: EM: episodic migraine; HRQoL: health-related quality of life; MMD: monthly migraine days; SE: standard error; TF: treatment failure.

Table 3: HRQoL regression coefficients and SE in CM (overall population)

	Coefficient	SE
Response-based, Active definition: 30%		
Intercept	[redacted]	[redacted]
MMD	[redacted]	[redacted]
Response	[redacted]	[redacted]
MMD only		
Intercept	[redacted]	[redacted]
MMD	[redacted]	[redacted]
Treatment-based		
Intercept	[redacted]	[redacted]
MMD	[redacted]	[redacted]
Treatment	[redacted]	[redacted]

Abbreviations: CM: chronic migraine; HRQoL: health-related quality of life; MMD: monthly migraine days; SE: standard error.

4. The EAG acknowledges the company's response to clarification question B5 and has been able to validate the point estimates in Table 42 of the CS using the method described. However, the EAG is unsure how the respective credible intervals (CrIs) for erenumab (and botulinum toxin in appendix O) have been obtained, particularly as they appear much narrower than those for comparators that were included in the NMA for 30% responders. Please can the company outline how CrIs were obtained for the 30% responders outcome for these two comparators (providing a worked example for one of the comparators may help).

AbbVie can confirm that the CrIs for erenumab and botulinum toxin type were calculated in the same way as the point estimate, given data were not available for either treatment within the NMA. These values were calculated using data from the ≥50% response rate endpoint. As the CrIs for ≥50% response rate were narrow for both comparators, the CrIs calculated for the ≥30% response rate for botulinum toxin type A and erenumab using the conversion method are therefore expectedly narrower than those for comparators that were included in the NMA for 30% responders. As the network for ≥50% response rate contained more available data across more of the relevant comparators than the ≥30% response rate network (see CS appendices Figure 16/Figure 17 [NMA network diagrams], and Table 21 [NMA input data], it is expected that these CrIs are narrower.

Please find below a worked example for the calculation of the lower/upper bound values for 30% response odds ratios for erenumab (based on the conversion from available 50% response data):

- The general conversion factor from 50% response to 30% response data ([redacted]) is based on the average relative difference between 50% response and 30% response odds ratios for the available comparator treatments across both networks (placebo, fremanezumab 225 mg, fremanezumab 675 mg, galcanezumab); i.e. on average for the treatments available in both networks, 30% response odds ratios were [redacted]% higher than the equivalent 50% response values
- This factor was then used to convert 30% response values (including median, lower and upper bound) for erenumab from the available 50% response data, through simple multiplication (economic model 'NMA' worksheet; columns EL–ER, rows 13–20):
    - Median: [redacted]
    - Lower bound: [redacted]
    - Upper bound: [redacted]

References

1. National Institute for Health and Care Excellence. Fremanezumab for preventing migraine [TA764], 2021.
2. National Institute for Health and Care Excellence. Rimegepant for preventing migraine [TA906]. Available at: https://www.nice.org.uk/guidance/ta906 [Last accessed: 01/08/2023].

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Cost Comparison Appraisal
Atogepant for preventing migraine [ID5090]
Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

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- Your response should not be longer than 10 pages.

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About you

1.Your name	[redacted]
2. Name of organisation	The Migraine Trust
3. Job title or position	
4a. Brief description of the organisation (including who funds it). How many members does it have?	The Migraine Trust is dedicated to helping the 10 million people affected by migraine. We are the only UK migraine charity providing information and support, campaigning for awareness and change, and funding and promoting research. One in seven people in the UK live with migraine, and this complex and debilitating neurological disorder significantly affects their lives. We have been leading and bringing the migraine community together to change this since 1965. Every year over two million people visit our website and thousands contact our helplines and other support services for information and support on all aspects of migraine and for help in managing it at work, in education, and in accessing healthcare. We campaign for increased awareness and understanding of migraine, and national policy change to improve the lives of people who get it. We have funded over 140 medical research projects and hold an international symposium every two years to bring together the world's leading experts on migraine. We are funded through legacies, individual donations, community and event fundraising, corporate partnerships, trusts and foundations, and industry. We are not a membership organisation. We have over 30,000 people signed up to receive our monthly e-bulletin.

4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	We have received the following funding in the last twelve months • £22,605 from Abbvie to support our work in devolved nations • £20,000 from Lundbeck for our support services. • £34,500 from Lilly to support a GP migraine awareness campaign • A commitment of £157,500 from Pfizer to support two research fellowships in 2022-23 and 2023-24 with £82,500 being given in 2022-23
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We regularly run surveys of people affected by migraine across the UK, to understand their experience and identify gaps of unmet needs to obtain information on their experience of the impact of migraine and treatments on their symptoms and ability to function. We also have regular contact on our helplines with people affected by migraine. We feel there is relevant data that can be drawn from these sources. Some recent surveys and sources: ***1.*** **CGRP user survey 2023:** We received 500 responses to this new survey around access and use of CGRP mAbs, which closed in early February. It also provides our most up to date data on feedback on the mAbs. Of the 186 people in the survey who have been prescribed CGRP mAbs: • 84% said they had reduced the frequency of their attacks, • 86% said it reduced the frequency of their symptoms,

- 86% said they have improved their migraine more than any other preventive and
- 87% said that they have improved the quality of their life.
- When asked 'How effective at treating your migraine are the non-CGRP mAb preventive treatments that you have tried?' 80% said not effective or a little effective. Only 6% said significantly effective.

2. **CGRP user survey 2022:**

We received 304 responses from active users of CGRP mAbs. Of those 30-50% found it had improved their quality of life in some aspect namely: the treatment was effective, well tolerated with manageable or no side effects and by its impact on their quality of life.

3. **Women's survey Jan-Mar 2022:**

We received over 700 responses on the impact of migraine on their lives and relationships

4. **Men's survey 2021:**

We surveyed 350 men and found similar results to those in our Women's survey. This demonstrates the impact of migraine upon both men and women and the need to provide treatments that work and access to all who need it.

5. **Migraine community survey 2019:**

This was completed by over 1,800 people affected by migraine, including patients, their carers, friends and family.

6. **CGRP Patient Experience Survey (2019):**

We received 203 responses from patients who were taking (or had recently taken) a CGRP drug for the prevention of their migraine. It showed that for patients who had tried both botox and a cgrp monoclonal antibody at different times, 78% agreed or strongly agreed that the CGRP drug was more effective at controlling their migraine and 76% felt it had improved their quality of life.

	7. **'Dismissed for too long' our report launched in September 2021:** this included a nationally representative commissioned censuswide poll in July 2021 and FOI requests to NHS Trusts across the UK in May 2021, which included questions around migraine care and access to CGRP mAbs.

Current treatment of the condition in the NHS

6. Do people using the technology feel that it works in the same way as the comparator(s)?	Atogepant is not approved for use in the UK hence we have not received feedback from users. However, we have heard that the current migraine preventive treatment is inadequate. In response to a question in our recent CGRP mAbs survey (Feb 23) that asked 'How effective at treating your migraine are the non-CGRP mAb preventive treatments that you have tried?' 80% said not effective or a little effective. Only 6% said significantly effective. Our CGRP Patient Experience Survey found that 90% of respondees had experienced adverse side-effects from migraine preventives, excluding CGRP. They told us: ""Propranolol side-effects were so bad that I had to take a month off of work." "Low blood pressure from beta blockers and horrendous brain fog from Topamax. It was so intense that I had to come off the drug." "I tried Botox and had a reaction to it. My throat swelled and I had a hard time breathing." "Some preventives have caused me to have brain fog, taste changes, musculoskeletal pain, and sleepiness during the day." Regardless of these side-effects, it is also important to stress that these 'first line' preventives also don't work for everyone with migraine, or they can stop working relatively quickly. Our CGRP Patient Experience Survey shows that 78% of respondees had tried more than five different preventives and 70% had also failed to respond to more than five different preventives. Patients told us: "No preventives have been successful, apart from topiramate which works for a couple of months and then stops completely." Topiramate is very poorly tolerated in greater than 50% of patients and is not advised for women of child-bearing age. "I have tried everything there is to try! Anti-depressants, anti-convulsants, HRT, etc. I experienced unpleasant side-effects to a greater or lesser extent from everything and no relief from migraine at all."

7. Are there any key differences?	Atogepant targets the mechanism of migraine and is not a re-purposed medication. Therefore, we feel it has the potential to better control migraine frequency and severity and positively impact people affected by migraine.
8. Will this technology be easier, the same, or more difficult to take than the comparator(s)? If so, please explain why	Migraine specialist preventive treatments such as mAbs and botulinum toxin A, have helped many people but access to a specialist and specialist preventive treatments, has been unequal and inadequate across the country. An oral treatment, accessible in primary care would have the advantage of reaching more people with migraine sooner.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	If we draw parallels from the responses to the CGRP mAbs, as the currently available CGRP preventive option, some patient responses received were: "I now only use only sumatriptan and cyclizine for the sickness. I use no other drugs which is wonderful. My triptan use has gone from the max allowed of 10 per month to max of 3 per month." " it has reduced the number of days dramatically that I need to go to bed, and reduced the uncertainty of having to cancel social events with the result that my mood is much better." "I managed to stop taking triptans and I drastically reduced my intake of over the counter medications." "Head feels clearer. More able to tackle major jobs." "Fewer severe headaches". "Migraines are less intense so I may recover from the pain phase with a few hours rather than a few days". From our 2023 CGRP user survey 84% said they had reduced the frequency of their attacks: • 86% said it reduced the frequency of their symptoms, • 86% said they have improved their migraine more than any other preventive and • 87% said that they have improved the quality of their life. • When asked 'How effective at treating your migraine are the non-CGRP mAb preventive treatments that you have tried?' 80% said not effective or a little effective. Only 6% said significantly effective From our CGRP user survey 2022 with 304 responses of active users of cgrp mAbs: • 30-50% found it had improved their quality of life in some aspect namely: the treatment was effective, well tolerated with manageable or no side effects and by its impact on their quality of life. • However, 26% felt it did not meet their expectation.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Lack of familiarity with the treatment will require education and guidance for primary care clinicians.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Atogepant may be beneficial to meet the needs of patients who cannot self-inject (eg mAbs), or cannot tolerate multiple injections (eg Botulinum toxin A) are needle-phobic or cannot make multiple trips to hospital for regular injectable preventive treatment due to other health conditions as well as patients who have experienced intolerable side effects from the non-migraine specific oral medications (e.g. tricyclic antidepressants, betablockers, topiramate) and those at risk of medication overuse complications with acute treatments.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	• Migraine can be classed as a disability under the Equality Act 2010 • We need to ensure that appropriate treatments are available for everyone including those who cannot self-administer due to physical, cognitive or other disability, are needle-phobic and those who may have additional disability due to side effects when taking multiple oral medications. • Our recent research showed that there were similar levels of impact in general and across work, social life, family, and mental health, but all significantly high. Best available care will not adequately meet the need of a number of people with migraine.

	Men	Women
General	75%	80%
Work	84%	85%
Social	82%	88%
Family	71%	76%
Mental health	73%	65%

Key messages

13. In up to 5 bullet points, please summarise the key messages of your submission.	**Many patients have not found benefit or adequate benefit, satisfactory tolerability, or access to an appropriate treatment***:* • *Having a treatment that is beneficial and specifically targets the range of migraine symptoms with minimal side effects is crucial.* • *There is an unmet need for patients who cannot self-inject (eg mAbs), are needle-phobic, cannot tolerate multiple injections (eg Botulinum toxin A), or gain access to a specialist headache clinic.* • *A well tolerated preventive treatment will help with patient adherence and limit or reduce reliance on acute and over the counter medications that are implicated in medication overuse and associated complications.* • *Making such a treatment available in primary care would enable more equitable access, with fewer potential delays and costs incurred for specialist services.* Access to the treatment from any headache specialist clinician (e.g. headache nurses), across healthcare services should be considered. • *Having an effective treatment will improve the quality of life and the ability to function for people debilitated by migraine, which will hugely impact work, education, family and social life and reduce the demand for healthcare services (including GP, emergency and specialist services).*

Thank you for your time.

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Cost Comparison Appraisal

Atogepant for preventing migraine [ID5090]

Professional organisation submission

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You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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- Your response should not be longer than 13 pages.

1. Your name	[redacted]
2. Name of organisation	Association of British Neurologists headache and pain advisory group
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	• An employee or representative of a healthcare professional organisation that represents clinicians? Yes • A specialist in the treatment of people with this condition? Yes • A specialist in the clinical evidence base for this condition or technology? No • Other (please specify):
5. Brief description of the organisation (including who funds it).	The Association of British Neurologists is the professional body that represents neurologists in the UK to 'promote excellent standards of care and champion high-quality education and world-class research in neurology'. The ABN is funded by subscriptions from members. The advisory group members are self-nominated and selected by the elected council members, the Chair is nominated from the members by ABN council
6. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] If so, please state the name of manufacturer, amount, and purpose of funding.	no
7. Do you have any direct or indirect links with, or funding from, the tobacco industry?	no

8. Is the technology clinically similar to the comparator(s)? Does it have the same mechanism of action, or a completely different mechanism-of-action? Or in what way is it different to the comparator(s)?	Atogepant is a Calcitonin Gene-Related Peptide (CGRP) receptor antagonist, pharmacologically similar to rimegepant and administered as a daily tablet. However, rimegepant is used not only for prevention of migraine but also for acute treatment. Although atogepant acts on the same biochemical pathway as the CGRP monoclonal antibodies that have been approved by NICE (fremanezumab, galcanezumab, erenumab and eptinezumab) the route of administration, frequency of dosing and pharmacokinetics are different and there may be differences in clinical effectiveness. This class of drugs have a completely different mechanism of action from standard migraine preventatives such as tricyclics and beta-blockers as they target the putative underling pathogenic mechanism of migraine: reducing the biological activity of CGRP.
9. If there are differences in effectiveness between the technology and its comparator(s) are these clinically meaningful?	The differences in trial design and placebo rates between studies makes direct comparisons difficult. A direct comparison between atogepant and rimegepant is also difficult as the phase 3 study of atogepant (Ailani NEJM 2021) was conducted in patients with episodic migraine (mean range of 7.5- 7.9 monthly migraine days at baseline) whereas the phase 2/3 study of rimegepant (Croop Lancet 2021) included patients with chronic migraine (mean range of 10.2 monthly migraine days at baseline). Similarly, the randomised controlled trials (RCTs) of the CGRP monoclonal antibodies included those with chronic migraine. Patient were excluded from the Ailani study if they had failed more than 4 other preventatives from at least 2 other classes: this is the group of patients in whom a novel agent is most likely to be used, and direct comparison with the RCTs examining CGRP monoclonal antibody therapies, that included this difficult to treat population, cannot be made. Based on the published RCTs above, there is a clinically meaningful difference in the reduction of mean monthly migraine days comparing atogepant (range dependent on dose -1.2 to -1.7 v placebo) to rimegepant (-0.8 v placebo), but this may be predictable from the daily dosing schedule for atogepant compared to the alternative daily dosing schedule of rimegepant whilst half lives are similar. The reduction in monthly migraine days is less than that reported with CGRP monoclonal antibodies

10. What impact would the technology have on the current pathway of care?	Atogepant would be another option for patients with episodic migraine. It is easy to administer and current data suggest that has tolerability and safety profile similar to placebo: use of many preventative medications is limited by their side effects e.g. somnolence, weight gain, depression, and hypotension. This may be a technology that could safely be used in primary care thus avoiding the burden on secondary care pathways.
11. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The treatment could be prescribed by those with special expertise in headache disorders – both in primary and secondary care. It would lend itself well to care models of community-based clinics supported by specialist consultants in secondary care.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Similar: patients should have a holistic approach to headache care involving life-style factors, optimising acute treatment and choice of preventative based on efficacy, safety and tolerability. There is a need in the UK for better models of headache care involving community based clinics supported by specialist consultants in secondary care.
13. Have there been substantial changes to the treatment pathway since the comparator appraisal that might impact the relevance of the comparator's appraisal?	Epitinezumab, an intravenous CGRP monoclonal antibody has been approved by NICE Publication of The Optimum Clinical Pathway for adults with headache and facial pain by the NATIONAL Neurociences Advisory Group https://www.nnag.org.uk/optimal-clinical-pathway-for-adults-with-headache-facial-pain should be taken into consideration

14. Overall, is the treatment likely to offer similar or improved health benefits compared with the NICE-recommended comparator?	Similar to rimegepant, but improved compared to existing standard of care – potentially better tolerability
15. Do the clinical trials on the technology reflect current UK clinical practice?	No: the clinical trials excluded those who had previously failed 4 or more preventives from at least 2 classes of drugs, it is likely that atogepant would, at least initially, be used in those refractory to standard care
16. Is the technology likely to affect the downstream costs of managing the condition (for example, does it affect the subsequent treatments)	Better preventive treatment of migraine reduces acute care costs both in terms of medication used and health care resources including emergency care
17. Are there any potential equality issues that should be taken into account when considering this treatment? Consider whether these issues are different from issues with current care and why	Migraine is more common in women (22%) compared to men (8%).

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- Your response should not be longer than 13 pages.

1. Your name	[redacted]
2. Name of organisation	British Association for the Study of Headache (BASH)
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	• An employee or representative of a healthcare professional organisation that represents clinicians? Yes • A specialist in the treatment of people with this condition? Yes • A specialist in the clinical evidence base for this condition or technology? No • Other (please specify):
5. Brief description of the organisation (including who funds it).	The aim of BASH is to promote education on headache disorders both among professionals and members of the general public. It is funded by subscriptions from members. The advisory group members are self-nominated and selected by the elected council members, the Chair is nominated from the members by BASH council
6. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] If so, please state the name of manufacturer, amount, and purpose of funding.	no
7. Do you have any direct or indirect links with, or funding from, the tobacco industry?	no

8. Is the technology clinically similar to the comparator(s)? Does it have the same mechanism of action, or a completely different mechanism-of-action? Or in what way is it different to the comparator(s)?	Atogepant is a Calcitonin Gene-Related Peptide (CGRP) receptor antagonist. It is a CGRP receptor antagonist and pharmacologically similar to Rimegepant. It is administered as a daily tablet and used for prevention of migraine. Rimegepant is used for migraine prevention and for acute treatment. Although atogepant acts on the same biochemical pathway as the CGRP monoclonal antibodies that have already been approved by NICE (fremanezumab, galcanezumab, erenumab and eptinezumab) the route of administration, frequency of dosing and pharmacokinetics are different and there may be differences in clinical effectiveness. This class of drugs has a completely different mechanism of action from standard migraine preventatives such (e.g. tricyclic antidepressants and beta blockers) as they target the putative underling pathogenic mechanism of migraine and reduce the biological activity of CGRP.
9. If there are differences in effectiveness between the technology and its comparator(s) are these clinically meaningful?	Differences in trial design and placebo rates between studies makes direct comparisons difficult. Direct comparison between atogepant and rimegepant is also made difficult as the main trials were conducted in different types of migraine patients. Atogepant (Ailani NEJM 2021) was conducted in patients with episodic migraine (mean range of 7.5- 7.9 monthly migraine days at baseline) whereas rimegepant (Croop Lancet 2021) included patients with chronic migraine (mean range of 10.2 monthly migraine days at baseline). Similarly, the randomised controlled trials (RCTs) of the CGRP monoclonal antibodies included those with chronic migraine. Furthermore, patients were excluded from the atogepant study if they had failed more than 4 other migraine preventatives from at least 2 other classes: this is the group of patients in whom a novel agent is most likely to be used. Direct comparison with the RCTs examining CGRP monoclonal antibody therapies, which included this difficult to treat population, therefore cannot be made. The small difference in reduction of mean monthly migraine days between atogepant (range dependent on dose -1.2 to -1.7 v placebo) and rimegepant (0.8 v placebo), can probably be explained by the dosing regimens: atogepant is taken daily, whereas rimegepant is taken on alternate days. The reduction in monthly migraine days is less than that reported with CGRP monoclonal antibodies.

10. What impact would the technology have on the current pathway of care?	Atogepant would be another option for patients with episodic migraine. Oral administration is easy and current data suggest that atogepant has tolerability and safety profile similar to placebo. Use of many other oral preventative medications is limited by their side effects e.g. somnolence, weight gain, depression, hypotension. This may be a technology that could safely be used in primary care, thus avoiding the burden on secondary care pathways.
11. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Atogepant could be prescribed in primary and secondary care by those with special expertise in headache disorders. This would therefore lend itself to care models of community-based headache clinics supported by specialist consultants in secondary care.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Atogepant would be used in a similar way to other migraine preventatives. All migraine patients should have a holistic approach to management. This includes addressing life-style factors and optimising acute treatment and preventative medication based on efficacy, safety, tolerability and where possible, patient choice.
13. Have there been substantial changes to the treatment pathway since the comparator appraisal that might impact the relevance of the comparator's appraisal?	Recently, epitinezumab, an intravenous anti-CGRP monoclonal antibody therapy was approved by NICE. Publication of The Optimum Clinical Pathway for adults with headache and facial pain by the NATIONAL Neurociences Advisory Group https://www.nnag.org.uk/optimal-clinical-pathway-for-adults-with-headache-facial-pain should be taken into consideration.

14. Overall, is the treatment likely to offer similar or improved health benefits compared with the NICE-recommended comparator?	Similar to Rimegepant. Improved compared to existing standard of care (e.g. Tricyclic antidepressants, beta blockers) and potentially has better tolerability.
15. Do the clinical trials on the technology reflect current UK clinical practice?	No: the clinical trial excluded those who had previously failed 4 or more preventives from at least 2 classes of drugs. It is likely that atogepant would, at least initially, be used in those refractory to standard care.
16. Is the technology likely to affect the downstream costs of managing the condition (for example, does it affect the subsequent treatments)	Yes: Better preventive treatment of migraine reduces acute care costs both in terms of medication used and health care resources including emergency care.
17. Are there any potential equality issues that should be taken into account when considering this treatment? Consider whether these issues are different from issues with current care and why	Migraine is significantly more common in women (22%) compared to men (8%).

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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BMJ TAG

Atogepant for preventing migraine [ID5090]

STA Report

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Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Nicole Downes	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies and analyses; and drafted the clinical sections
Victoria Wakefield	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; and assisted with clinical sections
Isaac Mackenzie	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

All authors read and commented on draft versions of the EAG report.

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List of Abbreviations

3+ TF	Patients in whom ≥3 prior preventive treatments have failed
A&E	Accident and emergency
AE	Adverse event
BASH	British Association for the Study of Headache
BNF	British National Formulary
BoNT/A	Botulinum toxin type A
BSC	Best supportive care
CCE	Cost-comparison evaluation
CFB	Change from baseline
CGRP	Calcitonin gene-related peptide
CI	Confidence interval
CM	Chronic migraine
CQ	Clarification question
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company submission
CSR	Clinical study report
CYP3A4	Cytochrome P450 3A4
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	External Assessment Group
eDiary	Electronic diary
EM	Episodic migraine
Epti	Eptinezumab
EQ-5D	European Quality of Life 5 Dimensions
EQ-5D-3L	European Quality of Life 5 Dimensions 3 Level Version
Ere	Erenumab
FE	Fixed effect
Fre	Fremanezumab
Gal	Galcanezumab
GP	General practitioner
HCRU	Healthcare resource use
HIT-6	Headache impact test-6
HR	Hazard ratio
HRG	Healthcare resource group
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ITT	Intent-to-treat
IWRS	Interactive Web Response System

IV	Intravenous
LS	Least squares
LSMD	Least squares mean difference
mAb	Monoclonal antibody
MAIC	Matching-adjusted indirect comparison
MAR	Missing-at-random
MD	Mean difference
MHD	Monthly headache day
mITT	Modified intent-to-treat
MMD	Monthly migraine days
MMRM	Mixed Model for Repeated Measures
MSQ	Migraine-specific quality of life questionnaire
MSQ-EF	Migraine specific quality of life emotional function subdomain
MSQ-RFP	Migraine specific quality of life role function-preventive subdomain
MSQ-RFR	Migraine specific quality of life role function-restrictive subdomain
MUD	Medication use day
N/A	Not applicable
NCT	National Clinical Trial
NHB	Net health benefit
NHS	National Health Service
NHWS	National Health and Wellness Survey
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
OATP	Organic anion transporting polypeptide
OR	Odds ratio
PAS	Patient access scheme
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PSSRU	Personal social services research unit
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RE	Random effect
Rim	Rimegepant
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of Product Characteristics

STA	Single technology appraisal
TA	Technology appraisal
TE	Treatment effect
TEAE	Treatment-emergent adverse event
TF	Treatment failure
Tx	Treatment
UK	United Kingdom
WTP	Willingness-to-pay

1 Executive summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Section 1.3 explains the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1. Summary of key issues

Issue	Summary of issue	Report sections
1	Exclusion of BoNT/A, rimegepant and eptinezumab as comparators in this STA	2.2.1, 2.3.3, 3.4.5, 4.2.3.3
2	NMAs within the overall migraine population vs 3+ TF subgroup for MMD-related outcomes in EM	3.4.1, 3.4.3, 4.2.6.4
3	Company preference for results from RE unadjusted NMAs for all outcomes in EM and CM	3.4.1, 3.4.3, 4.2.6.4
4	Uncertainty concerning the efficacy of atogepant vs comparators due to a lack of direct evidence and limitations of the NMAs	3.4.4
5	Uncertainty in the justification for the presence of monitoring costs	4.2.10.4
6	Inadequate source for injection related disutility	4.2.7.1
7	Incorrect calculation of long-term discontinuation	4.2.6.4

Abbreviations: 3+ TF, patients in whom ≥3 prior oral preventive treatments have failed; BoNT/A, botulinum toxin type A; CM, chronic migraine; EAG, External Assessment Group; EM, episodic migraine; MMD, monthly migraine days; NMA, network meta-analysis; RE, random effects; STA, single technology appraisal.

1.2 Overview of key model outcomes

Overall, the technology is modelled to affect quality-adjusted life years (QALYs) by:

- Reducing the number of monthly migraine days (MMDs) – the monoclonal antibodies (mAbs) are similarly effective at reducing MMDs as atogepant and therefore atogepant results in similar QALYs to the mAbs.

Overall, the technology is modelled to affect costs by:

- Reducing the number of MMDs which reduces the number of healthcare costs (the difference between the mAbs reduction in MMDs and atogepant is not statistically significant;
- Negative discontinuation rules, a higher proportion of mAb patients discontinue before the assessment period though a higher proportion achieve the assessment goal of more than or equal to 50% reduction in MMDs and so stay on treatment;
- Its lower unit price compared to the mAbs;
- Being given as a tablet, rather than intravenously (incurring one-off training costs on how to self-administer treatment and ongoing administration costs for patients who cannot self-administer treatment).

The modelling assumptions that have the greatest effect on the ICER are:

- Unit drug cost;
- Response;
- Long-term discontinuation.

1.3 Summary of the EAG's key issues

Table 2. Issue 1: Exclusion of BoNT/A, rimegepant and eptinezumab as comparators in this STA

Report section	2.2.1, 2.3.3, 3.4.5
Description of issue and why the EAG has identified it as important	In the CS, the company states that BoNT/A (CM only), rimegepant (EM only) and eptinezumab (EM and CM) are not relevant comparators for atogepant in the 3+ TF subgroup outlined in the decision problem. The company has provided NMA results for BoNT/A and included it in the economic model as a scenario, but the same was not done for rimegepant or eptinezumab. Given that the NICE recommendations for all three of these treatments is the same as that outlined for atogepant (albeit specific to CM and EM populations, respectively, for BoNT/A and rimegepant), the EAG considers it important that these treatments are also explored as comparators.[1-3] Furthermore, feedback from the EAG's clinical experts supports the inclusion of BoNT/A and rimegepant as comparators in the relevant populations, although there was less concern about eptinezumab being included as they considered it to be more resource intensive.
What alternative approach has the EAG suggested?	The EAG considers it important that these three comparators are included in this appraisal and considered as comparators during the decision-making process. The consideration of BoNT/A as a comparator in CM has already been facilitated by the company given NMA results have been provided and a scenario performed in the economic model. For rimegepant and eptinezumab, in response to CQ A1, the company reiterated its rationale for not including these two treatments as comparators and did not update NMAs or the economic model. The EAG has, therefore, updated the NMAs to include data for these treatments in the NMAs and included them as comparators in the economic model.
What is the expected effect on the cost-effectiveness estimates?	The inclusion of these treatments will not impact the pairwise cost-effectiveness estimates of treatments that the company already considers to be relevant comparators for this appraisal vs atogepant 60 mg (erenumab, galcanezumab and fremanezumab) but the results of the fully incremental analysis may change. ICERs for these additional treatments are included in Sections 6.2 and 6.3.
What additional evidence or analyses might help to resolve this key issue?	The EAG considers that the EAG-updated NMAs and economic model allow consideration of the clinical and cost-effectiveness of atogepant vs these additional comparators. Further clinical expert input may be useful to determine whether consideration of these treatments as comparators is important.

Abbreviations: 3+ TF, patients in whom ≥3 prior preventive treatments have failed; BoNT/A, botulinum toxin type A; CM, chronic migraine; CQ, clarification question; CS, company submission; EAG, External Assessment Group; EM, episodic migraine; ICER, incremental cost-effectiveness ratio; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; STA, single technology appraisal.

Table 3. Issue 2: NMAs within the overall migraine population vs 3+ TF subgroup for MMD-related outcomes in EM

Report section	3.4.1, 3.4.3
Description of issue and why the EAG has identified it as important	For EM, the company has a preference for NMAs of MMD-related outcomes performed within the 3+ TF subgroup of ELEVATE given this trial was stratified for this factor at randomisation. However, the EAG notes that the comparator trials that provide 3+ TF subgroup data for EM (CONQUER, FOCUS and LIBERTY) were not stratified for this factor at randomisation (and baseline characteristics for this subgroup are not well reported), meaning bias for this analysis could be increased compared to the overall migraine population analyses in EM. Furthermore, the company prefers the RE unadjusted versions of these NMAs, which the EAG disagrees with given there does not appear to be sufficient data to inform between-study heterogeneity and uncertainty may be exacerbated unnecessarily. The company uses a lack of stratification for 3+ TF in the PROGRESS trial as a reason not to prefer analyses within the 3+ TF subgroup for MMD-related outcomes in CM, which the EAG accepts. Given this preference within the CM population, the potentially increased bias for the 3+ TF EM analyses, scarceness of the data in this specific subgroup (only one study for each comparison and smaller sample sizes included) and feedback from the EAG's clinical experts that there are no concerning differences between the 3+ TF and overall population of ELEVATE in terms of baseline characteristics, the EAG prefers the NMAs within the overall migraine population for EM, as well as CM, are used to inform the economic model. Given the results of these analyses differ at least slightly compared to the company's preferred analyses, this has the potential to alter cost-effectiveness outputs from the economic model. The EAG agrees with the company's preference for analyses in the overall migraine population for all other analyses, including all outcomes in CM and HRQoL, discontinuation and TEAE outcomes in EM. While it notes that using the overall migraine population for NMAs may reduce the applicability of these analyses to the population outlined in the decision problem (3+ TF), it acknowledges that data for discontinuation, TEAEs and HRQoL are particularly scarce for this subgroup and considers the analyses for MMD-related outcomes to be more robust in the overall migraine population.
What alternative approach has the EAG suggested?	For MMD-related efficacy outcomes in EM, the EAG has a preference for the overall migraine population analyses rather than the 3+ TF subgroup preferred by the company. The results of these are presented as the EAG's preferred NMAs within Section 3.4.3.1 Furthermore, the EAG considers the RE unadjusted NMAs for this 3+ TF subgroup in EM to be inappropriate given there appears to be insufficient data to inform between-study heterogeneity in these analyses and that a FE analysis would be more appropriate should the results in this subgroup be favoured.
What is the expected effect on the cost-effectiveness estimates?	In the CS, the use of the overall migraine population NMA data was explored as scenario 7a. This scenario was associated with [redacted] in NHB vs galcanezumab, erenumab and 225 and 675 mg fremanezumab, most notable for the comparison vs galcanezumab (Table 56 below). In terms of ICERs, when this preference was incorporated in addition to the EAG's other preferred changes to NMAs used in the model (see Key Issue 3 described in Table 4 below), it had a positive impact on atogepant results, with erenumab and galcanezumab remaining [redacted] and other comparators included by the company (fremanezumab 225 mg and 675 mg) also now [redacted] (see Table 60).

What additional evidence or analyses might help to resolve this key issue?	The EAG does not consider that any further evidence is required.

Abbreviations: 3+ TF, patients in whom ≥3 prior preventive treatments have failed; CM, chronic migraine; CS, company submission; EAG, External Assessment Group; EM, episodic migraine; FE, fixed effects; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; MMD, monthly migraine days; NHB, net health benefit; NMA, network meta-analysis; RE, random effects; STA, single technology appraisal; TEAE, treatment-emergent adverse events.

Table 4. Issue 3: Company preference for results from RE unadjusted NMAs for all outcomes in EM and CM

Report section	3.4.1, 3.4.3
Description of issue and why the EAG has identified it as important	The company has a preference for RE unadjusted NMAs for all outcomes in EM and CM populations, explaining that this is because there is reason to believe that heterogeneity exists amongst studies (meaning RE analyses are appropriate) and that RE analyses adjusted for baseline risk (placebo response) across studies do not lead to a substantially improved model fit. While the EAG agrees with RE analyses in most cases (the exception being when the 3+ TF subgroup results in EM are used by the company, although the EAG does not have a preference for 3+ TF analyses as described in Table 3), on review of model fit and impact on between-study heterogeneity, the EAG has a preference for alternative analyses for many outcomes. In most (but not all) cases this is a preference for RE adjusted rather than RE unadjusted analyses given the between-study heterogeneity estimated within the network is reduced with adjustment. Given the results of these analyses differ at least slightly compared to the company's preferred analyses, this has the potential to alter cost-effectiveness outputs from the economic model. EAG preferences that differ to the company's preferences are outlined below: • RE adjusted analyses for all MMD-related outcomes in EM (and within the overall migraine population rather than 3+ TF as already discussed in Table 3); • RE adjusted analyses for CFB in MMDs and ≥50% MMD reduction outcomes in CM; • FE unadjusted analysis for ≥30% MMD reduction in CM, given there appears to be insufficient data to inform between-study heterogeneity in the RE analysis (and adjusted analyses would not converge); • RE adjusted analysis for discontinuation in EM. The EAG notes that analyses adjusting for baseline risk (placebo response) were not performed for HRQoL or TEAE outcomes and the company and EAG has a preference for RE over FE analyses. While a lack of analyses with adjustment for these outcomes may be a limitation, the EAG notes that none of these analyses are used to inform the economic model.
What alternative approach has the EAG suggested?	Outcomes for which the EAG's preferred NMA models differ to the company's preferred models are outlined in the previous row.
What is the expected effect on the cost-effectiveness estimates?	The impact of the EAG's preferences in terms of NMAs used in the economic model on ICERs is demonstrated in Table 60 and Table 61. For EM, the EAG notes that this is the combined effect of changes to preferred NMA models as well as a preference for the analysis in the overall migraine population (see Key Issue 2 in Table 3 above). For EM, these changes had a positive impact on atogepant results, with erenumab and galcanezumab remaining [redacted] and other comparators included by the company (fremanezumab 225 mg and 675 mg) also now [redacted] (see Table 60). Similar was observed for CM; results for all comparators other than erenumab were [redacted] when these preferences were incorporated.

What additional evidence or analyses might help to resolve this key issue?	The EAG does not consider that any additional evidence regarding MMD-related outcomes is required. It notes that a lack of baseline-adjusted analyses for HRQoL outcomes and TEAEs may be a limitation but does not consider this to be a priority given these outcomes are not used to inform the economic model.

Abbreviations: 3+ TF, patients in whom ≥3 prior preventive treatments have failed; CFB, change from baseline; CM, chronic migraine; EAG, External Assessment Group; EM, episodic migraine; FE, fixed effects; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; MMD, monthly migraine days; NMA, network meta-analysis; RE, random effects; TEAE, treatment-emergent adverse events.

Table 5. Issue 4: Uncertainty concerning the efficacy of atogepant vs comparators due to a lack of direct evidence and limitations of the NMAs

Report section	3.4.4
Description of issue and why the EAG has identified it as important	The EAG notes that there is no direct evidence available for atogepant vs any of the comparators included in this appraisal, and clinical effectiveness estimates used in the economic model are from indirect comparisons. The company highlights various factors that differ across studies included in the NMAs, particularly overall migraine population analyses, which the EAG has discussed and added to in Section 3.4.4. This includes differences in terms of study population and concomitant treatments received, outcome definitions and time-points, methods of analysis and differences in placebo response. The EAG considers these differences to be unavoidable given data that can be used for comparator studies depends on what methods have been used in those trials and what has been published. Where appropriate, the EAG has a preference for analyses that have adjusted for baseline risk (placebo response), which should reduce some uncertainty related to this aspect. Furthermore, the use of RE analyses over FE analyses in most cases should capture some of this remaining uncertainty, although the EAG notes that this does not completely resolve concerns about any heterogeneity that may remain unaccounted for. Differences between studies, such as clinical and methodological heterogeneity, that may not be completely accounted for even in the EAG's preferred NMAs may reduce the certainty with which conclusions about the relative effect of atogepant vs comparators can be made (and the resulting cost-effectiveness estimates).
What alternative approach has the EAG suggested?	The EAG considers the remaining heterogeneity between studies to be an unresolvable limitation of the data available for comparator studies given data analysed for comparator studies is reliant on data that has been published.
What is the expected effect on the cost-effectiveness estimates?	Any potential impact on the cost-effectiveness estimates is unclear.
What additional evidence or analyses might help to resolve this key issue?	The EAG considers these to be unresolvable limitations of the data available for comparator studies.

Abbreviations: 3+ TF, patients in whom ≥3 prior preventive treatments have failed; EAG, External Assessment Group; FE, fixed effects; NMA, network meta-analysis; RE, random effects.

Table 6. Issue 5: Potential double counting of monitoring costs

Report section	4.2.10
Description of issue and why the EAG has identified it as important	Healthcare specialist costs are already incorporated into the model under the umbrella of healthcare resource use, which applies these costs by patient MMD. There is no reason to believe these costs excluded monitoring. The company suggests prescription/monitoring costs will be lower for atogepant since prescriptions/monitoring can be provided 50:50 by specialists/GP to atogepant patients as opposed to 100% specialists with mAb/BoNT/A. The EAG is uncertain if this would be possible since in order to apply for a confidential PAS a treatment cannot be regularly prescribed in primary care and part of the company's case for lower monitoring costs is an expectation of different prescribing behaviour/ Furthermore, rimegepant, another oral treatment for prevention of migraine did not include any difference in monitoring costs, versus mAbs, in the final model base case accepted by committee.
What alternative approach has the EAG suggested?	Remove monitoring costs.
What is the expected effect on the cost-effectiveness estimates?	This is expected to make atogepant less cost effective compared to all relevant comparators.
What additional evidence or analyses might help to resolve this key issue?	The EAG would require evidence showing the treatment can continue to be prescribed in secondary care, in order to meet the PAS restrictions, whilst receiving an alternate form of monitoring.

Abbreviations: BoNT/A, botulinum toxin type A; EAG, External Assessment Group; GP, general practitioner; mAbs, monoclonal antibodies; MMD, monthly migraine days. PAS, patient access scheme.

Table 7. Issue 6: The source for injection related utility is inadequate

Report section	4.2.7.1
Description of issue and why the EAG has identified it as important	The company used a UK study which performed a time trade-off task to derive injection related disutility. The value for SC injections (mAb administration was not statistically significant. Furthermore, the utility values are not based on EQ-5D. The EAG believes this disqualifies it from being used in the model.
What alternative approach has the EAG suggested?	Remove injection related disutility.
What is the expected effect on the cost-effectiveness estimates?	This is expected to make atogepant less cost effective compared to all relevant comparators aside from rimegepant.
What additional evidence or analyses might help to resolve this key issue?	The EAG would require evidence from a source that used UK data, EQ-5D utility and showed a statistically significant difference in utility.

Abbreviations: EAG, External Assessment Group; mAb, monoclonal antibody; SC, subcutaneous.

Table 8. Issue 7: Long term discontinuation appears to have been incorrectly calculated

Report section	4.2.6.4
Description of issue and why the EAG has identified it as important	The company's calculation appears to be based on an assumption that the total number of patients who discontinue in a study will have discontinued by the mean time to discontinuation. This will significantly over-estimate long-term discontinuation.
What alternative approach has the EAG suggested?	Use long-term discontinuation from TA659 (0.44%).
What is the expected effect on the cost-effectiveness estimates?	This should improve the cost-effectiveness of whichever treatment is the most effective, since a lower long-term discontinuation will provide a bigger benefit to whichever treatment has the most patients remaining on treatment, after the assessment phase.
What additional evidence or analyses might help to resolve this key issue?	The EAG would require further explanation of the rationale/justification behind the calculation method.

Abbreviations: EAG, External Assessment Group; TA, technology appraisal.

1.4 Other key issues

The EAG also had a number of other issues with the company's modelling assumptions, these are summarised in Table 9.

Table 9. Other key issues

Item	Section
In the EM arm the minimum MMD restriction of 1 does not appear justified. The EAG preference is for this restriction to be 0.	4.2.6.4
Some of the acute medications listed appear to not have used the cheapest price from BNF/eMIT available for the given dose/pack size.	4.2.10.4

Abbreviations: BNF, British National Formulary; EAG, External Assessment Group; EM, episodic migraine; eMIT, electronic market information tool; MMD, monthly migraine day.

1.5 Summary of EAG's preferred assumptions and resulting ICER

Table 10 summarises the EAG's preferred assumptions for the prevention model and the cumulative impact these assumptions have on the ICER. All ICERs in Table 10 are south-west or south-east quadrant ICERs aside from rimegepant (rimegepant is cheaper and less effective than the comparators). Based on willingness-to-pay (WTP) thresholds of £20,000 or £30,000 per QALY, atogepant could be considered cost-effective compared to each mAb as the EAG's preferred base case ICERs are above these WTP thresholds. Botulinum toxin (BoNT/A) is more cost-effective than

atogepant at £20,000 and £30,000 (chronic migraine only) and rimegepant is more cost-effective at a WTP threshold of £20,000 (episodic migraine only).

Table 10. Summary of EAG's preferred model assumptions and cumulative results (Episodic migraine)

Preferred assumption	Cumulative ICER (£/QALY) Atogepant vs comparator					
	Epti	Rim	Ere	Gal	Fre	Fre
Company base case	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Removal of monitoring costs. Section 4.2.10.4	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Removal of injection related disutility. Section 4.2.7.1	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Alternate long-term discontinuation source (0.44%). Section 4.2.6.3	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
MMD limit set to 0 Section 4.2.6.4	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Updated acute medication costs Section 4.2.10.4	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Updates to the NMA - Using mITT population for EM, addition of rimegepant and eptinezumab, alternate use of RE/FE and adjusted/unadjusted where justified Section 4.2.6.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*SW quadrant ICER (atogepant is cheaper and less effective than the comparator)

Abbreviations: EAG, External Assessment Group; EM, episodic migraine; Ept, eptinezumab; Ere, erenumab; FE, fixed effects; Fre, fremanezumab; Gal, galcanezumab; ICER, incremental cost-effectiveness ratio; mAb, monoclonal antibody; mITT, modified intention to treat; MMD, monthly migraine day; NA, not applicable; NMA, network meta-analysis; QALY, quality adjusted life year; RE, random effects; Rim, rimegepant.

Table 11. Summary of EAG's preferred model assumptions and cumulative results (Chronic migraine)

Preferred assumption	Cumulative ICER (£/QALY) Atogepant vs comparator					
	Epti	Bot	Ere	Gal	Fre	Fre
Company base case	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Removal of monitoring costs. Section 4.2.10.4	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Removal of injection related disutility. Section 4.2.7.1	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternate long-term discontinuation source (0.44%). Section 4.2.6.3	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated acute medication costs Section 4.2.10.4	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Updates to the NMA - Using mITT population for EM, addition of rimegepant and eptinezumab, alternate use of RE/FE and adjusted/unadjusted where justified Section 4.2.6.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*SW quadrant ICER

Abbreviations: Bot, botulinum toxin type A; EAG, External Assessment Group; EM, episodic migraine; Epti, eptinezumab; Ere, erenumab; FE, fixed effects; Fre, fremanezumab; Gal, galcanezumab; ICER, incremental cost-effectiveness ratio; mAb, monoclonal antibody; mITT, modified intention to treat; MMD, monthly migraine day; NA, not applicable; NMA, network meta-analysis; QALY, quality adjusted life year; RE, random effects; Rim, rimegepant.

2 Introduction and background

2.1 Introduction

Herein is a critique of the evidence submitted to the Single Technology Appraisal (STA) in support of the clinical and cost-effectiveness of atogepant (Aquipta™; AbbVie) for the prevention of migraine in adults who have ≥4 migraine days per month, as covered by the UK marketing authorisation for this treatment.[4] As noted in Section 2.2.1, the indication assessed in this STA is narrower than the marketing authorisation as it is specific to those in whom ≥3 prior oral preventive drug treatments have failed (3+ TF). This includes episodic migraine (EM) and chronic migraine (CM), which are defined as <15 headache days per month and ≥15 headache days per month with ≥8 days qualifying as migraine, respectively, by the International Headache Society.[5-7]

2.2 Background

Within Section B.1 of the company submission (CS), the company provides an overview of:

- atogepant, including its mechanism of action, indications, dose and method of administration (Section B.1.2 of the CS);
- migraine, including diagnosis and classification, clinical presentation, epidemiology, disease burden, and current treatment options (Section B.1.3 of the CS).

In this section, the External Assessment Group (EAG) focuses mostly on areas that were commented on by the EAG's clinical experts. The clinical experts largely agree with the company's statements in Section B.1 of the CS; however, they consider botulinum toxin (BoNT/A) to be a relevant treatment in CM, noting that waiting lists can also be an issue for the monoclonal antibody (mAb) treatments erenumab, fremanezumab and galcanezumab, not just for BoNT/A. They also note that there are other factors that may impact the decision between mAbs and BoNT/A in CM, such as patient preference (for example, willingness to travel to have BoNT/A treatment), and contraindications and side effects of mAbs which may mean that BoNT/A is the treatment of choice (see Key Issue 1 in Table 2).

The company suggests that as an oral treatment, atogepant may be more likely to be prescribed and/or monitored by secondary care general neurologists and in primary care. Its base case includes initiation for atogepant by either a headache specialist or general neurologist (50:50), with follow-up conducted in primary care by GPs. A scenario with prescribing by GPs is included in Section 5.1.4 (given there may be potential for this in the future). One of the EAG's clinical experts noted that, in

their opinion, it would be reasonable for it to be prescribed in secondary headache clinics by a neurologist who is a specialist in headache or by general practitioners (GPs) with a specialist interest in headache, but the second expert explained that this may not be realistic at least initially, although it may be a possibility over time. They note that the recently recommended rimegepant (also an oral treatment) requires initiation in secondary care or headache clinics and that general neurology services may struggle to follow-up patients after 12 weeks to assess response even if they did prescribe atogepant, meaning this may need to be done in tertiary care by a headache specialist.

2.2.1 Position of atogepant in the UK treatment pathway

A summary of the treatment pathway described by the company is presented in Figure 1 below, which includes division into EM and CM once three oral preventive treatments (drugs that are not migraine-specific) have failed, which is the population of relevance to this appraisal; the EAG's clinical experts consider this to be an accurate representation of the current pathway for migraine prevention in UK clinical practice. However, they note that in their respective centres mAbs are currently only used for CM patients and that EM services are not yet established.

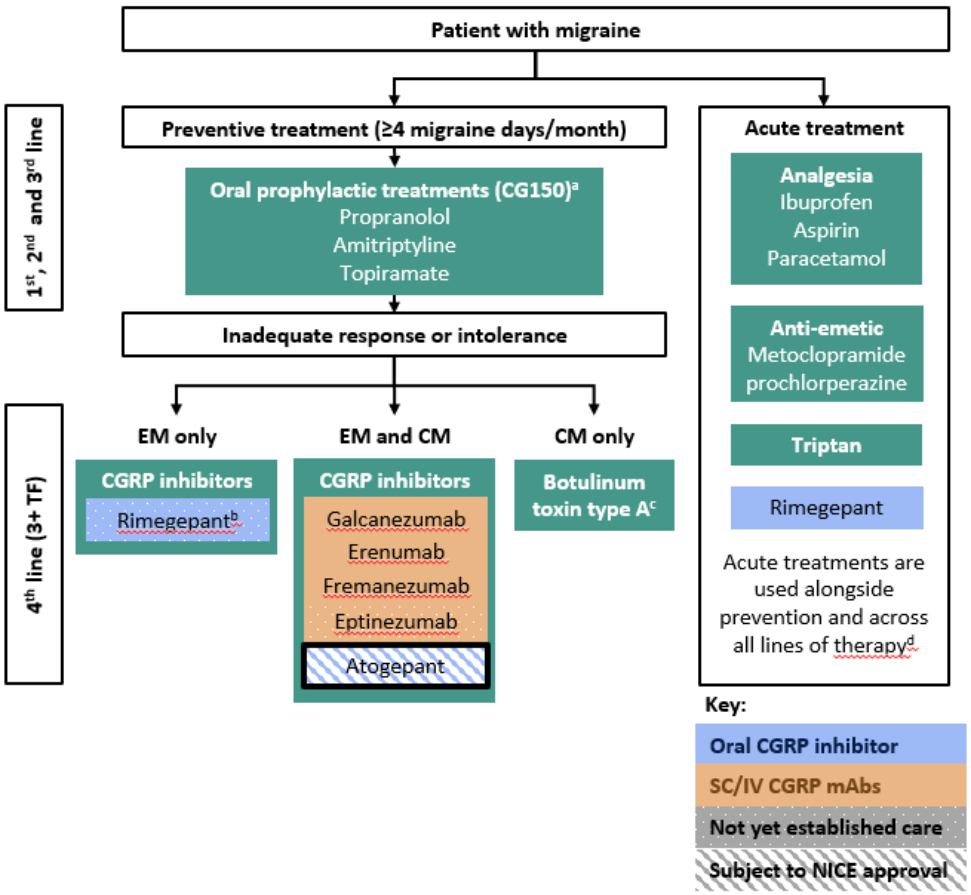
Current options recommended by the National Institute for Health and Care Excellence (NICE) for those in whom three oral preventives have failed (and who have ≥4 monthly migraine days [MMDs]) include three mAbs (erenumab, galcanezumab and fremanezumab; NICE TA682, TA659 and TA764, respectively) for EM and CM,[8-10] BoNT/A for CM only (NICE TA260; requires headaches on at least 15 days per month of which at least 8 days are with migraine),[1] and the more recently recommended eptinezumab (NICE TA871; EM and CM) and rimegepant (NICE TA906; EM only).[2, 3] All but one of these treatments are administered via injection; subcutaneous for mAbs, intramuscular for BoNT/A and intravenous for eptinezumab. Rimegepant is the exception because, as for atogepant, it is an oral treatment.

In this appraisal, the company has focused on the three mAbs as comparators for atogepant. BoNT/A has also been included in network meta-analyses (NMAs) and as a scenario in the economic model for CM. However, the company does not focus on this comparison as, based on feedback from clinical experts it consulted, it considers access to BoNT/A to be restricted, it requires dedicated in-clinic time (unlike atogepant) and that its use in the NHS is in decline. The company also excludes eptinezumab and rimegepant as comparators in this appraisal given they have only recently been recommended, with NICE recommendations not published at the time of scoping (the EAG notes that they were, however, listed in the final scope subject to NICE evaluation). It does not consider them to be part of established clinical practice yet and does not anticipate them becoming

established practice at the point of committee decision, citing low market share in the 3+TF group, which is further supported by clinical expert opinion elicited by the company. The EAG's clinical experts agreed that eptinezumab may not be important to this appraisal, given that it is a recent recommendation with very low use currently. One expert noted that it may be considered too resource intensive to use in preference to other treatments, meaning the frequency of its use may not change considerably in the near future. While they agreed that rimegepant is not currently used often, one clinical expert noted that there is potential for this to change in the near future and, should atogepant be recommended and oral options preferred for an individual patient, it is likely that clinicians would be making a decision between atogepant and rimegepant in EM. Therefore, it may be particularly important to compare atogepant with rimegepant in this appraisal. Feedback regarding BoNT/A was that it is still a relevant treatment in CM as there is a choice to be made between mAbs and BoNT/A in patients with CM that are eligible for either (as noted above under Section 2.2). Regarding eptinezumab and rimegepant, the EAG considers it important to explore the inclusion of these treatments as comparators in this appraisal given they are both recommended within the same population as outlined for atogepant (although rimegepant is only recommended for EM patients) and have the potential to be used as options alongside atogepant if it were to be recommended, acknowledging that eptinezumab may be less important based on feedback from one clinical expert discussed earlier.

Overall, the EAG considers that the positioning of atogepant as a treatment after at least three prior preventive oral treatments have failed is appropriate but that there may be additional comparators worth considering in the appraisal (see Key Issue 1 in Table 2), which the EAG has included as part of this report. Further discussion of the comparators that are currently not considered relevant by the company is provided in Section 2.3.

Figure 1. Anticipated clinical pathway of care for migraine patients (reproduced from Figure 3 of the CS)



Abbreviations: CGRP, calcitonin gene-related peptide; CM, chronic migraine; CS, company submission; EM, episodic migraine; IV, intravenous; NICE, National Institute for Health and Care Excellence; SC, subcutaneous; TF, treatment failures.

2.3 Critique of the company's definition of the decision problem

The company provided a summary of the final scope issued by NICE in Section B.1.1 of the CS, together with the rationale for any deviation from the final scope.[11] This is reproduced in Table 12 below with the EAG's critique included. Key differences between the decision problem addressed in the CS and the NICE final scope are discussed in greater detail in the sections that follow this table, but the EAG's main concern is around the complete exclusion of eptinezumab and rimegepant as comparators (see Key Issue 1 in Table 2). In addition, the EAG also considers BoNT/A to be a relevant comparator in CM, while the company does not (see Key Issue 1 in Table 2). Analyses including this comparator have, however, already been presented by the company as part of the CS.

Table 12. Summary of decision problem and differences relative to NICE final scope (adapted from Table 1 of the CS)

	Final scope issued by NICE[11]	Decision problem addressed in the submission	Rationale if different from the scope	EAG comment
Population	Adults with migraine who have 4 or more migraine days a month, in whom at least 3 preventive drug treatments have failed	As per the NICE final scope	The population is aligned to a subgroup of the UK marketing authorisation, the NICE-recommended population for the available CGRP mAbs, as well as the anticipated positioning of atogepant in UK clinical practice based on feedback from clinicians.[4, 8-10, 12] In addition, feedback from clinicians suggests that atogepant is suitable for use in patients for whom ≥3 prior preventive treatments have failed.[12]	The population covered in the CS is in line with the NICE final scope, although narrower than the marketing authorisation for atogepant.[4] It is also in line with NICE recommendations made for mAbs, botulinum toxin type A (CM only), eptinezumab and rimegepant (EM only). Clinical evidence from atogepant trials specific to the 3+ TF group is provided within the CS for EM and can be found in the CSR for CM. For efficacy outcomes in EM, NMAs within the 3+ TF group were presented in the CS but not for CM as the trial was not stratified by treatment history; these results were, however, provided as part of the CCE process for atogepant earlier in 2023. However, the EAG considers analyses in the overall populations for EM and CM, regardless of prior treatment history, to be more robust due to limited data availability for the 3+ TF subgroup and concerns about lack of trial stratification for treatment history.

				NMAs for other outcomes, including HRQoL, TEAEs and all-cause discontinuation, were not performed in the 3+ TF group due to a lack of data available for comparator treatments. These were instead performed in the overall EM and CM migraine populations, which the EAG considers to be reasonable. The EAG's clinical experts consider the 3+ TF and overall populations of the atogepant trials to be a reasonable reflection of the UK 3+ TF population, with no important differences in baseline characteristics between the 3+ TF and overall populations noted. They consider the exclusion of those with >4 prior treatments in the atogepant trials to be unfortunate but the potential impact of this on the results of the trial is unclear. See Section 2.3.1 below for further discussion.
Intervention	Atogepant	Atogepant (60 mg*); as per the NICE final scope	N/A	The intervention covered in the CS and atogepant clinical trials matches the NICE final scope, with the 60 mg dose of atogepant focused on. While the company highlight the availability of the 10 mg dose in the footnote of

				this table for specific patients, the EAG notes that evidence for the 10 mg dose of atogepant has not been included in the CS. The EAG is unsure whether the use of concomitant preventive treatments in some patients within the PROGRESS trial for CM is reflective of UK clinical practice and notes clinical expert feedback that opioids are not used as acute migraine treatment in UK practice, which was also permitted in PROGRESS. However, it does not consider these to be major concerns. See Section 2.3.2 below for further discussion.
Comparators	• Botulinum toxin type A (CM only) • Galcanezumab • Erenumab • Fremanezumab • Eptinezumab (subject to NICE evaluation) • Rimegepant (subject to NICE evaluation)	• Galcanezumab • Erenumab • Fremanezumab	CGRP mAbs (galcanezumab, erenumab, fremanezumab) are deemed to be the appropriate comparators for this appraisal; given that atogepant and the CGRP mAbs are preventive treatments that cover the same patient population which each work in a similar way to suppress CGRP activity, can be self-administered at home, and offer similar health benefits.	The three mAbs currently recommended by NICE in the 3+ TF population for EM and CM have been included in the CS.[8-10] The EAG does not agree with the company's decision not to focus on botulinum toxin type A as a comparator for CM in this appraisal given feedback from the EAG's clinical experts that there is a choice to be made currently between mAbs and botulinum toxin type A in CM in UK clinical practice. However, botulinum

			Eptinezumab (IV CGRP mAb) and rimegepant (oral CGRP receptor inhibitor) have both recently received recommendations from NICE (1 March 2023 and 5 July 2023, respectively).[2, 3] Due to recency of these recommendations, and wide variation in in-hospital administration capabilities for eptinezumab across the UK due to its IV route of administration, clinical experts and market share data have indicated that these drugs do not constitute established clinical practice.[13, 14] Moreover, the NICE recommendations associated with these therapies had not been published at the time of scoping. As such, neither are considered relevant comparators. Clinical experts noted that botulinum toxin type A is not a relevant comparator for atogepant due to the requirement for dedicated in-clinic time and upfront staff investment. It was also noted that the proportion of patients receiving botulinum toxin type A	toxin type A has been included in the NMAs and in the economic model as a scenario analysis. Given final guidance is now available for eptinezumab and rimegepant in the 3+ TF population,[2, 3] the EAG considers their exclusion from the CS may be inappropriate. While the EAG's clinical experts agree that currently their use in UK clinical practice is low, one expert noted that there could be an important decision to be made between rimegepant and atogepant, should atogepant be recommended and an oral option preferred in EM, while the use of eptinezumab may change less substantially given it is considered by the experts to be more resource intensive. The company did not include these treatments in response to CQ A1 but the EAG has incorporated them into its analyses. See Section 2.3.3 for further discussion.

			is likely to decrease for these reasons with market share forecasts indicating that the majority of patients experiencing ≥4 migraine days per month who are receiving treatment, receive CGRP mAbs as a preventive therapy.[12] Market share data further indicate that the large majority of patients across the UK are initiated on CGRP mAbs ahead of botulinum toxin type A, with clinical experts explaining that patients typically initiate on CGRP mAbs currently due to NHS capacity issues associated with botulinum-toxin type A administration and resulting waiting lists.[13, 14] As such, botulinum toxin type A is not considered by the company to be a relevant comparator.	
Outcomes	The outcome measures to be considered include: • Change in frequency of migraine days per month • Change in frequency of headache days per month • Change in severity of headaches and migraines • Change in number of cumulative hours of headache	As per the NICE final scope	N/A	Outcomes covered in the CS for atogepant trials match the NICE final scope. The time-point of 12 weeks for atogepant trials was considered reasonable by the EAG's clinical experts and the EAG considers the outcome definitions to be appropriate, such as the thresholds used to define responders which are in line with comparator appraisals.

	or migraine on headache or migraine days • Changes in acute pharmacological medication given • AEs of treatment • HRQoL			NMAs for multiple outcomes were performed, including efficacy outcomes important to the economic models of comparator appraisals as well as HRQoL, TEAEs and all-cause discontinuation. See further discussion in Section 2.3.4
Economic analysis	• The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. • The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. • Costs will be considered from an NHS and PSS perspective. • The availability of any commercial arrangements for the intervention, comparator and subsequent treatment	• A cost-effectiveness analysis has been conducted in Microsoft Excel to estimate the incremental costs of atogepant versus galcanezumab, erenumab, and fremanezumab • A lifetime time horizon for assessing costs was used • Costs were considered from an NHS and PSS perspective • A PAS for atogepant has been included as part of the analysis	The economic analysis presented is aligned with the final NICE scope for this submission.	The company has stated that atogepant has potential for use in primary care though they have also provided a confidential PAS discount for the treatment. For a treatment to be administered in primary care it must use the public tariff price.

	technologies will be taken into account. • The availability and cost of biosimilar and generic products should be taken into account.			
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • Those with either EM or CM • Subgroups defined by the number of previous prophylactic treatments • Subgroups defined by the frequency of EM (in those with EM)	This submission will focus on patients with ≥3 prior preventive treatment failures in line with the NICE final scope. Subgroup analyses were conducted where applicable. Subgroups defined by the frequency of EM are not provided.	Migraine is a disease continuum in which patients can be classified as having either EM or CM based on the frequency of monthly headache days. The patient population addressed in this submission represents two subgroups of the population specified in the NICE final scope: patients with EM and CM with ≥3 prior preventive treatment failures. This appraisal did not consider subgroups defined by frequency of EM. Evidence presented in the prior appraisal of galcanezumab (TA659) suggests that patients with high frequency EM have a similar disease burden as patients with CM,[9] while published literature have demonstrated that migraines are disabling for patients with 3 or more monthly migraine days.[15] However, due to a lack of consensus on the	Separate clinical and economic analyses have been provided in the CS for EM and CM, in line with comparator appraisals. Subgroups based on the number of prior prophylactic treatments have been explored in the CS for EM given results from ELEVATE are presented separately for the 3+ TF subgroup and the overall trial population of 2-4 TF. NMA results for the 3+ TF subgroup are also presented in the CS for EM. While this was not included in the current CS for CM, clinical data for this subgroup is available within the CSR for PROGRESS. While the EAG's clinical experts note that there may be some distinction between those with low- and high-frequency EM, with the latter potentially experiencing a burden of migraine disability similar to those with CM, there was a difference of opinion regarding whether this distinction is

			definition of, and clinical distinctiveness of high frequency EM, NICE concluded the frequency of migraines (in those with EM) was not an appropriate subgroup for economic analysis. As such, no subgroup analysis has been explored in this submission.	evident in clinical practice. Based on data provided as part of the CCE process earlier in 2023 and a decision made by the committee in TA659, the EAG does not consider further exploration of these subgroups to be important. See Section 2.3.5 for further discussion.
Special considerations, including issues related to equity or equality	N/A	N/A	N/A	Equality considerations are discussed by the company in Section B.1.3.4 of the CS, including a statement that atogepant may help to reduce inequity in access to current treatments that may vary geographically.

*Outside of the scope of this submission, atogepant 10 mg once daily is also licensed for patients who require dose modifications (concomitant use of strong CYP3A4 or OATP inhibitors), or for special populations with severe renal impairment or end-stage renal disease.

Abbreviations: 3+ TF, patients in whom ≥3 prior oral preventive treatments have failed; 2-4 TF, patients in whom 2-4 prior oral preventive treatments have failed; AE, adverse events; CCE, cost-comparison evaluation; CGRP, calcitonin gene-related peptide; CM, chronic migraine; CS, company submission; CSR, clinical study report; CQ, clarification question; CYP, cytochrome P450; EAG, External Assessment Group; EM, episodic migraine; HRQoL, health-related quality of life; IV, intravenous; mAbs, monoclonal antibodies; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; OATP, organic anion transporting polypeptide; PAS, patient access scheme; PSS, Personal Social Services; TA, technology appraisal; TEAE, treatment-emergent adverse events.

2.3.1 Population

The CS positions atogepant for use in adults with migraine who have at least four MMDs and in whom at least three preventive drug treatments have failed. This is narrower than the UK marketing authorisation for atogepant but is in line with the NICE final scope and is deemed reasonable by the EAG as it is in line with the population that the mAbs are recommended for in EM and CM.[4, 8-10] BoNT/A (CM only), eptinezumab (EM and CM) and rimegepant (EM only) are also recommended for the population with at least four MMDs and 3+ TF, although the requirement for MMDs is more strict for BoNT/A given its recommendation for CM only, with patients required to have at least 15 headache days per month of which 8 days are migraine.[1-3]

The main trials focused on in the CS (Section B.2.3) for EM (ELEVATE) and CM (PROGRESS) are not specific to the 3+ TF population, but relevant subgroup data have been provided in the CS for ELEVATE. The same has not been provided for the PROGRESS trial in CM as part of this STA submission given the company highlight the trial was not stratified for prior treatment failures at randomisation, unlike ELEVATE. However, the EAG notes that baseline characteristics and outcome data for this subgroup are available from the clinical study report (CSR) for PROGRESS; the EAG has included this outcome data in this report (Section 3.3). The EAG's clinical experts reviewed the baseline characteristics for the overall trial populations of ELEVATE and PROGRESS and considered them to be a reasonable representation of the UK 3+ TF population. They consider that no major differences would be expected in these characteristics compared with the 3+ TF population; the EAG also compared baseline characteristics between the overall trial populations and 3+ TF populations (Table 6 vs Table 7 in the CS for ELEVATE; Table 7 in the CS vs data provided in the CSR) and notes that there is very little difference for either trial. The most notable difference was within PROGRESS, where for the 3+ TF group values for monthly headache days and monthly acute medication use days (MUDs) were [redacted] compared to the overall trial population. However, the EAG's clinical experts consider the size of these differences unlikely to be important in terms of impact on efficacy.

The EAG notes that failures on prior treatments were based on oral preventive treatments and did not include mAbs or BoNT/A, meaning there is no evidence from atogepant trials in populations that have already failed on a mAb or BoNT/A. One of the EAG's clinical experts highlighted that evidence from a population that has failed mAbs would be required to support the use of atogepant in such as population, given they consider it clinically plausible that it may be less effective in this group. They

are less concerned about its used following failed BoNT/A treatment given the mechanism of action for BoNT/A and atogepant is clearly different. A failed treatment was defined as one in which there was no response by the defined time-point or discontinuation due to intolerability. Given that atogepant has been positioned as an alternative to mAbs in this STA rather than as a subsequent treatment, the EAG does not consider this to be a major limitation but notes that this is something that may need consideration when considering options for patients in clinical practice that have already received mAbs and the order in which treatments should be used. The EAG notes that the same concern may apply for rimegepant and eptinezumab given that the studies (BHV3000-305 for rimegepant and DELIVER for eptinezumab) that the respective NICE appraisals focused on did not include failure on mAbs as one of the treatment failure categories (although BoNT/A was included in the lists for the two studies).[2, 3, 16, 17] However, it may be unlikely that eptinezumab would be used following erenumab, galcanezumab or fremanezumab given it is also a mAb targeting the calcitonin gene-related peptide (CGRP) pathway.

NMAs for efficacy analyses within EM were provided in the CS for the 3+ TF subgroup as well as for the overall migraine population. As noted above, PROGRESS was not stratified for prior treatment failures and efficacy analyses within the 3+ TF population were therefore not provided as part of this STA for CM; however, they were previously provided as part of the cost-comparison evaluation (CCE) process earlier in 2023. At clarification (clarification question [CQ] A9), the EAG requested that these NMAs be provided as part of the STA so that they can be compared. The company did not provide these data and instead reiterated its rationale for not performing NMAs using this subgroup data in this STA. The EAG comments briefly on how the NMA results provided as part of the CCE for this subgroup in CM compare to the company- and EAG-preferred analyses in this report in Section 3.4.3.1. For reasons described further in Section 3.4.1, the EAG considers NMAs for efficacy analyses performed within the overall trial populations to be more robust than those within the 3+ TF (see Key Issue 2 in Table 3); however, it considers a comparison between the two populations useful, with acknowledgement of the additional limitations for the 3+ TF subgroup analyses.

In terms of NMAs performed for other outcomes in the CS, including health-related quality of life (HRQoL), treatment-emergent adverse events (TEAEs) and all-cause discontinuation, for EM and CM analyses were only available within the overall migraine population. This was because of a lack of data for comparator interventions within the 3+ TF subgroup for these outcomes. The EAG considers this to be reasonable and notes that as part of the CCE process earlier in 2023, the company explored HRQoL analyses in 2+ and 3+ TF subgroups in response to clarification; the EAG concluded

that it did not prefer these analyses given data was much scarcer and only allowed comparisons with fremanezumab and/or galcanezumab. See Section 3.4 for further details and critique of the NMAs performed.

The EAG's clinical experts considered it unfortunate that patients with >4 prior treatment failures in ELEVATE and PROGRESS were excluded, given this is a group that would be relevant in UK clinical practice. While the experts consider they would not expect a large difference compared to those with three or four failures, they note that the chance of each successive agent working is reduced which may mean a group that are more complex and less likely to respond have been excluded. The EAG notes that this is not inconsistent with comparator trials focusing on refractory populations (such as FOCUS, CONQUER and LIBERTY), which include those with two to four prior treatment failures.[18-20] For further detail on atogepant clinical trials, see Section B.2.3 of the CS and Section 3.2 below.

2.3.2 Intervention

The intervention in the CS is atogepant (Aquipta™; AbbVie), matching the NICE final scope, which is an oral migraine prevention treatment.[11] The dose covered in the CS is atogepant 60 mg, which is to be taken once daily. UK marketing authorisation has been granted and covers adults with ≥4 MMDs and in whom ≥3 prior oral preventive treatments have failed.[4]

Concomitant medications permitted in the atogepant clinical trials were considered reasonable by the EAG's clinical experts, other than opioids as an acute treatment in CM (PROGRESS), which are not used in UK clinical practice. However, the EAG notes that, based on the clinical study report (CSR), opioids were rarely used in PROGRESS with only [redacted] of it being prescribed for migraine in the placebo group. There were other instances where it was prescribed for other indications such as the common cold, but [redacted] patients per treatment group.

Furthermore, the PROGRESS trial in CM allowed concomitant use of another preventive migraine treatment; the EAG's clinical experts note that while this is fairly uncommon, it may sometimes be done in clinical practice and can improve outcomes. The EAG notes that this was more common in the [redacted] arm ([redacted]% vs [redacted]%). Were the use of concomitant treatments to improve outcomes in this trial, this would potentially have a [redacted] impact given more patients in the [redacted] arm used them. The EAG notes that this is not uncommon among migraine trials as some trials for comparators allowed use of concomitant preventive medications (see Section 3.4.4.1).

2.3.3 Comparators

Within the CS, the three mAbs recommended by NICE for the population of interest are included as comparators for atogepant in EM and CM, as per the final scope.[8-11] While mAbs are recommended for use in EM and CM, the EAG's clinical experts note that capacity issues often mean that mAb services for EM are limited or not yet established.

Use of BoNT/A for CM has not been included as a formal comparator by the company in the CS, for reasons described in Sections B.1.1 and B.1.3.3, although it has been included in the relevant NMAs and as a scenario analysis in the economic model (Appendix O of the CS). The company does not consider BoNT/A to be a relevant comparator in CM given feedback from clinical experts consulted that patients often choose mAbs due to extensive waiting lists for BoNT/A and the need to travel to clinics that administer this treatment.[12, 13] It suggests that BoNT/A use is on the decline according to market share data and IQVIA™ in-hospital pharmacy dispensing data reports that [redacted] of new fourth-line patients received treatment with erenumab, fremanezumab or galcanezumab rather than BoNT/A between the second half of 2022 and first half of 2023 across the UK (the EAG notes that experts consulted by the company estimated this to be 70-80%; see the company's response to CQ B1).[14] Furthermore, the company notes that differences compared to atogepant in terms of requirement for dedicated in-clinic time and upfront staff investment for BoNT/A administration are also reasons that atogepant would not be considered an alternative to BoNT/A.[13] Furthermore, it notes that the exclusion of BoNT/A is in line with the recent NICE appraisal of eptinezumab (TA871), which was recommended for EM and CM.[3]

As discussed earlier in Section 2.2, feedback from the EAG's clinical experts was that BoNT/A is a relevant treatment option in CM. While they acknowledge that waiting lists may exist, this can also be an issue for mAbs. There is considered to be a choice between mAbs and BoNT/A for those who are eligible, which may be made based on patient preferences (for example, willingness to travel to a BoNT/A centre if required or the side effect profile of mAbs) as well as certain contraindications for mAbs that mean BoNT/A would be used. In addition, BoNT/A requires a shorter time off treatment before trying to become pregnant which may also be a factor that patients and clinicians consider. Based on this, the EAG considers BoNT/A to be an equally appropriate comparator in CM that should be considered alongside mAbs. In terms of the eptinezumab appraisal, while the EAG acknowledges that BoNT/A is not mentioned in the final guidance document,[21] it was included in the CS as can be seen from the committee papers.[22] The EAG is unsure of the reason for this but does not consider its

omission from the final guidance document to be an adequate reason for it to be excluded from this STA, particularly given the feedback obtained from the EAG's clinical experts (see Key Issue 1 in Table 2).

The company has excluded eptinezumab and rimegepant as comparators in this STA, citing the recency of their recommendation by NICE and market share data (in addition to clinical expert feedback) indicating that they are not yet established UK clinical practice, with eptinezumab and rimegepant accounting for up to [redacted] and [redacted] of all treated migraine patients within the 3+ TF group, respectively, according to market share data (see Section 4.2.3.2 for a critique of the argument based on market share data; on review of the Clarivate™ reference provided, the EAG considers that the [redacted]% figure likely refers to rimegepant rather than eptinezumab and it could not validate the percentage cited for eptinezumab).[13, 14] Clinical experts consulted by the EAG agreed that the use of these two treatments is very low at the moment in UK clinical practice. However, while feedback from one of the clinical experts also suggested that the use of eptinezumab may not increase substantially in the near future as the expert considered it may be too resource intensive to use in preference to other treatments, particularly oral treatments, they considered rimegepant to be an important comparator given that there may be a decision between rimegepant and atogepant if both are recommended and an oral option is preferred in EM.

While raised by the company, the EAG does not consider the fact that rimegepant is only recommended for EM to be a reason for its exclusion either. The company notes that eptinezumab may be reserved for patients with severe migraine attacks or those unable to self-administer mAbs subcutaneously based on clinical expert feedback as part of the eptinezumab appraisal (Section 3.2 of the final draft guidance for eptinezumab). The EAG's clinical expert feedback suggests similar as one expert described eptinezumab as being more resource intensive.[3] Regardless, the EAG considers it useful for this treatment to be included as a comparator in this appraisal given the recommendation made by NICE is not specific to this population and it is unclear as yet how it will be used in UK clinical practice (see Key Issue 1 in Table 2).[3] The inclusion of eptinezumab and rimegepant as comparators was requested as part of the clarification stage (CQ A1) but the company did not perform this request. Therefore, the EAG has updated NMAs to include data from eptinezumab and rimegepant trials (Section 3.4) and included these treatments as comparators in the economic model (Section 6). The EAG provides a critique of the rationale and evidence supplied by the company to support not including these treatments in Section 3.4.5.

Clinical experts advising the EAG note that in terms of mAbs, in their experience, erenumab is normally the mAb that is used in clinical practice, with galcanezumab used instead if there are any contraindications to using erenumab. The choice between mAbs reflects local formulary committee decisions, which in this instance are based on drug costs as the mAbs are considered to have similar effectiveness. As erenumab has the lowest acquisition cost, it is often the first choice. Galcanezumab is the next least expensive, which is why it is often employed if erenumab is contraindicated. This may be centre-dependent as a clinician that peer reviewed the EAG's report notes that fremanezumab is more easily accessible for them.

No direct evidence comparing atogepant with any of the listed comparators was available and NMAs were instead performed (Section 3.4). Overall, the EAG considers the comparator randomised controlled trials included to be a good representation of the comparator interventions in terms of doses used in practice and does not consider that any have been inappropriately excluded.

2.3.4 Outcomes

Outcomes covered in the CS for atogepant trials match the NICE final scope. The EAG considers that "change in number of cumulative hours of headache or migraine on headache or migraine days" in the NICE final scope may not have been covered in the CS but does not consider this to be a major omission given it was not an outcome key to comparator appraisals.[11]

Outcomes for which NMAs were performed included outcomes that were important in comparator appraisals, such as response based on 50% reduction in MMDs for EM. NMAs were performed for the following outcomes (see Section 3.4 for discussion of these NMAs):

- Change from baseline in MMDs;
- Proportion of patients with 50% reduction in MMDs from baseline (and 30% reduction for CM);
- Change from baseline in days with use of acute MUDs;
- HRQoL outcomes including Headache Impact Test-6 (HIT-6) and three subdomains of the migraine-specific quality of life questionnaire (MSQ);
- TEAEs;
- And all-cause discontinuation.

Of the above outcomes, results for change from baseline in MMDs, proportion with 50% (EM) or 30% reduction in MMDs vs baseline, change from baseline in MUDs and all-cause discontinuation were used in some form in the economic model (see Section 4.2.6). HRQoL data from ELEVATE and PROGRESS were used in the economic model but NMAs were not utilised.

The time-point of 12 weeks for atogepant trials was considered reasonable by the EAG's clinical experts and in line with comparator mAbs (BoNT/A trials assessed response at 24 weeks). It is also the time-point included in the recent recommendations for eptinezumab and rimegepant in terms of assessing response to migraine prevention treatment.[2, 3] Time points reported for trials included in the NMAs varied but were between 12 and 24 weeks in most cases, with some follow-up for TEAEs being longer (see Section 3.4.4.2). The EAG considers the outcome definitions in atogepant trials to be appropriate, such as the thresholds used to define responders which are in line with comparator appraisals.

2.3.5 Subgroups

EM and CM subgroups, and subgroups based on the number of prior prophylactic treatments, listed in the NICE final scope are covered in the submission. While the CS does not present results for the 3+ TF subgroup for CM, or include NMAs for this subgroup, results for this subgroup within the PROGRESS trial are available in the CSR. A comparison of these results is discussed in Section 3.3 for atogepant clinical trials and Section 3.4.3.1 for NMAs; while not provided as part of this STA, NMAs within the 3+ TF population for CM were provided as part of the CCE process for atogepant earlier in 2023. The EAG has not included these results in Section 3.4.3.1 but has commented briefly on how they compared to analyses preferred by the company and the EAG in this STA.

Clinical experts advising the EAG note that high-frequency and low-frequency EM subgroups may represent distinct groups, with those with high-frequency EM possibly experiencing a burden of migraine-related disability more similar to those with CM. However, based on feedback from a clinician peer reviewing this report, the EAG notes that opinion on this differs and it is unclear whether this distinction is evident in clinical practice. As part of the CCE process earlier in 2023, the EAG asked at clarification for efficacy results for these EM subgroups from ELEVATE. Based on the response to this clarification question within the CCE, the EAG is not concerned about major differences existing between these two subgroups. Both subgroups are considered relevant to the appraisal and, given the proportion with high and low frequency EM is similar between atogepant and placebo arms in the overall populations of the atogepant trials, the EAG is not concerned about

the impact of these subgroups on results. Based on this, and the fact that in NICE TA659 for galcanezumab it was concluded that high-frequency EM is not a clinically distinct subgroup,[9] the EAG does not consider further exploration of these subgroups to be important.

In Section B.2.6 of the CS, the company concludes that migraine is a disease continuum and that clinical experts have highlighted that data in patients with EM and CM are complementary and should be viewed holistically. They note that this was also discussed in the NICE appraisal for eptinezumab (TA871) and that clinical experts confirmed that there is no biological rationale for a calcitonin gene-related peptide inhibitor to be effective in only one of the two populations. While the EAG's clinical experts agree that there may be debate about how important differences in migraine burden are between those at the higher end of the EM classification and those at the lower end of the CM classification, they note that efficacy of treatments may reduce with increasing migraine burden (i.e. the potential to reduce MMDs by ≥30% or ≥50% may be more difficult with increased baseline MMD), which could differ for different treatments (i.e. the impact of any differences vs placebo across these groups may be less notable for treatments that are slightly more efficacious than others). Based on this, the EAG considers it appropriate that separate analyses for EM and CM have been performed in this appraisal.

3 Clinical effectiveness

3.1 Critique of the methods review

The company conducted a systematic literature review (SLR) to identify clinical evidence from randomised controlled trials (RCTs) of atogepant or any other pharmaceutical intervention for migraine prevention in episodic migraine (EM) or chronic migraine (CM). Separate SLRs were performed for EM and CM. These RCTs were used to inform network meta-analyses (NMAs), described in Section 3.4. Detailed methods involved in this SLR are described in Appendix D.1 of the company submission (CS) appendices.

The External Assessment Group (EAG) considers these searches to be robust and likely to have captured all relevant RCTs up to the search date; however, it notes that the last update searches were performed in September 2022 (a year prior to this submission) and any relevant RCTs published since then will not have been captured. While the EAG's clinical experts are not aware of any new RCTs published since the last update that would be relevant for inclusion in this SLR, the EAG cannot be sure that RCTs have not been missed as a result; as part of clarification question (CQ) A10, the EAG requested that searches were updated. In response to this, the company performed targeted searches using PubMed; given the time available, the EAG considers this to be a reasonable compromise and it is satisfied that is unlikely that any additional evidence relevant for inclusion in the NMAs was missed. The EAG notes that all RCTs focused on in previous appraisals for comparators relevant to this Single Technology Appraisal (STA) were identified and mentioned in the CS, including eptinezumab and rimegepant RCTs should they be deemed relevant comparators.

The searches for the SLR were broader than the National Institute for Health and Care Excellence (NICE) final scope and the decision problem described in the CS as the whole migraine population was searched for and comparators were not limited to those used after at least three oral preventives had failed. Data extraction was also performed for a broader set of studies than outlined in the decision problem (201 unique studies from 908 publications for EM and 32 unique studies from 596 publications for CM). The list included in the NMAs was in line with the decision problem outlined by the company in terms of comparators, but still wider in terms of population given analyses in the overall migraine population were performed in addition to the group with at least three prior oral preventive treatment failures. A total of 16 and 10 RCTs were identified as relevant

for the NMAs in EM and CM populations, respectively (Section B.2.9 of the CS). This increased to 18 and 12, respectively, when the EAG included rimegepant and eptinezumab studies.

The EAG considers the inclusion criteria used to be reasonable and notes that an issue raised by the EAG as part of the cost-comparison evaluation (CCE) process (exclusion of RCTs solely in Asian populations) was rectified as part of the STA submission, with these RCTs now included in relevant NMAs. The company did not include RCTs covering rimegepant and eptinezumab in NMAs even in response to CQ A1 but the EAG subsequently included them given the discussion in Section 2.2.1 and 2.3.3.

The EAG considers the methodology used in the SLR process to be reasonable, including screening by two independent reviewers and following Cochrane, NICE and PRISMA processes.

Table 13. Summary of EAG's critique of the methods implemented by the company to identify evidence relevant this appraisal

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods
Data sources	Appendix D.1.1	**The EAG considers the sources and dates searched to be comprehensive and appropriate.** Databases searched: • Embase (Embase.com); MEDLINE (Embase.com); MEDLINE In-Process (Pubmed.com); PsychINFO; CDSR and CENTRAL Registries: • Clinicaltrials.gov Conference proceedings: • American Headache Society (2018-2022) • International Headache Society (2017-2022) • European Headache Federation Congress (2018-2022) • American Academy of Neurology (2019-2022) • Migraine Trust International Symposium (2018-2022) Bibliographies of key systematic review and meta-analysis articles were screened to ensure that initial searches captured all relevant clinical studies. Original searches were conducted in May 2020 with multiple update searches performed, including the most recent in September 2022.
Search strategies	Appendix D.1.1	**The EAG considers the search strategies used to be appropriate** The search strategies for the literature review used free-text keywords, MeSH and EMTREE terms for the population and interventions of interest. Search

		filters were used in MEDLINE, Embase and PsychINFO searches to identify RCTs but the EAG is unsure which specific filters were used. The EAG had some concerns about the last SLR updated being performed in September 2022 and whether any additional RCTs relevant to the NMAs in particular have been published since this last update, a year prior to this submission. However, given the results of the targeted searches performed in response to CQ A10 and based on clinical expert feedback, the EAG considers that it is unlikely any have been missed.
Inclusion criteria	Appendix D.1.2, appendix D.2.1 and Section B.2.9.2 of the CS	**The EAG considers the inclusion criteria for the SLR and NMAs to be reasonable** Inclusion criteria for extraction in the SLR were broad and there were few exclusion criteria. Exclusion criteria that were applied at this stage are deemed appropriate by the EAG. To be included in the NMAs, further criteria were applied. The EAG generally considered these to be reasonable and in line with the NICE final scope; however, rimegepant and eptinezumab RCTs were excluded given they were not considered relevant comparators. The company did not include these comparators in response to CQ A1 but the EAG has included them as part of this report. Table 17 in the CS also indicates that RCTs with small sample sizes (fewer than ~30 patients per treatment arm) were considered for exclusion, as were open-label trials. The EAG understands the rationale behind open-label RCTs being excluded, particularly as migraine outcomes are subjective and more likely to suffer from bias introduced as a result of open label RCTs. While excluding RCTs because of small patient numbers may not be ideal, the EAG considers these studies would have a limited impact on results. Tables 9 and 10 of the CS do not appear to contain a full list of RCTs included in the SLR but excluded from NMAs but the EAG notes that none of those listed here were excluded solely because they were open-label and two small BoNT/A RCTs were excluded because of sample size.[23, 24] On review of these RCTs, the EAG does not consider that they would substantially change the available evidence base and they were not included for other appraisals that made comparisons with BoNT/A. In addition, one was a crossover RCT (unlike other included studies which were all parallel RCTs) and the other used a dose that was lower than that recommended by NICE in TA260 (100 units vs 155-195 units). Therefore, the EAG considers the exclusion of these two RCTs to be reasonable.
Screening	Appendix D.1.2	**The EAG considers the methods for screening to be robust** Abstract and title reviews of all references identified from the database searches were reported to be performed independently by two reviewers with any discrepancies resolved by a third reviewer. The same process was applied to articles that were selected for full-text review. Searches of conference proceedings and clinical trial registries were performed by a single reviewer and checked by a second reviewer. Results of the literature screening processes were summarised in a PRISMA diagram.

Data extraction	N/A	**Methods for data extraction in the clinical SLR are not described but processes similar to those described for economic searches may have been used** The EAG notes that a description of the process for extracting studies is not described in Appendix D.1.2 with regards to the clinical SLR. However, it considers it likely that similar processes to those described in Appendix H.3.2, I.2.2 and J.2.2 were performed. This involved one researcher extracting the data and a second researcher independently reviewing all data extracted, which the EAG considers to be reasonable. A third independent individual provided input in cases of uncertainty.
Tool for quality assessment of included study or studies	Appendix D.2.7 and Section B.2.5 of the CS	**The EAG considers the quality assessment tool used for RCTs to be appropriate** The company used the University of York's Centre for Reviews and Dissemination (CRD) checklist for RCTs. These assessments are included in Table 11 of the CS for ELEVATE and PROGRESS (main atogepant trials of interest covered in the CS) and in Tables 33 and 34 of the CS appendices for other included atogepant trials and comparator trials. The EAG notes that the latter two tables include additional studies that were excluded from NMAs, as the criteria for study data extraction was wider than that of the final decision problem set out in the CS.

Abbreviations: BoNT/A, botulinum toxin type A; CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; CQ, clarification question; CS, company submission; EAG, External Assessment Group; EMTREE, Embase subject headings; MeSH, Medical Subject Headings; NICE, National Institute for Health and Care Excellence; N/A, not applicable; NMA, network meta-analysis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial; SLR, systematic literature review; TA, technology appraisal.

3.2 Critique of trials of the technology of interest

Four RCTs involving atogepant are included as part of the CS,[25-28] with all four of these studies included in NMAs within the overall migraine population (see Section 3.4). However, for EM in the CS, the company focuses mostly on ELEVATE given it provides data for the group with at least three prior oral preventive treatment failures (3+ TF) and was stratified at randomisation for this factor. PROGRESS is the only available atogepant RCT within the CM population but results from the overall migraine population are focused on in the CS; while some data for a 3+ TF subgroup were available, the trial was not stratified for this factor at randomisation and the company considers that results within this subgroup cannot be used to draw reliable conclusions based on baseline imbalances between arms and comments from clinical experts that artefactually high placebo rates are present for this subgroup within PROGRESS (see Section B.2.2 of the CS).

The EAG acknowledges the company's concerns about 3+ TF subgroup data from PROGRESS but considers these data useful in providing some insight into outcomes in the subgroup outlined in the decision problem, despite their additional limitations. The EAG has access to these via the clinical study report (CSR) and has included information in its report where required to support decision-making. The EAG notes that information for the overall population and 3+ TF subgroup was provided in the CS for ELEVATE. The company's and EAG's preferred analysis populations for NMAs is discussed in Section 3.4.1.

The EAG notes that a further atogepant RCT in EM is listed as excluded in Table 9 of the CS appendices (NCT03700320; study 3101-302-002).[29] This is because it compares atogepant 60 mg with standard of care migraine preventive treatments, which the EAG considers would include first- to third-line oral options currently recommended by NICE CG150 2021.[30] This differs to all other RCTs included in the NMA (including for comparator treatments), which are compared with placebo and the EAG considers its exclusion from the submission to be reasonable.

While meta-analyses of the three EM atogepant trials could have been presented in the CS rather than focusing on ELEVATE, the EAG does not consider this to be a major omission given the company focuses on the 3+ TF subgroup data for EM in the CS and the other two trials have only a handful or no patients with 3+ TF. All three trials have been included in the overall migraine population NMAs and the EAG presents meta-analysed clinical results from the overall populations of these three trials in Appendix 8.1.

Quality assessments performed by the company for ELEVATE and PROGRESS,[25, 28] the main atogepant RCTs focused on in the CS for EM and CM, respectively, are presented in Table 11 of the CS. The EAG presents its own critique of these studies below in Table 14. Given two additional atogepant RCTs (CGP-MD-01 and ADVANCE) were also included in EM overall population NMAs for health-related quality of life (HRQoL) and/or treatment-emergent adverse events (TEAEs),[26, 27] the EAG has also commented on their quality in this table.

Unlike the company's conclusions, the EAG considers that the included atogepant RCTs have some risk of bias, for example, dropouts are [redacted] for atogepant in ELEVATE, and there are [redacted] in missing data between arms at certain time-points for ELEVATE and PROGRESS, although these are less notable when overall populations are focused on compared to 3+ TF subgroups, which is the EAG's preference as described in Section 3.4.1.

It is unclear if a missing at random assumption, as used in these studies, is appropriate. Although the EAG acknowledge that the robustness of primary outcome (change from baseline [CFB] in monthly migraine days [MMDs]) to this missing at random assumption was assessed to some extent in ELEVATE, PROGRESS and ADVANCE using a copy-reference and jump-to-reference approach, this was not the case for other outcomes, including efficacy outcomes used in the economic model. While the EAG considers that an alternative approach such as reversion to baseline for missing data may provide further insight into the impact of missing data, the company did not provide this in response to CQ A3. Given that similar missing at random approaches have been used in certain studies for comparator treatments (while details for a number of studies were unclear, most studies across EM and CM relied on missing at random assumptions for MMD-related outcome data, with a similar proportion of these analysing observed data only with no imputation as per the atogepant trials and others using alternative methods such as proration/normalisation and/or last observation carried forward methods depending on the level of missing data), and that the sensitivity analyses that have been performed by the company show robustness of the primary outcome to missing data assumption, the EAG does not consider this to be a major limitation.

In addition, subgroup data from PROGRESS for the group with 3+ TF may be at a higher risk of bias given these subgroups were not stratified for at randomisation, with [redacted] and proportion with [redacted] at baseline (see Section 3.3). Despite these limitations, the EAG notes that similar is true for some comparator RCTs included in the NMAs, in terms of assumptions made for missing data (see previous paragraph) and

not being stratified by 3+ TF (none of the comparator studies included in the 3+ TF NMAs for EM stratified for this at randomisation,[18-20] neither did any of the studies included in 3+ TF NMAs for CM as part of the CCE process for atogepant earlier in 2023).[18, 19, 31-34] See Section 3.4.4 for further discussion of differences between studies included in NMAs in this STA.

Overall, the EAG does not consider there to be a large degree of bias associated with the atogepant clinical trials, particularly if the overall migraine populations are focused on.

Table 14. EAG's quality assessment of atogepant clinical trials included in the submission

Question	ELEVATE (EM)[28]	PROGRESS (CM)[25]	CGP-MD-01 (EM)[27]	ADVANCE (EM)[26]
Was randomisation carried out appropriately?	**Yes** Automated IWRS Stratified at randomisation for 3+ TF (subgroups of 2 vs 3-4 treatment class failures)	**Yes** Automated IWRS Not stratified at randomisation for 3+ TF*	**Yes** Automated IWRS Used only for overall migraine population analyses as no efficacy data was reported for those with were reported for patients 3+ TF	**Yes** Automated IWRS Used only for overall migraine population analyses as very few patients in 3+ TF subgroup
Was the concealment of treatme	**Yes** Production of randomisation scheme appears to be separate from those enrolling patients in trial	**Yes** Production of randomisation scheme appears to be separate from those enrolling patients in trial	**Yes** Production of randomisation scheme appears to be separate from those enrolling patients in trial	**Unclear** No details about whether third-party/separate group responsible for randomisation scheme

nt allocated adequate?				
Were the groups similar at the outset of the study in terms of prognostic factors?	**Yes** (overall mITT trial population) Slightly [redacted] between arms in 3+ TF subgroup but [redacted], including continuous outcomes at baseline	**Yes** (overall mITT trial population), although there was a slightly [redacted] proportion using an additional preventive medication during the treatment period in the [redacted] arm ([redacted]% vs [redacted]%) Some [redacted] in 3+ TF subgroup (i.e. [redacted] and proportion with [redacted]†) but others [redacted], including continuous outcomes at baseline (other than MSQ-EF where there was [redacted], with	**Yes** (overall mITT trial population) No 3+ TF subgroup reported	**Yes** (overall mITT trial population) No 3+ TF subgroup used from this trial

		values [redacted] in the placebo group)		
Were the care providers, participants, and outcomes assessors blind to treatment allocation?	**Yes** Said to be double-blind and tablets matched	**Yes** Said to be double-blind and tablets matched	**Yes** Said to be double-blind and tablets matched	**Yes** Said to be double-blind and tablets matched

Were there any unexpected imbalances in dropouts between groups?	**Yes** (from ITT population – proportion discontinuing slightly [redacted] in atogepant group, [redacted]) Slightly [redacted] was due to [redacted] numbers discontinuing due to AE, protocol deviation or lack of efficacy, although these were only differences of [redacted] events per reason Unclear if similar was true for the 3+ TF subgroup	**No** (from ITT population, similar in atogepant 60 mg and placebo groups – [redacted]% vs [redacted]%) Unclear if similar was true for the 3+ TF subgroup	**Yes** (from ITT population – proportion discontinuing [redacted] in atogepant 60 mg group vs placebo, [redacted]) Most of this difference was due to patients [redacted]; withdrawals due to [redacted] between groups	**Yes** (from ITT population – proportion discontinuing [redacted] in atogepant 60 mg group vs placebo, [redacted]) Proportions with each specific reason for discontinuation were, however, [redacted] between arms. Other than [redacted], which occurred [redacted] in the atogepant 60 mg arm vs placebo ([redacted])
Is there any evidence to suggest	**No** Outcome data relevant to the appraisal focused on in CS	**No** Outcome data relevant to the appraisal focused on in CS	**No** Outcome data relevant to the appraisal focused on in CS.	**No** Outcome data relevant to the appraisal focused on in CS.

that the authors measured more outcomes than they reported?				
Did the analysis include an intention-to-	**Yes, some concerns about missing at random assumption** mITT population for efficacy and HRQoL analyses‡ Safety population for AEs§ Missing data handled using MMRM for continuous outcomes – assumed to be MAR, may not	**Yes, some concerns about missing at random assumption** mITT population for efficacy and HRQoL analyses‡ Safety population for AEs§	**Yes, some concerns about missing at random assumption** mITT population for efficacy analyses‡ Safety population for AEs§ [redacted]	**Yes, some concerns about missing at random assumption** mITT population for efficacy and HRQoL analyses‡ Safety population for AEs§ [redacted]

treat analysis? If so, was this appropriate and were appropriate methods used to account for missing	be plausible. Logistic regression used for binary outcomes. In the 3+ TF subgroup at weeks 9-12 for MMD data, [redacted] patients in the atogepant arm had missing data ([redacted], difference of [redacted] patients), while proportions were [redacted] at earlier time-points. There was a similar but [redacted] difference in the overall mITT population ([redacted]%; difference of [redacted] patients)[ll] For HRQoL data in the overall mITT population, missing data was [redacted] between arms at 12 weeks.	Missing data handled using MMRM for continuous outcomes – assumed to be MAR, may not be plausible. Logistic regression used for binary outcomes. In the 3+ TF subgroup for MMD data, while proportions with missing data were slightly [redacted] for placebo at weeks 5-8 and weeks 9-12 ([redacted]), this was based on a difference of [redacted] patients. For the overall mITT population, there was a slight difference in proportions with missing data at weeks 9-12 ([redacted]% in placebo vs atogepant 60 mg groups) but not at earlier time-points[ll]	Detailed information on missing data rates not available.	Detailed information on missing data rates not available.

data?		For HRQoL data in the overall mITT population, missing data was [redacted] between arms at 12 weeks.		
Sample size and power	Planned enrolment of 150 patients per group provided 97% and 95% power to detect a treatment difference for CFB in MMDs vs placebo (-1.7 days for US and -1.6 days for EU, SD 3.5 days). This sample size was also said to have been selected to provide sufficient power for [redacted]. Just over 150 patients per arm were enrolled but the EAG notes that missing data at weeks 9-12 meant that [redacted] patients had available data in atogepant 60 mg (MMD or MUD outcomes) or both treatment arms (HRQoL outcomes). Power calculations were said to have been based on results from	Planned enrolment of 250 patients per group provided ≥96% power to detect a treatment difference between each atogepant dose (assumed equally effective) and placebo for CFB in MMDs (treatment difference assumed to be -2.0 days with 5.5 SD). This sample size was also considered to provide sufficient power for [redacted]. Just over 250 patients were enrolled but the EAG notes that just	Planned enrolment of [redacted] for 60 mg twice daily, 30 mg twice daily and 10 mg once daily, and [redacted] for 60 mg once daily, 30 mg once daily and placebo groups. Assuming treatment difference of [redacted] (SD [redacted]) for the dose relevant to the CS (60 mg atogepant once daily). This was estimated to give a power of [redacted]% for the primary outcome (CFB in MMDs). Numbers outlined above were successfully randomised into the trial, although those completing the trial were less than those specified for each treatment. Power calculations were based on results from other EM prevention studies, including [redacted] Unclear why the specific studies selected were chosen.	Sample size of 218 participants per trial group was calculated to provide at least 98% power to detect a difference of 1.5 migraine days between each of the three atogepant doses (assumed to be equally effective) and placebo for the primary efficacy end point (CFB in MMDs), assuming a standard deviation of 3.5 days for each. Also estimated to provide at least 89% power for first three secondary endpoints (CFB in MHDs, CFB in acute MUDs and 50% MMD reduction). A total of 218 patients for each group were successfully randomised into the trial, although fewer than 218 in each group completed the treatment period. Power calculations were based on results from other EM prevention studies, including CGP-MD-01 for atogepant and selected studies for telcagepant, galcanezumab, fremanezumab and eptinezumab. Unclear why the specific studies selected were chosen.

	[redacted] Unclear why other mAb studies not considered.	under 250 were included in the mITT population for the placebo group. Missing data at weeks 9-12 also meant that data was available from [redacted] in each treatment group for MMD/MUD and HRQoL outcomes. Power calculations were based on assumptions that treatment differences vs placebo will be similar to [redacted] Unclear why [redacted] studies not considered.		This information could not be located in the CSR but was identified in a publication for this study.[35]
Outcome assessment	Migraine outcomes were assessed using eDiaries completed by patients at relevant time-points, which are valid but subjective measures of assessment meaning blinding is particularly important. HRQoL	Migraine outcomes were assessed using eDiaries completed by patients at relevant time-points, which are valid but subjective measures of	Migraine outcomes were assessed using eDiaries completed by patients at relevant time-points, which are valid but subjective measures of assessment meaning blinding is particularly important.	Migraine outcomes were assessed using eDiaries completed by patients at relevant time-points, which are valid but subjective measures of assessment meaning blinding is particularly important. HRQoL outcomes were assessed using validated questionnaires.

	outcomes were assessed using validated questionnaires.	assessment meaning blinding is particularly important. HRQoL outcomes were assessed using validated questionnaires.		

*This trial was stratified based on failing 0 or ≥1 medications with same mechanism of action vs failed 2-4 medications with different mechanisms of action but not for the specific subgroup used in the CS (≥3 prior treatment failures); [†]data provided in response to CQ A5 as part of the CCE process for atogepant earlier in 2023; [‡]mITT defined as patients randomised, receiving at least one dose of study drug, with baseline eDiary data and ≥1 post-baseline 4-week period of eDiary data during double-blind treatment period – of the ITT population, this led to the exclusion of [redacted] and [redacted] in atogepant 60 mg and placebo groups, respectively, in ELEVATE. The equivalent proportions were [redacted] and [redacted] for PROGRESS, [redacted] and [redacted] for CGP-MD-01, and [redacted] and [redacted] for ADVANCE; [§]safety population defined as those with ≥1 dose of study drug, analysed according to treatment received – of the ITT population, this led to the exclusion of [redacted] and [redacted] in atogepant 60 mg and placebo groups, respectively in ELEVATE. The equivalent proportions were [redacted] and [redacted] for PROGRESS, [redacted] for CGP-MD-01, and [redacted] and [redacted] for ADVANCE. It is unclear if any patients switched groups and were analysed in the opposite group to that they were assigned to at randomisation for safety analyses; [‖]data provided in response to CQ A7 as part of the CCE process for atogepant earlier in 2023.

The EAG used the template completed by the company with the addition of rows on sample size and power and outcome assessment.

Abbreviations: 3+ TF, patients in whom ≥3 prior preventive treatments have failed; AEs, adverse events; CCE, cost-comparison evaluation; CM, chronic migraine; CQ, clarification question; CS, company submission; EAG, External Assessment Group; eDiary, electronic diary; EM, episodic migraine; HRQoL, health-related quality of life; ITT, intention to treat; IWRS, interactive web-response system; MAR, missing at random; mITT, modified intention to treat; MMD, monthly migraine day; MMRM, mixed model for repeated measures; MSQ-EF, migraine-specific quality of life questionnaire – emotional function.

3.3 Critique of the clinical effectiveness analysis and interpretation

In Section B.2.6 of the CS, the company outlines results for primary and secondary outcomes of ELEVATE (EM) and PROGRESS trials. While three atogepant RCTs within the EM population were included in the submission for the overall migraine population (see Section 3.2), these are not focused on in the CS given they included no or very few patients with 3+ TF, unlike ELEVATE which included a 3+ TF group which was stratified for at randomisation. For PROGRESS, in the original CS the company only presented results for the overall mITT population, as it notes that the 3+ TF subgroup was not stratified for at randomisation and the results are, therefore, unreliable (see Section 3.2). However, results for both the 3+ TF subgroup and overall mITT population in ELEVATE are included in the CS.

While the EAG agrees that the ELEVATE trial in EM is more relevant to the decision problem population (3+ TF) than ADVANCE and CGP-MD-01 as it includes a proportion of 3+ TF patients and is specifically in those with 2-4 TF, given its preference for NMAs within the mITT population for EM as well as CM (as described in Section 3.4.1), the EAG has also presented results from ADVANCE and CGP-MD-01 within the mITT population. Meta-analysed results are also presented by the EAG in Appendix 8.1. In addition, while the EAG acknowledges the additional bias likely to be associated with 3+ TF subgroup results from PROGRESS, the EAG considers it useful that these results be presented for comparative purposes, given this is the group outlined in the decision problem, and has obtained these results from the PROGRESS CSR.

The EAG considers that the results from the overall population for PROGRESS may be more reliable compared to the 3+ TF subgroup given some larger imbalances were observed for the latter; while the EAG's clinical experts did not consider a notable imbalance in [redacted] white in placebo and atogepant groups, respectively) to be important, the EAG notes that there is a [redacted] in the proportion with ≥18 MMDs within this subgroup ([redacted] in placebo and atogepant groups, respectively; response to CQ A5 as part of the CCE process for atogepant earlier in 2023) which may indicate a difference in migraine burden that could impact relative efficacy outcomes (i.e. more people with higher initial baseline MMDs [redacted] group may mean fewer patients are able to achieve a 30% or 50% reduction in MMDs at follow-up than would have had this been more balanced). There are no major concerns about imbalances for the 3+ TF population from ELEVATE but for reasons described in Section 3.4.1 the EAG also prefers NMAs within the overall migraine population for EM (see Key Issue 2 in Table 3). As noted in Section

2.3.1, the EAG's clinical experts had no major concerns about differences in baseline characteristics between the 3+ TF and overall migraine populations for ELEVATE or PROGRESS; in both cases they consider that either of them would be a reasonable representation of a 3+ TF group.

Of the outcomes described in the sections that follow, data from ELEVATE (3+ TF subgroup for all outcomes) and PROGRESS (overall mITT population for all outcomes) were used in the economic model by the company to inform absolute values for CFB in MMDs, CFB in acute medication use days (MUDs), 50% (EM) or 30% (CM) reduction in MMDs and discontinuation for atogepant. For scenarios using the overall migraine population for EM in the economic model, ADVANCE was used as the source of atogepant data, which the EAG considers to be reasonable. Relative treatment effects from NMAs described in Section 3.4.3 were then used to obtain values for each comparator for use within the economic model (see Section 4.2 for further discussion regarding the economic model). For CM, results for the 50% MMD reduction threshold have also been presented given limited data was available for the 30% threshold in the NMAs (see Section 3.4.3.1), but the EAG notes that 30% is the threshold normally used in CM and is what is used in the base case of the company's economic model. The company performed a scenario analysis in CM where the 50% threshold was used in the economic model instead (see Section 5.1.3). HRQoL outcomes and TEAEs were not used in the economic model but are discussed briefly for completeness.

3.3.1 Migraine day-related outcomes

Migraine day-related outcomes from ELEVATE and PROGRESS that were used to inform the economic model, within the 3+ TF and overall mITT populations, are presented in Table 15 below. For comparison within the EM mITT population, the EAG presents results from ELEVATE alongside ADVANCE and CGP-MD-01 in Table 16 below.

As concluded by the company in Section B.2.6.1 of the CS, the EAG agrees that results in the 3+ TF and overall mITT populations for ELEVATE in EM demonstrate a statistically significant benefit of atogepant compared to placebo in terms of reducing MMDs. Results for EM in these two populations are [redacted] with a slightly [redacted] benefit observed in the 3+ TF subgroup. In terms of CM, the EAG agrees with the company's conclusion that there is a statistically significant difference between atogepant and placebo groups in terms of reducing MMDs, with the benefit observed for atogepant. [redacted], the 3+ TF subgroup results from PROGRESS are [redacted] the overall mITT population, with the point estimate for the difference between treatments suggesting a [redacted] in the 3+ TF subgroup compared to

the overall mITT population; however, the results are [redacted] when this subgroup is considered, which may partially be due to [redacted] in this analysis in addition to the fact that PROGRESS (unlike ELEVATE) was not powered to assess the primary outcome in the 3+ TF subpopulation.

For EM, the same conclusions can be made for the other two outcomes included in Table 15 below; results in both populations are similar in terms of direction and statistical significance, with results [redacted] for atogepant in the 3+ TF subgroup, which is most notable for the ≥50% reduction in MMD outcome. Given the similarity of results between 3+ TF and overall mITT population results in EM from ELEVATE, the EAG considers this provides further support for its preference for the overall migraine population NMAs for the EM population (see Section 3.4.1). The conclusions for other outcomes in Table 15 for CM are also similar to those made for the CFB in MMD outcome; 3+ TF and overall mITT population analyses [redacted] a benefit of atogepant over placebo, but most 3+ TF analyses (with the exception of the CFB in acute MUDs outcome) [redacted]. The remaining outcomes in CM again suggest [redacted] in the 3+ TF subgroup compared to the overall mITT population, with the exception of proportion with ≥30% reduction in MMDs where the OR for the 3+ TF subgroup is [redacted] for atogepant. Nonetheless, the EAG accepts the potential limitations associated with this subgroup in PROGRESS and, overall, considers the use of the mITT population results to be reasonable given they do not differ hugely.

With regards to the three atogepant RCTs in the EM population that are included in NMAs within the migraine population analyses, the EAG notes that across the three outcomes included in Table 16, the most favourable outcomes for atogepant come from the ELEVATE study. However, the EAG notes that results from ELEVATE and ADVANCE are broadly similar in that [redacted] of atogepant 60 mg once daily vs placebo is observed for [redacted]. The same is also true for CGP-MD-01 for the CFB acute MUDs outcome, but not for CFB in MMDs or proportion with ≥50% reduction in MMDs. The EAG is unsure exactly why this may be the case but notes that it may be related to placebo response as it is highest in this study for all three outcomes, with the [redacted]. Nonetheless, the EAG concludes that all three studies suggest a benefit of atogepant 60 mg daily over placebo for these three outcomes in the overall mITT population of included studies, but notes that the [redacted] across the three RCTs. As noted in the introductory text to

Section 3.3, the EAG agrees that ELEVATE is most relevant to the decision problem given it provides data for the 3+ TF subgroup and the whole mITT population is specific to those with 2-4 TF.

Table 15. Primary and secondary MMD day-related outcomes used to inform the economic model – ELEVATE and PROGRESS, 3+ TF and overall mITT populations, across 12-week treatment period – adapted from Tables 12 and 13 of the CS

Outcome	3+ TF subgroup			Overall mITT population		
EM - ELEVATE[28, 36]	**Placebo (N=[redacted])**	**Atogepant 60 mg once daily (N=[redacted])**	**TE* (95% CI)**	**Placebo (N=[redacted])**	**Atogepant 60 mg once daily (N=[redacted])**	**TE* (95% CI)**
CFB in mean MMDs, LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Achievement of ≥50% reduction in mean MMDs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB in mean monthly acute MUDs, LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CM - PROGRESS[25, 37]	**Placebo (N=[redacted])**	**Atogepant 60 mg once daily (N=[redacted])**	**TE*,§ (95% CI)**	**Placebo (N=246)**	**Atogepant 60 mg once daily (N=256)**	**TE* (95% CI)**
CFB in mean MMDs, LS mean (SE)	[redacted]	[redacted]	[redacted]	-5.05 (0.411)	-6.88 (0.406)	**MD -1.82 (-2.89 to -0.75)‡**
Achievement of ≥30% reduction in mean MMDs, n (%)	[redacted]	[redacted]	[redacted]¶	[redacted]	[redacted]	[redacted]‡
Achievement of ≥50% reduction in mean MMDs**, n (%)	[redacted]	[redacted]	[redacted]††	64 (26.0)	105 (41.0)	**OR 2.04 (1.38 to 3.00)‡**
CFB in mean monthly acute MUDs, LS mean (SE)	[redacted]	[redacted]	[redacted]‡‡	-4.10 (0.392)	-6.23 (0.386)	**MD -2.13 (-3.13 to -1.13)‡**

*TE was LSMD for all endpoints apart from the achievement of ≥50% or ≥30% reduction in mean MMDs where it was OR; †p<0.001; ‡p<0.0001; §data obtained from additional tables (Tables 901.3-1.1.3, 901.3-18.1.3, 901.3-2.1.3 and 901.3-4.1.3 for CFB in MMDs,

≥30% reduction in MMDs, ≥50% reduction in MMDs and CFB in acute MUDs, respectively) provided as part of the PROGRESS CSR for the 3+ TF subgroup;[37] ‖p-value = [redacted]; ¶p-value = [redacted]; **for CM, the 50% MMD reduction threshold was not used in the base case of the economic model but was explored by the company in a scenario analysis (Table 67 of the CS); ††p-value = [redacted]; ‡‡p-value = [redacted]. Bolded values indicate statistically significant differences.

Abbreviations: 3+ TF, patients in whom ≥3 prior oral preventive treatments have failed; CFB, change from baseline; CI, confidence interval; CM, chronic migraine; CS, company submission; CSR, clinical study report; EM, episodic migraine; LS, least squares; LSMD, least squares mean difference; MD, mean difference; mITT, modified intention to treat; MMD, monthly migraine days; MUDs, medication use days; OR, odds ratio; SE, standard error; TE, treatment effect.

Table 16. Comparison of migraine day-related outcomes in ELEVATE, ADVANCE and CGP-MD-01 RCTs within the EM mITT population – adapted from Table 12 of the CS and CSRs for ADVANCE and CGP-MD-01

Outcome	ELEVATE[28]			ADVANCE[26,*]			CGP-MD-01[27,†]		
	Placebo (N=[redacted])	Atogepant 60 mg once daily (N=[redacted])	TE‡ (95% CI)	Placebo (N=[redacted])	Atogepant 60 mg once daily (N=[redacted])	TE‡ (95% CI)	Placebo (N=[redacted])	Atogepant 60 mg once daily (N=[redacted])	TE‡ (95% CI)
CFB in mean MMDs, LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Achievement of ≥50% reduction in mean MMDs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB in mean monthly acute MUDs, LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Data was obtained from Tables 11-2, 11-9 and 11-8 for CFB in MMDs, proportion with ≥50% MMD reduction and CFB in acute MUDs, respectively; †data was obtained from Tables 11-2, 11-5 and 11-6 for CFB in MMDs, proportion with ≥50% MMD reduction and CFB in acute MUDs, respectively; ‡TE was LSMD for all endpoints apart from the achievement of ≥50% reduction in mean MMDs where it was OR; §p<0.001; ‖p<0.0001; ¶p-value = [redacted]; **p-value = [redacted]. Bolded values indicate statistically significant differences.

Abbreviations: CFB, change from baseline; CI, confidence interval; CS, company submission; EM, episodic migraine; LS, least squares; LSMD, least squares mean difference; MD, mean difference; mITT, modified intention to treat; MMD, monthly migraine days; MUDs, medication use days; OR, odds ratio; SE, standard error; TE, treatment effect.

3.3.2 Discontinuation

Given NMAs are also performed as part of this submission for all-cause discontinuation (see Section 3.4.3.2), the results of which inform the proportion of patients discontinuing treatment prior to response assessment for comparator treatments in the economic model (see Section 4.2.6.1 of this report and Section B.3.3.2 of the CS), the EAG also touches on the results for discontinuation from atogepant RCTs here.

While the EAG presents discontinuations with the 3+ TF subgroup as well as the overall mITT populations for ELEVATE and PROGRESS in Table 17 below for completeness, it notes that NMAs for EM and CM were only possible within the overall migraine population, given these data were not well reported for comparator RCTs (see Section 3.4.1).

The EAG notes that within the overall mITT population for EM, there does not appear to be a consistent pattern in terms of whether there were more discontinuations in the placebo or atogepant 60 mg once daily group; while it was [redacted] for atogepant in ELEVATE [redacted], the opposite was observed for [redacted]. Within ELEVATE, percentages suggest that there is a [redacted] difference between atogepant and placebo groups in the 3+ TF subgroup compared to the overall mITT population ([redacted] discontinuation for atogepant in both analyses), although the EAG notes that there is a difference of [redacted] events between atogepant and placebo groups in both populations. For CM, the overall mITT population of the PROGRESS trial indicated [redacted] discontinuation in atogepant 60 mg once daily and placebo groups, with there [redacted] based on percentages for the 3+ TF subgroup; however, the EAG notes that there is only a difference of [redacted] events in the 3+ TF subgroup.

Overall, the EAG concludes that while there are some differences in proportions discontinuing for the EM studies ([redacted] for atogepant in two and [redacted] for placebo in one), these are generally based on differences of [redacted] patients, other than the CGP-MD-01 study. For CM, there is limited difference between treatment arms in 3+ TF and overall mITT populations.

Table 17. All-cause discontinuation across atogepant RCTs for EM and CM, 3+ TF and overall mITT populations

Study	3+ TF subgroup		Overall mITT population	
	Placebo, n/N (%)	Atogepant 60 mg once daily, n/N (%)	Placebo, n/N (%)	Atogepant 60 mg once daily, n/N (%)
ELEVATE (EM)[28, 36]	[redacted]	[redacted]	[redacted]	[redacted]
ADVANCE (EM)	N/A	N/A	[redacted]	[redacted]
CGP-MD-01 (EM)	N/A	N/A	[redacted]	[redacted]
PROGRESS (CM)	[redacted]	[redacted]	29/259 (11.2%)	29/262 (11.1%)

Abbreviations: 3+ TF, patients in whom ≥3 prior oral preventive treatments have failed; CM, chronic migraine; EM, episodic migraine; mITT, modified intention to treat; N/A, not applicable; RCT, randomised controlled trial.

3.3.3 Quality of life

HRQoL was included in the CS by reporting results for various validated questionnaires (three subscores of the migraine-specific quality of life questionnaire [MSQ] v2.1 questionnaire and the Headache Impact Test [HIT]-6) assessed in the atogepant RCTs. While NMAs were performed for these outcomes (see Section 3.4.3.3), the results of these NMAs were not used in the economic model. As discussed further in Section 4.2.9, utilities in the economic model are considered by mapping MSQ v2.1 data from the overall mITT populations of ELEVATE and PROGRESS studies to EQ-5D-3L. Given the overall mITT population was used for this purpose in the economic model and was the population used for NMAs of HRQoL outcomes, the EAG only presents mITT results here. However, the EAG agrees with the company's conclusions in Section B.2.6.3 of the CS that within ELEVATE, results for the 3+ TF population are consistent with those in the overall mITT population, although slightly [redacted] for atogepant in the 3+ TF subgroup (but with increased uncertainty). On review of the 3+ data for the PROGRESS trial within the CSR tables provided,[37] the EAG also considers that the same is true for this trial, again with increased uncertainty. The EAG has included data from the ADVANCE and CGP-MD-01 RCTs in EM for comparison, as these were also included in overall migraine population NMAs.

In terms of the results, the EAG agrees with the company's conclusions in Section B.2.6.3 of the CS that overall mITT populations for ELEVATE and PROGRESS demonstrate statistically significant benefits of atogepant 60 mg once daily compared to placebo for the three MSQ v2.1 subscores and HIT-6. The EAG also agrees that these differences are higher than the thresholds considered to be

clinically meaningful for these outcomes according to the sources cited by the company,[38-40] apart from MSQ-EF in PROGRESS for CM where the point estimate was just below the threshold of 7.5 points. While the EAG notes that the results in Table 18 below indicate that [redacted] of atogepant vs placebo was observed in ADVANCE compared to ELEVATE, the results for all outcomes [redacted] the clinically meaningful thresholds reported. The CGP-MD-01 study did not report MSQ v2.1 outcomes; the result for HIT-6 was [redacted] for atogepant compared to ELEVATE and ADVANCE studies as there was [redacted] and the point estimate for the difference vs placebo was [redacted] cited as clinically meaningful by the company.[39, 40]

Overall, the EAG considers that evidence from the atogepant RCTs included in this submission, particularly ELEVATE and PROGRESS, which are focused on by the company, provide evidence that atogepant 60 mg once daily leads to clinically meaningful improvements in HRQoL outcomes compared to placebo.

Table 18. CFB in HRQoL outcomes in atogepant RCTs within the mITT population, EM and CM

Outcome	ELEVATE (EM)[28]			ADVANCE (EM)[26]			CGP-MD-01 (EM)[27]			PROGRESS (CM)		
	Placebo	Atogepant 60 mg once daily	TE* (95% CI)	Placebo	Atogepant 60 mg once daily	TE* (95% CI)	Placebo	Atogepant 60 mg once daily	TE* (95% CI)	Placebo	Atogepant 60 mg once daily	TE* (95% CI)
CFB in mean MSQ-RFP score, LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]
CFB in mean MSQ-RFR score, LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]
CFB in mean MSQ-EF score, LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]
CFB in mean HIT-6 score, LS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

mean (SE)												

*TE was LSMD for all endpoints; †p<0.0001; ‡p<0.001; §p-value = [redacted]. Bolded values indicate statistically significant differences.

Abbreviations: CFB, change from baseline; CI, confidence interval; CM, chronic migraine; EM, episodic migraine; HIT-6, Headache Impact Test-6; HRQoL, health-related quality of life; LS, least squares; LSMD, least squares mean difference; MD, mean difference; mITT, modified intention to treat; MSQ, migraine-specific quality of life questionnaire; MSQ-EF, emotional function subdomain of MSQ; MSQ-RFP, role function-preventive subdomain of MSQ; MSQ-RFR, role function-restrictive subdomain of MSQ; N/A, not applicable; RCT, randomised controlled trial; SE, standard error; TE, treatment effect.

3.3.4 *Safety*

Given adverse events (AEs) are not included in the economic model, the EAG only briefly discusses AEs in this section. AEs for the overall safety populations of ELEVATE and PROGRESS are summarised in Section B.2.10 of the CS. While TEAEs related to treatment were higher in both trials for atogepant 60 mg once daily, the EAG notes that similar proportions in each group experienced serious events or those leading to treatment discontinuation. The biggest differences between atogepant and placebo arms appeared to be for [redacted] in both trials, with more of these events in the atogepant groups. Similar was observed for CGP-MD-01 and ADVANCE atogepant trials.[26, 27]

The EAG's clinical experts are not aware of any AEs of particular concern for atogepant but note that there are certain AEs that can be an issue for monoclonal antibodies (mAbs; erenumab, galcanezumab and fremanezumab) and botulinum toxin type A (BoNT/A) and are more common, such as injection site-related AEs. Omission of AEs from the economic model may be conservative, however, injection site-related AE disutility was indirectly included, by the company applying a utility decrement associated with route of administration (see Section 4.2.7). NMAs for TEAEs were performed as part of the CS (see Section 3.4.3.4) but the EAG notes that usually AEs of a specific severity are included in economic models, rather than any TEAEs, and so the results of these NMAs are not useful in confirming the conclusions made by the EAG's clinical experts. Furthermore, the EAG notes that no AEs of concern for atogepant are reported in the marketing authorisation.[4]

3.4 Summary of the indirect treatment comparison

3.4.1 *Statistical methods and approach*

In the absence of direct evidence comparing atogepant with any of the comparators in the decision problem, NMAs were performed. The EAG focuses on outcomes where NMA results were directly used in the economic model (CFB in MMD, proportion with ≥30 or 50% reduction in MMDs, CFB in acute MUDs and all-cause discontinuation; Sections 3.4.3.1 and 3.4.3.2), but also touches on results of NMAs for HRQoL outcomes and TEAEs (Sections 3.4.3.3 and 3.4.3.4, respectively).

For the EM population, NMAs for MMD-based outcomes were performed in the 3+ TF population (company's preferred analysis) as well as the overall migraine population, but the same was not performed for the CM population. This is because the ELEVATE study in EM stratified for the 3+ TF subgroup at randomisation and this subgroup was said by the company to be adequately powered,

whereas the PROGRESS trial in CM was not stratified for this subgroup or adequately powered within this subgroup. The company states that the lack of stratification in the PROGRESS trial, as well as small sample size, may explain comments from the clinical experts that they consulted that this subgroup within PROGRESS has artefactually high placebo response rates; the company concludes that the 3+ TF subgroup within PROGRESS is not suitable for decision-making and NMAs within the overall migraine population are instead preferred. While NMAs within the 3+ TF population for CM were performed as part of the CCE earlier in 2023, these were not provided as part of this STA; the EAG has touched on these results briefly in Section 3.4.3.1 for CM in terms of how different they are to the company- and EAG-preferred analyses in this report. The EAG agrees with the company's concerns about the 3+ TF subgroup from PROGRESS and the impact this may have on the results of NMAs; however, it considers the same issues apply to EM given many comparator studies were not stratified for 3+ TF. Based on this, the EAG has a preference for NMAs performed within the overall migraine population for EM and CM populations (see Key Issue 2 in Table 3).

For HRQoL, all-cause discontinuation and TEAE NMAs, analyses were performed only in the overall migraine population given a lack of reporting of these outcomes for comparator studies within the 3+ TF population. The EAG considers this to be reasonable and notes that the EAG's concern about the overall migraine population analyses during the CCE has been resolved as part of the STA, as these analyses now include all migraine RCTs rather than excluding those that were specifically in refractory populations (i.e. 2-4 treatment failures). Studies solely in Asian populations were also included in these NMAs, as requested by the EAG during the CCE process. The company also provided HRQoL NMAs within more refractory populations (2+ and 3+ TF groups) as part of the CCE process, which demonstrated that data was much scarcer for these populations, with only one or two comparators being included; the EAG considers that this supports the need for the overall migraine population to be used for these additional outcomes.

The clinical experts advising the EAG note that it may be reasonable to use overall analyses for discontinuation and TEAE outcomes, as they do not expect them to differ across patients with different numbers of treatment failures. One expert noted that if reasons for prior treatment failure included side effects then it may be an issue, as people who experience side effects on one treatment may be at a higher general risk with other treatments. This was the case for the ELEVATE and PROGRESS trials when classifying treatment failure, and the FOCUS, CONQUER and LIBERTY trials, but the proportion failing due to side effects rather than a lack of efficacy is unclear. However, the second expert did not agree with the concerns raised. On balance, the EAG is not concerned that

looking at an overall population rather than focusing only on the 3+ TF subgroup would affect conclusions, particularly as, in most cases where a comparison is possible for the same intervention, relative differences in TEAE rates vs placebo in studies in a general population are similar to those from studies that only include patients with 2-4 prior treatment failures (Tables 17 and 23 of the CS appendices).

The EAG considers the methods used for the NMAs to be appropriate. Fixed (FE) and random effects (RE) models were performed by the company, with RE favoured as the company highlight heterogeneity between the trials included in the NMAs. While the EAG also has a preference for RE analyses in the overall migraine population NMAs given they are generally a better fit and there is reason to believe there is clinical and methodological heterogeneity between trials, the EAG disagrees with the company's preference for RE analyses within the 3+ TF population for EM (see Key Issue 3 in Table 4), given that on rerunning the analyses, in most cases the distribution of between-study heterogeneity was dominated by the priors (uniform [0,5]) that had been set for between-study heterogeneity in the NMAs, which is highlighted as an important issue in points 5 and 6 of a technical support document written by the NICE Decision Support Unit (DSU).[41] In effect, the prior distribution is dictating the uncertainty in the NMAs as there are insufficient data in the analyses to appropriately inform the between-study heterogeneity. The EAG therefore considers that there is not enough data to support the use of RE analysis in the 3+ TF analyses, which is not surprising given in most cases there was only one study per treatment comparison with some having only small subgroups of the original trial included. The EAG also notes that credible intervals (CrIs) for one outcome when RE analyses are used within the EM 3+ TF population are extremely wide (see Section 3.3.1), and while less extreme for other outcomes, CrIs indicate substantial uncertainty for all three MMD-related outcomes in EM within the 3+ TF population, making conclusions difficult. As noted above, the EAG does not have a preference for EM analyses to be conducted within the 3+ TF population.

Within the overall migraine population analyses, RE and FE analyses with adjustment for baseline risk, accounting for differences in placebo responses between studies (discussed as an issue associated with NMAs in this STA in Section 3.4.4.3), were also performed by the company for some outcomes, including MMD-related outcomes and all-cause discontinuation. The company does not favour any of the baseline-adjusted NMA results in the base case of the economic model for either EM or CM populations, stating that, "regression coefficients were not significant and model fit statistics for these models did not show meaningful improvements over unadjusted models". For

MMD-related outcomes in EM, the EAG notes that adjusted versions did not converge in the 3+ TF subgroup, which is the population that the company favoured in its base case for these analyses. While the EAG acknowledges that there may be limited difference between adjusted and unadjusted RE analyses in terms of model fit, it notes that this is not the case for every outcome within EM and CM populations and the EAG has based its decisions about which analysis is most appropriate on model fit as well as other factors such as impact on between-study standard deviation (heterogeneity; see Key Issue 3 in Table 4). The EAG's preferred analyses for each outcome are discussed in the sections that follow.

For discontinuation and TEAE outcomes, NMAs were analysed using both logit and cloglog models. The company has a preference for cloglog models, outlining the potential for the event rates for these types of outcomes to differ with differing study durations, which is an issue for studies included in these NMAs. The EAG considers that cloglog models are a reasonable option for these outcomes based on a guidance document produced by the NICE Guidelines Decision Support Unit.[42] However, the EAG also notes that there is very little difference between logit and cloglog models on the NMA results in most cases, other than TEAEs in CM where differences are more notable but not hugely different (Table 27 of the CS).

The EAG is satisfied that appropriate methods and code have been used for the NMAs included in this STA. While the EAG had issues validating some of the data going into NMAs, the EAG considers that this is because not all of the supplementary papers used to obtain data for secondary outcomes or within certain subgroups have been provided or clearly referenced, making it difficult to locate the data used in the NMAs. The EAG notes that this was primarily an issue for HRQoL outcomes (results of NMAs not used in the economic model), and the EAG was able to validate all of the data for efficacy, TEAE and discontinuation outcomes. On validating the NMAs, the EAG made minor changes to the data analysed where slight errors in input data were identified relative to the publications and more substantial additions were also made by the EAG, for example to include rimegepant and eptinezumab studies given these may be appropriate comparators for this appraisal, as discussed in Section 2.3.3. Any amendments to data analysed for each outcome are discussed in Appendix 8.2.

3.4.2 Included studies

Studies included in the NMAs were RCTs, including phase 2 and phase 3 RCTs. The company performed a quality assessment of all comparator studies, including those for rimegepant and

eptinezumab, which is presented in Tables 33 and 34 of the CS appendices. This assessment was performed for all studies deemed relevant to the SLR, before the final set of studies relevant to this appraisal were selected (see Section 3.1), meaning many more studies are included in these appendix tables. The EAG has presented those relevant to the NMAs in Appendix 8.3. The assessments for all but one study (EVOLVE-1 in EM) suggest that there is low risk of bias for all studies across EM and CM. EVOLVE-1 is stated by the company not to have used appropriate methods for missing data but no further information is provided. The EAG could not identify why this was the case for EVOLVE-1 on review of the primary publication and statistical analysis plan, as there did not appear to be anything different about the methods discussed here compared to other studies.[43]

The EAG has no major concerns about differences in terms of risk of bias that could have an impact on the conclusions of the NMAs, other than differences in analysis methods for missing data already described in Section 3.4.4.2; studies were similar in terms of trial design and all were double-blind, but the EAG notes that the potential for unmasking in trials of BoNT/A due to changes in muscle tone has been previously raised.

When additional rimegepant and eptinezumab studies were included by the EAG, a total of 18 studies in EM and 12 studies in CM were included, although data was not available for all outcomes from each study. Included studies are outlined in Table 19 below. The company further discusses studies included in the NMAs (with the exception of rimegepant and eptinezumab studies) in Section B.2.9.2 and B.2.9.4 of the CS, as well as Section D.2.3 of the CS appendices.

The EAG considers that the doses used in the included comparator studies are in line with those recommended as part of NICE guidance for each treatment.

Table 19. Included studies for EM and CM overall migraine population analyses

Included studies – EM	Relevant treatments
ELEVATE[28]	Atogepant 60 mg
ADVANCE[26]	Atogepant 60 mg
CGP-MD-01[27]	Atogepant 60 mg
LIBERTY[20]	Erenumab 140 mg
STRIVE[44]	Erenumab 140 mg
Sakai 2019[45]	Erenumab 140 mg
EMPOwER[46]	Erenumab 140 mg
CONQUER[19]	Galcanezumab 120 mg

EVOLVE-1[43]	Galcanezumab 120 mg
EVOLVE-2[47]	Galcanezumab 120 mg
Sakai 2020[48]	Galcanezumab 120 mg
PERSIST[49]	Galcanezumab 120 mg
FOCUS[18]	Fremanezumab 225 and 675 mg
HALO EM[50]	Fremanezumab 225 and 675 mg
Sakai 2021[51]	Fremanezumab 225 and 675 mg
Bigal 2015[52]	Fremanezumab 225 mg
BHV3000-305[17]	Rimegepant 75 mg
PROMISE-1[53]	Eptinezumab 100 and 300 mg
Included studies – CM	**Relevant treatments**
PROGRESS[25]	Atogepant 60 mg
Tepper 2017[32]	Erenumab 140 mg
CONQUER[19]	Galcanezumab 120 mg
REGAIN[31]	Galcanezumab 120 mg
FOCUS[18]	Fremanezumab 225 and 675 mg
HALO CM[54]	Fremanezumab 225 and 675 mg
Sakai 2021[55]	Fremanezumab 225 and 675 mg
Bigal 2015[56]	Fremanezumab 225 mg
PREEMPT-1[33]	Botulinum toxin type A
PREEMPT-2[34]	Botulinum toxin type A
PROMISE-2[57]	Eptinezumab 100 and 300 mg
Dodick 2019[58]	Eptinezumab 100 and 300 mg

Abbreviations: EM, episodic migraine; CM, chronic migraine.

3.4.3 Results

3.4.3.1 MMD-based outcomes

For these outcomes, the company preferred RE unadjusted analyses in the 3+ TF population for EM and RE unadjusted analyses in the overall migraine population for CM for reasons outlined in Section 3.4.1. All of these NMA results were used to inform the economic model (note that 50% MMD reduction for CM was used in a scenario analysis in the economic model instead of the 30% MMD reduction threshold). As described in Section 3.4.1, the EAG's preferred analyses are within the overall migraine population for EM as well as CM, and the EAG has additional concerns about using RE analyses in the 3+ TF population for EM (which is the company's preference), given there appears to be insufficient data in the analyses to appropriately inform the between-study heterogeneity and

may be introducing additional and unwarranted uncertainty in the results, which is particularly notable for the ≥50% MMD reduction outcome for EM in Table 20 below with extremely wide and difficult to interpret CrIs (the most extreme CrI ranges from [redacted]; see Key Issue 2 in Table 3).

In general, within the overall migraine population analyses, the EAG has a preference for RE analyses given these are a better fit than FE models and there is reason to believe clinical and methodological heterogeneity exists across the included studies (see Section 3.4.4). Furthermore, while model fits for RE unadjusted and adjusted analyses are similar, in most cases the adjusted analyses reduced between-study heterogeneity; where this was true or where there was very little difference in between-study heterogeneity and other model fit statistics, the EAG prefers RE adjusted analyses (see Key Issue 3 in Table 4). Exceptions to this are as follows:

- 30% MMD reduction in CM – FE unadjusted preferred as there appear to be issues with between-study heterogeneity being driven by priors which would make an RE analysis inappropriate (as noted earlier for 3+ TF analyses in EM), and the FE adjusted analysis did not converge;
- CFB in MUDs in CM – RE unadjusted preferred as model fit statistics are similar for unadjusted and adjusted versions, and the adjusted version appears to increase between-study heterogeneity.

Company- and EAG-preferred analyses for EM and CM populations are presented in Table 20 and Table 21, respectively. The EAG's analyses include rimegepant and eptinezumab data where available (note that data were not reported for some outcomes and that rimegepant is only relevant to the EM population).

Feedback from the EAG's clinical experts was that it is difficult to assess whether differences in mean CFB for MMDs and acute MUDs between treatments are clinically meaningful, given each patient will be different and may consider different levels of MMD (or acute MUDs) reduction beneficial or not. They note that the proportion of patients with ≥50% (EM) or ≥30% (CM) reduction in MMDs are most informative in terms of assessing differences in the efficacy of treatments, as these are the thresholds used in clinical practice to determine response.

Episodic migraine

For EM, the company's preferred analyses are associated with increased uncertainty compared to the EAG's preferred analyses, as expected given fewer studies with data within the 3+ TF population are available and smaller sample sizes analysed within each of the studies that do report data. The company's preferred results may be conservative for comparisons against the two fremanezumab doses relative to the estimates from the EAG's preferred analyses, but the opposite appears to be true for erenumab and galcanezumab comparisons as [redacted] are not as large based on point estimates in the EAG's preferred NMAs. All of the company's preferred NMAs are associated with uncertainty in terms of direction of effect (no statistically significant differences), with wide CrIs making it unclear whether outcomes are better or worse with atogepant, as well as uncertainty about the size of any impact.

While results from most of the EAG's preferred NMAs also suggest no statistically significant differences, the EAG notes that uncertainty is reduced and erenumab can be included for the CFB in acute MUDs outcome when the overall migraine population analysis is used. As data for erenumab are not available within the 3+ TF population for CFB in acute MUDs, the company used a conversion factor (see response to CQ B5) to obtain an estimate for this comparator that could be used in the economic model (atogepant vs erenumab: median CFB [redacted]. This is conservative relative to the estimate the EAG obtained from its preferred NMAs and used in its base case (see Section 6).

The EAG considers that the point estimates obtained from its preferred NMAs (RE adjusted) indicate only [redacted] in terms of CFB in MMDs ([redacted] for all comparisons), suggested [redacted] vs all comparators in terms of proportion with ≥50% reduction in MMDs and [redacted] for the CFB in acute MUDs outcome, with the exception of comparisons against erenumab and the two eptinezumab doses, where [redacted] are indicated. While the company's preferred NMAs also indicate fairly [redacted] between treatments in terms of CFB in MMD and acute MUDs outcomes, these differences are [redacted] in the EAG's preferred analyses and results for the two fremanezumab doses are quite different compared to the EAG's preferred analyses (more conservative in the company's preferred analyses). The EAG considers its preferred NMAs to be more robust and, therefore, more appropriate for use in the economic model. While the EAG was able to rerun NMAs with rimegepant and eptinezumab studies included, data for rimegepant were not available for the CFB in acute MUDs outcome. To allow inclusion in the economic model, the EAG made the assumption that rimegepant efficacy with regards to this

outcome is the same as atogepant (see Section 4.2.6.4). Unadjusted FE versions of the company's preferred analyses (within the 3+ TF population for EM) can be found in Table 26 of the CS appendices; results are very similar to unadjusted RE analyses but with CrIs that are narrower. Unadjusted RE versions of the EAG's preferred analyses are presented in Appendix 8.2.1; these results are similar to the adjusted RE results in that differences are [redacted], but point estimates for the ≥50% reduction in MMDs outcome do not always [redacted] in these analyses and there are no [redacted] for any comparators for the CFB in acute MUDs outcome.

Table 20. Relative effect of atogepant 60 mg once daily vs comparators in EM for MMD outcomes – EAG- and company-preferred analyses

Atogepant 60 mg once daily vs	Company-preferred NMA*	EAG-preferred NMA†
CFB in MMD, MD (95% CrI)		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
Rimegepant 75 mg every other day	-	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]
≥50% reduction in MMDs, OR (95% CrI)		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
Rimegepant 75 mg every other day	-	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]
CFB in acute MUDs, MD (95% CrI)		
Erenumab 140 mg once monthly	-‡	[redacted]

Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
Rimegepant 75 mg every other day	-	-[§]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]

*Company preferred NMAs for all MMD-related outcomes in EM are from the NMAs performed specifically using 3+ TF data in this population. RE unadjusted analyses are preferred for all outcomes; [†]EAG-preferred NMAs for all MMD-related outcomes in EM are from the NMAs performed in the overall migraine population. For all three outcomes, the EAG prefers results from RE adjusted analyses. The EAG reran NMAs to include data for rimegepant and eptinezumab given, as described in Section 2.3.3, they may be considered important comparators; [‡]no data for erenumab 140 mg were available to include within the NMA for the CFB in acute MUDs outcome within the 3+ TF population. The company used a conversion factor (see CQ B5) to obtain data for erenumab to use in the economic model (median CFB [redacted] for atogepant vs erenumab; see Table 46 of the CS); [§]rimegepant could not be included in the NMA for CFB in acute MUDs when rerun by the EAG given this outcome was not reported for the only available rimegepant study.

Outputs from the NMAs are means for the CFB outcomes and median OR for the proportion with ≥50% reduction in MMD from baseline. Bold values indicate statistically significant differences.

Abbreviations: 3+ TF, patients in whom ≥3 prior oral preventive treatments have failed; CFB, change from baseline; CrI, credible interval; CQ, clarification question; CS, company submission; EAG, External Assessment Group; EM, episodic migraine; MD, mean difference; MMD, monthly migraine days; MUDs, medication use days; NMA, network meta-analysis; OR, odds ratio; RE, random effects;

Chronic migraine

For CM, the EAG's preferred NMAs are also associated with less uncertainty compared to the company's preferred analyses. While the company's preferred analyses may be slightly conservative for CFB in MMDs and ≥50% reduction in MMDs for comparisons vs mAbs, this is not the case for the comparison against BoNT/A. For ≥30% reduction in MMDs and CFB in acute MUDs outcomes, the point estimates of the company's preferred analyses are more favourable for atogepant compared to the results from EAG-preferred analyses (other than vs galcanezumab). The EAG and company both have a preference for the RE unadjusted analysis for the CFB in acute MUDs outcome, which explains the similarity of these results. Slight differences may be due to minor errors corrected by the EAG before NMAs were run (see Section 8.2.2). There were no statistically significant differences vs any of the comparators in the company's preferred analyses, but some were identified for the [redacted] outcome in the EAG's preferred analyses.

Based on the EAG's preferred analyses, the EAG considers that point estimates suggest fairly [redacted] between atogepant and comparators in terms of CFB in MMDs and CFB in

acute MUDs, with point estimates either favouring atogepant or there being a difference of [redacted] in the opposite direction. While comparisons against the two fremanezumab doses indicate [redacted] for the ≥30% reduction in MMDs outcome, the EAG considers this analysis to be limited given the fact that a FE unadjusted analysis had to be used due to insufficient data to inform between-study heterogeneity for this outcome and the adjusted analyses did not converge. The EAG notes that results for the ≥50% MMD reduction threshold are similar in that point estimates suggest the fremanezumab doses may [redacted] than atogepant, but the extent of the difference is reduced and differences [redacted]; an RE analysis with adjustment for baseline risk was able to be performed for this outcome, which the EAG considers to be more robust than the unadjusted FE analysis performed for the ≥30% threshold. Based on point estimates, results for the ≥50% reduction in MMD outcome suggest that atogepant is [redacted] achieving this outcome vs all comparators other than galcanezumab, although there remains uncertainty based on CrIs.

To be included in the economic model, the company used a conversion factor to calculate estimates of the odds ratios (ORs) for erenumab 140 mg and BoNT/A that may be observed had data for the ≥30% MMD reduction outcome been available for inclusion in the NMAs. The EAG considers the methodology used for this, as described in response to CQ B5, to be reasonable in terms of obtaining point estimates given that there are no data for these comparators, but notes that it is an assumption that should be considered to be associated with substantial uncertainty, given it uses an average of the ratios observed for comparators with available data and it is not possible to determine if this is robust across all comparators. The conversion factor calculated based on point estimates was also applied to the CrIs from the company's ≥50% MMD reduction analysis to calculate 95% CrIs for the comparators with missing data for the ≥30% MMD reduction outcome. This results in the 95% CrIs for erenumab and BoNT/A being much narrower compared to the three comparators that had data and were included in the ≥30% MMD reduction NMA (for example, the 95% CrI estimated for erenumab is [redacted], whereas that obtained from the NMA for fremanezumab 225 mg is [redacted]). The EAG considers that obtaining separate conversion factors for point estimates and the upper and lower values of the CrI would lead to CrIs for erenumab and BoNT/A that are more similar to those obtained from the company's preferred NMA for ≥30% MMD reduction for comparators with available data.

While the EAG was able to rerun NMAs with eptinezumab studies included, data for eptinezumab were not available for the ≥30% reduction in MMDs outcome. The EAG recalculated the conversion factors described above using its preferred analyses for the ≥30% (FE unadjusted) and ≥50% (RE adjusted) NMAs to calculate ORs to be used for erenumab 140 mg and BoNT/A, and also did the same to allow inclusion of eptinezumab for the ≥30% threshold. The EAG used the same method as the company by applying the same conversion factors to the CrIs for each comparator, but notes that when separate conversion factors were calculated for the EAG's preferred analyses, estimated CrIs were either unchanged or differed by only 0.01. Estimated ORs and CrIs used by the company and the EAG for comparators with missing ≥30% MMD reduction data in CM are presented in Table 22 below. The EAG acknowledges the uncertainty associated with these ORs and CrIs but notes that options are limited given the lack of data for these comparators.

Unadjusted RE versions of the EAG's preferred analyses for CFB in MMDs and ≥50% reduction in MMDs are presented in Appendix 8.2.2; these results are very similar to company's preferred results in Table 21 below given the company preferred unadjusted RE analyses, with minor differences likely due to minor corrections made by the EAG to the data analysed or random sampling.

While not presented as part of this STA, the company provided results from 3+ TF population NMAs within CM as part of the CCE process for atogepant earlier in 2023. The EAG does not have a preference for these results and has not presented them here given limitations raised by the company (which the EAG agrees with) but notes that the point estimates obtained from these analyses were generally [redacted] for atogepant compared to both the EAG- and company-preferred NMAs presented in Table 21 below, albeit with [redacted] based on CrIs, potentially associated with more bias and based on more scarce data. Differences between the analyses in terms of CFB in MMDs [redacted] exist for the ≥30 and ≥50% MMD reduction outcomes.

Table 21. Relative effect of atogepant 60 mg once daily vs comparators in CM for MMD outcomes – EAG- and company-preferred analyses

Atogepant 60 mg once daily vs	Company-preferred NMA*	EAG-preferred NMA†
CFB in MMD, MD (95% CrI)		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]

Galcanezumab 120 mg once monthly	[redacted]	[redacted]
BoNT/A	[redacted]	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]
≥30% reduction in MMDs, OR (95% CrI)		
Erenumab 140 mg once monthly‡	-	-
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
BoNT/A‡	-	-
Eptinezumab 100 mg once every three months‡	-	-
Eptinezumab 300 mg once every three months‡	-	-
≥50% reduction in MMDs, OR (95% CrI)		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
BoNT/A	[redacted]	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]
CFB in acute MUDs, MD (95% CrI)		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
BoNT/A	[redacted]	[redacted]

Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]

*Company preferred NMAs for all MMD-related outcomes in CM are from the NMAs performed in the overall migraine population. RE unadjusted analyses are preferred for all outcomes; †EAG-preferred NMAs for all MMD-related outcomes in EM are from the NMAs performed in the overall migraine population. The EAG's preference is RE adjusted analyses for CFB in MMDs and ≥50% reduction in MMDs, FE unadjusted for ≥30% reduction in MMDs and RE unadjusted for CFB in acute MUDs. The EAG reran NMAs to include data for eptinezumab given, as described in Section 2.3.3, it may be considered an important comparator in CM; ‡no data for erenumab 140 mg, BoNT/A or 100 mg or 300 mg doses of eptinezumab were available to include within the NMA for the ≥30% MMD reduction outcome within the overall migraine population in CM.

Outputs from the NMAs are means for the CFB outcome and median OR for the proportion with ≥50% reduction in MMD from baseline. Bold values indicate statistically significant differences.

Abbreviations: BoNT/A, botulinum toxin type A; CFB, change from baseline; CM, chronic migraine; CrI, credible interval; EAG, External Assessment Group; FE, fixed effects; MD, mean difference; MMD, monthly migraine days; MUDs, medication use days; NMA, network meta-analysis; OR, odds ratio; RE, random effects.

Table 22. Relative effect of atogepant 60 mg once daily vs comparators in CM for ≥30% MMD reduction – ORs estimated for comparators with no data for this threshold

Atogepant 60 mg once daily vs	Company estimation*	EAG estimation†
≥30% reduction in MMDs, OR (95% CrI)		
Erenumab 140 mg once monthly	[redacted]	[redacted]
BoNT/A	[redacted]	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]

*Based on the company's preference for RE unadjusted analyses for ≥30% and ≥50% MMD reduction outcomes (inverted versions of values in Table 42 of the CS and Table 119 of the CS appendices); †based on the EAG's preference for an FE unadjusted analysis for ≥30% MMD reduction and an RE adjusted analysis for ≥50% MMD reduction.

ORs for atogepant 60 mg vs placebo for ≥30% and ≥50% MMD reduction outcomes were also used in the calculations and were as follows for company- and EAG-preferred analyses: company, [redacted] for ≥30% and [redacted] for ≥50%; EAG, [redacted] for ≥30% and [redacted] for ≥50%. The company obtained a conversion factor of 1.24 which was applied to the ≥50% ORs for the comparators (ORs divided by 1.24) with missing ≥30% data. The equivalent conversion factor obtained by the EAG using its preferred analyses was 1.82. To calculate 95% CrIs, the company applied the same conversion factor (1.24); the EAG did the same using the conversion factor it calculated.

Abbreviations: BoNT/A, botulinum toxin type A; CM, chronic migraine; CrI, credible interval; CS, company submission; EAG, External Assessment Group; FE, fixed effects; MMD, monthly migraine days; OR, odds ratio; RE, random effects.

3.4.3.2 All-cause discontinuation

As noted above in Section 3.4.3.1, within the overall migraine population analyses, the EAG has a preference for RE analyses given these are on the whole a better fit than FE models and there is

reason to believe clinical and methodological heterogeneity exists across the included studies (see Section 3.4.4).

For discontinuation, model fits for RE unadjusted and adjusted analyses were similar but the adjusted analysis in EM led to reduced between-study heterogeneity, resulting in the EAG preferring this analysis (see Key Issue 3 in Table 4). For CM, model fit statistics regardless of adjustment but the adjusted version appears to increase between-study heterogeneity; therefore, the EAG's preference is for the unadjusted RE analysis in this population. The company's preference is for RE unadjusted analyses in both cases. As noted in Section 3.4.1, the company's preference is for cloglog models, which the EAG considers to be reasonable. Cloglog models were, therefore, used by the EAG when running analyses to include additional comparators. Results of the company's and EAG's preferred analyses of discontinuation are presented below in Table 23.

While the EAG and company preferred the RE unadjusted analyses for all-cause discontinuation in CM, the EAG notes that there are some apparent differences in the values estimated between the two analyses (largest for erenumab, but also notable for galcanezumab). The EAG did not make any changes to the data analysed by the company for this outcome and notes that results for erenumab and galcanezumab are more in line with those obtained in the EAG's analysis when it reran the analysis using the company's data spreadsheet. The EAG, therefore, considers that these may be errors in reporting in Table 27 of the CS for this analysis.

For EM, the EAG's preferred NMA results lead to point estimates suggesting slightly [redacted] discontinuation for atogepant compared to the four mAbs in the company's preferred NMAs. Results suggest similar for the comparisons against eptinezumab 100 mg and 300 mg, while discontinuation may be [redacted] for atogepant compared to rimegepant. For CM, the EAG and company's preferred analysis was the same and results almost identical; point estimates suggest that discontinuation may be [redacted] for atogepant compared to some comparators (erenumab, fremanezumab 675 mg and galcanezumab) but [redacted] compared with the remaining treatments. Across EM and CM, some of the differences between treatments are [redacted], with hazard ratios (HRs) only [redacted]. Furthermore, the EAG notes that there is uncertainty in all estimates, given CrIs cross 1.00 and are fairly wide in either direction. As noted earlier, HRs were used to inform discontinuation up to 12 weeks in the economic model (see Section 4.2.6.1).

Alternative RE analyses performed by the EAG for discontinuation in the two populations are presented in Appendix 8.2.3. The RE unadjusted analysis for EM aligns well with the company's results in Table 23 below (as expected given it is the same analysis) and there are no large differences in results for the adjusted RE analysis in CM compared with the EAG- and company-preferred RE unadjusted analysis in Table 23 below.

Table 23. Relative effect of atogepant 60 mg once daily vs comparators in EM and CM for discontinuation (cloglog analyses) – EAG- and company-preferred analyses

Atogepant 60 mg once daily vs	Company-preferred NMA*	EAG-preferred NMA†
EM, HR (95% CrIs)		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
Rimegepant 75 mg every other day	-	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]
CM, HR (95% CrIs)		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
BoNT/A	[redacted]	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]

*The company's preferred NMAs for discontinuation in EM and CM are the RE unadjusted analyses within the overall migraine population; †the EAG's preferred NMA for discontinuation in EM is the RE adjusted analysis, while for CM it is the RE unadjusted analysis (as per the company's preference). The EAG reran NMAs to include data for rimegepant and eptinezumab given, as described in Section 2.3.3, they may be considered important comparators; ‡when the EAG reran the company's analysis using the exact same spreadsheet, it obtained an estimate that was more in line with the EAG's estimate ([redacted]); §when the EAG reran the company' s analysis using the exact same spreadsheet, it obtained an estimate that was more in line with the EAG's estimate ([redacted]).

Outputs from the NMAs are median HR for the company analyses; the EAG was only able to obtain mean HRs for comparisons between atogepant and other treatments, but was able to verify that means and medians are likely to be

similar given mean and median HRs for all treatments vs placebo could be obtained and were similar. Bold values indicate statistically significant differences.

Abbreviations: BoNT/A, botulinum toxin type A; CM, chronic migraine; CrI, credible interval; EAG, External Assessment Group; EM, episodic migraine; HR, hazard ratio; NMA, network meta-analysis; RE, random effects.

3.4.3.3 Health-related quality of life outcomes

The company performed NMAs for a number of HRQoL outcomes, including three subdomains of the MSQ v2.1 questionnaire and HIT-6. The results of these NMAs did not inform the economic model and the EAG discusses them only briefly here. The EAG reran the NMAs to validate the results and included eptinezumab and rimegepant studies where possible; however, HRQoL outcomes were poorly reported for these two comparators. The EAG did not identify any corrections required to data included in the HRQoL analyses performed by the company, but was not able to validate all of the data analysed given supplementary papers were not provided.

As noted above in Section 3.4.3.1, within the overall migraine population analyses, the EAG has a preference for RE analyses given these are on the whole a better fit than FE models and there is reason to believe clinical and methodological heterogeneity exists across the included studies (see Section 3.4.3.3). Adjusted analyses were not performed by the company for HRQoL outcomes so the results presented below in Table 24 are from unadjusted RE analyses.

The results of the analyses rerun by the EAG (presented in Table 24 below) are in line with those presented by the company on the whole; however, there are some slight discrepancies for certain outcomes and comparators. The EAG considers that these could be due to a mixture of random sampling variation and the EAG needing to run certain NMAs using contrast rather than arm-based data to allow the inclusion of eptinezumab or rimegepant studies. The EAG does not consider that any of these differences would change conclusions. See Table 26 of the CS (and Appendix O of the CS for BoNT/A) for comparison to the company-reported results for HRQoL outcomes.

Higher MSQ v2.1 scores indicate better outcome, while the opposite is true for HIT-6. For EM, point estimates suggest [redacted] outcome for atogepant or very small differences across the HRQoL scores compared to all comparators where data was available, some of which are statistically significant differences. Some of these differences are larger than the thresholds referenced by the company and described in Section 3.3.3 as indicative of clinically important differences. The EAG notes that data were only available for one outcome for rimegepant and no HRQoL outcome data were

available for eptinezumab in EM, and fewer comparators were available for the HIT-6 outcome. For CM, differences appear to be smaller between atogepant and comparators, with some point estimates in favour of comparator treatments rather than atogepant. Only one of these point estimates appears to be above the thresholds cited by the company as being indicative of clinically important differences.

The EAG concludes that, point estimates suggest that there could be benefits of atogepant vs comparators in terms of HRQoL outcomes in EM and that results are more mixed in CM, with differences in either direction here unlikely to be clinically meaningful based on thresholds cited by the company. However, the EAG notes that uncertainty in these conclusions remains based on CrIs as well as the fact that these NMAs were not adjusted for placebo differences unlike other outcomes discussed in Section 3.4.3.1 and 3.4.3.2.

Table 24. Relative effect of atogepant 60 mg once daily vs comparators in EM and CM for HRQoL outcomes – RE unadjusted analyses, EAG results

Atogepant 60 mg once daily vs	EM, MD (95% CrI)	CM, MD (95% CrI)
CFB in MSQ-RFR		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
BoNT/A	N/A	[redacted]
Rimegepant 75 mg every other day	[redacted]	N/A
Eptinezumab 100 mg once every three months*	-	-
Eptinezumab 300 mg once every three months*	-	-
CFB in MSQ-RFP		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
BoNT/A	N/A	[redacted]

Rimegepant 75 mg every other day†	-	N/A
Eptinezumab 100 mg once every three months*	-	-
Eptinezumab 300 mg once every three months*	-	-
CFB in MSQ-EF		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
BoNT/A	N/A	[redacted]
Rimegepant 75 mg every other day†	-	N/A
Eptinezumab 100 mg once every three months*	-	-
Eptinezumab 300 mg once every three months*	-	-
CFB in HIT-6		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly‡	-	-
BoNT/A	N/A	[redacted]
Rimegepant 75 mg every other day†	-	N/A
Eptinezumab 100 mg once every three months§	-	[redacted]
Eptinezumab 300 mg once every three months§	-	[redacted]

*No data was available for eptinezumab in terms of MSQ v2.1outcomes in EM or CM; †no data was available for rimegepant in terms of the MQS-EF, MSQ-RFP or HIT-6 questionnaires in EM; ‡no data was available for galcanezumab in terms of the HIT-6 questionnaire in either EM or CM; §no data was available for eptinezumab in terms of the HIT-6 questionnaire in EM.

Outputs from the NMAs are mean CFB values as run by the EAG. Bold values indicate statistically significant differences.

Abbreviations: BoNT/A, botulinum toxin type A; CFB, change from baseline; CM, chronic migraine; CrI, credible interval; EAG, External Assessment Group; EM, episodic migraine; HIT-6, Headache Impact Test-6; HRQoL, health-related quality of life; MD, mean difference; MSQ, migraine-specific quality of life questionnaire; MSQ-EF, emotional function subdomain of MSQ; MSQ-RFP, role function-preventive subdomain of MSQ; MSQ-RFR, role function-restrictive subdomain of MSQ; N/A, not applicable; NMA, network meta-analysis; RE, random effects.

3.4.3.4 Adverse events

The company also performed NMAs to analyse TEAEs across treatments within the overall migraine population. Given that no AEs were included in the economic model, the EAG does not discuss these in detail here. The EAG reran the NMAs to validate the results and included eptinezumab and rimegepant studies. The EAG did not identify any corrections required to data included in the TEAE analyses performed by the company. The results of the analyses rerun by the EAG are in line with those presented by the company on the whole, but the HR for erenumab in EM is higher in the results presented in the CS compared to when rerun by the EAG. The EAG is unsure whether this is variation due to sampling or whether there was a reporting error in Table 27 of the CS for erenumab.

As noted above in Section 3.4.3.1, within the overall migraine population analyses, the EAG has a preference for RE analyses given these are on the whole a better fit than FE models and there is reason to believe clinical and methodological heterogeneity exists across the included studies (see Section 3.4.3.3). Adjusted analyses were not performed by the company for TEAEs so the results presented below in Table 25 are from unadjusted RE analyses. As discussed for discontinuation (Section 3.4.3.2), cloglog analyses were preferred by the company for TEAEs.

The results based on point estimates for EM suggest that there may be slightly [redacted] rates of TEAEs for atogepant compared to fremanezumab 675 mg, galcanezumab 120 mg and eptinezumab 100 mg, with the opposite observed vs other comparators. For CM, the results suggest slightly [redacted] rates of TEAEs for atogepant compared to all comparators. However, the EAG acknowledges the uncertainty based on CrIs for all but one of the outcomes below. Given that, as discussed in Section 3.3.4, most AEs for atogepant were symptoms such as [redacted], the EAG is not concerned about the omission of AEs from the economic model.

Table 25. Relative effect of atogepant 60 mg once daily vs comparators in EM and CM for TEAEs (cloglog analyses) – RE unadjusted analyses, company and EAG results

Atogepant 60 mg once daily vs	Company results	EAG results
EM, HR (95% CrIs)		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]

Galcanezumab 120 mg once monthly	[redacted]	[redacted]
Rimegepant 75 mg every other day	-	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]
CM, HR (95% CrIs)		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
BoNT/A	[redacted]	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]

Outputs from the NMAs are median HR for the company analyses; the EAG was only able to obtain mean HRs for comparisons between atogepant and other treatments, but was able to verify that means and medians are likely to be similar given mean and median HRs for all treatments vs placebo could be obtained and were similar. Bold values indicate statistically significant differences.

Abbreviations: BoNT/A, botulinum toxin type A; CM, chronic migraine; CrI, credible interval; EAG, External Assessment Group; EM, episodic migraine; HR, hazard ratio; RE, random effects; TEAEs, treatment-emergent adverse events.

3.4.4 Critique of the indirect treatment comparison

In section B.2.9.4 of the CS, the company highlight various differences between trials included in the NMA. These are discussed in the subsections that follow, as well as any additional issues identified by the EAG. While the EAG notes that many of the issues described below lead to uncertainty in the NMAs, the same issues have been raised in other NICE appraisals in migraine, most recently for rimegepant (TA906),[2] where many of the same studies were included in overall migraine population analyses. These issues are one reason for the EAG's preference for RE analyses where possible, to capture this increased uncertainty. These concerns are collectively captured in Key Issue 4 (Table 5) as uncertainty within the NMAs that may not be fully captured by analysis methods used (such as using RE analyses with or without adjustment for baseline risk) but that are considered to unresolvable limitations based on data available from comparator studies.

3.4.4.1 *Differences in study populations included and concomitant treatments*

Studies included in the NMAs differed in terms of the number of prior treatment failures. Some studies only focused on patients with two to four prior treatment failures (ELEVATE, FOCUS, CONQUER, LIBERTY),[18-20, 28] while others included any patient regardless of prior treatment failure. The EAG notes that some studies (including the PROGRESS and ELEVATE trials for atogepant) excluded patients with a certain number of treatment failures (e.g. four or more failures in the PROGRESS and ELEVATE trials, as well as FOCUS, CONQUER and LIBERTY trials,[18-20, 25, 28] or more than two failures in other studies such as HALO-EM and the only available trial for rimegepant (BHV3000-305).[50] Given that clinical experts advising the EAG consider prior treatment failures to be a factor that could impact the efficacy of preventive treatments for migraine, this could be an important source of clinical heterogeneity between trials, particularly within the overall migraine population analyses. The impact of prior treatment failures on safety outcomes may be less important based on feedback from the EAG's clinical experts discussed in Section 3.4.1.

Most studies included in the NMAs did not stratify randomisation by number of prior treatments and there is potential for imbalance in patient characteristics between trial arms; this was not an issue for ELEVATE as this trial was stratified for this factor, but [redacted] in PROGRESS and it is unclear for comparator trials given characteristics for this subgroup are not well reported.

For EM overall migraine analyses preferred by the EAG, some variation in mean age across studies was identified but the EAG considers the range of means between ~37 and ~46 years may not have a large impact on results (Figures 29 and 30 of the CS appendices). Distribution of sex across studies was largely consistent (Figures 31 and 32 of the CS appendices) but there were some substantial differences in terms of race, which is the result of some studies focusing solely on Asian population (Figures 33 and 34 of the CS appendices); the EAG is not too concerned about differences in race distribution across studies as feedback from the EAG's clinical experts was that there is no reason to expect the efficacy of drugs to differ in Asian vs non-Asian populations. There was variation for baseline MMDs across EM studies, ranging from a mean of ~7.5 days to ~11.5 days (Figures 35 and 36 of the CS appendices); while it is possible that baseline MMDs could impact the ability of individuals to achieve a ≥50% reduction in MMDs, the EAG is unsure as to the impact on relative efficacy outcomes given randomisation should ensure baseline MMDs are similar within each trial

for intervention and placebo groups. The EAG notes that the only available study for rimegepant also included a proportion of patients with CM (23%) rather than EM.[17]

Similar variation was observed for trials within the overall migraine population analyses for CM (Figures 45 to 52 of the CS appendices), with mean baseline MMD values ranging from ~15.5 to 19.5 days in this population. The EAG also reviewed rimegepant and eptinezumab studies that were added to the NMAs and values for these studies fell within the ranges already highlighted in the CS appendix figures, apart from mean age in Dodick 2019 which was slightly lower than the other studies originally included in the NMAs for CM (~37 years vs ~40-46 years).[17, 53, 57, 58]

The use of concomitant preventive therapies during the trial also differed; some studies excluded their use while others did not. Those allowing its use for EM included two of the mAb studies identified and the rimegepant study and eptinezumab studies in this population; the remaining mAb studies and all of the atogepant studies did not allow concomitant use of preventive migraine treatments. For CM, the PROGRESS trial for atogepant, three mAb studies and the two eptinezumab studies allowed the use of concomitant preventive migraine treatments (none of the BoNT/A studies allowed these to be used). The EAG considers this to be an area that may introduce uncertainty but the extent of any impact on results is unclear.

3.4.4.2 Differences in outcome definitions and time-points

Timepoints used for each study in the NMA varied, with this being reported at 12 weeks most commonly. For overall migraine population analyses in EM and CM, data for MMD-related and HRQoL outcomes were most commonly reported as an average across weeks 1-12 or values at 12 weeks for MMD-related and HRQoL outcomes but in some cases follow-up was up to 24/26 weeks or an average across weeks 9 to 12 was reported (Table 15 of the CS appendices and Appendix 8.4.1 of this report).

For discontinuation and TEAE, follow-up at 12 or 24 weeks was mostly available for discontinuation but time-points ranged between 12 and 49 weeks for TEAEs. It is unclear how this may affect results but it is a limitation of the data available from comparator studies. While this may not be ideal, the EAG is not concerned this would have a large impact on results given that when requested as part of the CCE process, an exploratory NMA analysis including only studies with 12-week data demonstrated similar results.

The company reports variation in the definition of endpoints across trials included in the NMA, particularly for MMD-related outcomes. The EAG acknowledges these differences and consider them to be a limitation of the data available across trials. Most variation appeared to be with regards to the length of time required for a migraine day to be confirmed (e.g. ≥4 continuous hours, ≥2 continuous hours or ≥30 min) and symptoms or features of migraine required to be present were, overall, similar. The likely impact of these different definitions on results is unclear.

The EAG also notes that definitions within individual trials for all-cause discontinuation (e.g. study withdrawal vs treatment discontinuation) and TEAEs (any adverse event vs TEAEs specifically) may differ slightly between trials. The EAG considers this to be based on available data reported across studies and is not concerned that these would have a large impact on results but acknowledge that it is a potential source of methodological heterogeneity.

For the change from baseline outcomes (e.g. CFB in MMDs, acute MUDs and HRQoL outcomes) the EAG notes that in EM and CM, most studies used mean values obtained from least squares regression. However, this was not consistent across all studies and may be another potential source of methodological heterogeneity. Differences in the approach to missing data may also be an important factor to consider (for example, some have used imputation while others have only analysed available data), although the EAG notes that it is another unavoidable difference given different studies have opted for different methods and the company is limited to data that is publicly available for comparator studies. For ≥30% and ≥50% MMD reduction outcomes, the EAG notes that methods of analysis in terms of missing data also differed across studies, with some assuming that those discontinuing for any reason were non-responders and others not making this assumption, which could introduce uncertainty within these NMAs. The observed effectiveness of treatments in the trials assuming non-response on discontinuation may be reduced compared to trials using less conservative assumptions.

3.4.4.3 Placebo rate differences

The EAG agrees with the company that differences in placebo rates across included studies are an issue, particularly for MMD-related outcomes. The EAG's clinical experts confirmed that varying placebo efficacy across migraine trials is an issue and makes it difficult to compare two individual studies. The EAG acknowledges these differences as a potential source of uncertainty within the NMAs, but given its preference for most MMD-related outcomes in EM and CM is RE analyses adjusted for baseline (placebo) risk, it considers these analyses should reduce the impact of these

differences (see Section 3.4.3.1). The exceptions were for the ≥30% MMD reduction outcome in CM as adjusted versions of this NMA would not converge and CFB in MUD in CM, as adjustment for baseline risk actually increased heterogeneity within the network based on between-study standard deviation values. The EAG notes that adjusted versions of analyses for HRQoL outcomes or TEAEs were not performed. The EAG considers that outcomes such as discontinuation and TEAEs may be less impacted by differences in placebo rates given they are less subjective outcomes; adjusted versions were performed for discontinuation but not for TEAEs (Section 3.4.3.2 and 3.4.3.4).

3.4.5 EAG critique of rimegepant and eptinezumab evidence provided by the company

In response to CQ A1, the company puts forward additional rationale to support the exclusion of rimegepant and eptinezumab as comparators from this appraisal, as well as some comparative evidence for atogepant vs rimegepant and eptinezumab. This issue is covered in Key Issue 1 in Table 2.

The company reiterates its statements in the CS that market shares for rimegepant and eptinezumab are currently low and are expected to remain low ([redacted] for rimegepant and [redacted] for eptinezumab) among patients eligible for NICE-recommended fourth line preventive therapies in 2024 based on Clarivate™ forecast data, suggesting the situation will not have changed by the time the committee meeting for this appraisal has been held. Feedback from clinical experts that the company consulted also suggested challenges in the local implementation of each treatment, such as the need to set up services for in-clinic infusion of eptinezumab. The company's clinical experts also suggest it would be unlikely for an infusion-based treatment requiring in-clinic time to be prioritised by services over a home-administered treatment, meaning atogepant would likely be positioned ahead of eptinezumab. One of the EAG's clinical experts agreed with this as they noted that it may be considered too resource intensive to be routinely used in preference to other available treatments. However, regarding rimegepant, they noted that there is potential for its low usage to change in the near future and, should atogepant be recommended and oral options preferred for an individual patient, it is likely that clinicians would be making a decision between atogepant and rimegepant in EM. Therefore, it may be particularly important to compare atogepant and rimegepant in this appraisal, which the EAG has done as part of this report. Given that eptinezumab is recommended in the same population as outlined for atogepant in this appraisal, the EAG has also explored its inclusion as part of this report, but it acknowledges that it may be less important than the other comparators included based on the feedback received.

Nonetheless, the company has provided some evidence to support the idea that conclusions would not change if either of these treatments had been included in the submission. This includes a matching-adjusted indirect comparison (MAIC) between rimegepant and atogepant that was presented at a recent conference (American Headache Society 2023) and a naïve comparison of results from one atogepant trial in EM and CM to one eptinezumab trial in each population.

For the anchored MAIC involving rimegepant,[59] the EAG confirms that the results suggest that atogepant may be more effective in reducing migraine frequency (CFB in MMDs) and in improving HRQoL outcomes (MSQ-RFR) compared to rimegepant. It also notes that non-statistically significant differences were identified suggesting reduced risk of TEAEs for atogepant but increased risk of discontinuation compared to rimegepant. Given the details of this analysis are only available in the form of a poster, information required to fully critique this MAIC is not available. Methods of aligning the atogepant population to the rimegepant trial population appear to have been performed, with ADVANCE (EM) and PROGRESS (CM) studies for atogepant being pooled in order to include a mixed EM/CM population in line with BHV3000-305, and adjustment for various treatment effect modifiers has been performed. The rationale for performing a MAIC rather than a standard indirect comparison was that there are differences between the populations enrolled in ADVANCE (EM) and PROGRESS (CM) studies for atogepant and the BHV3000-305 trial, which the EAG acknowledges in Section 3.4.4.1. While the EAG acknowledges that these results suggest that atogepant may improve efficacy and HRQoL outcomes compared to rimegepant, with small differences for TEAEs and discontinuation, the EAG considered it useful to also explore this via inclusion in NMAs as these do not break the randomisation of the original trials. The EAG notes that similar conclusions may be made based on the point estimates of the NMA results obtained but that differences were [redacted] for efficacy outcomes (Section 3.4.3).

While the EAG acknowledges the company's conclusions that the naïve comparisons suggest that the efficacy of atogepant and eptinezumab is likely to be comparable (Tables 1 and 2 of the response to CQ A1), there are limitations associated with these naïve analyses, including the fact that not all available trials for each treatment are included. The EAG considers the inclusion of eptinezumab in NMAs in Section 3.4.3 to make better use of the available data for each treatment, with results suggesting that for EM they may be comparable or there may be [redacted] for atogepant, but with estimates for some outcomes in CM [redacted] atogepant.

While the company notes that costs for atogepant and rimegepant are [redacted], and that costs for atogepant may be [redacted] than for eptinezumab, the EAG considers their inclusion in the economic model to be a more robust measure of whether the inclusion of these comparators would impact cost-effectiveness results and decisions.

3.4.6 EAG conclusions from the indirect treatment comparison

- NMAs performed to inform relative effects for atogepant compared to mAbs and BoNT/A (and eptinezumab and rimegepant in the EAG's preferred analyses) are deemed to be reasonable by the EAG, but they are not without limitations, including differences between included studies described in Section 3.4.4 (see Key Issue 4 in Table 5) and limited data for some analyses;
- the EAG considers it important that BoNT/A, rimegepant and eptinezumab are considered as comparators within the appraisal (see Key Issue 1 in Table 2) and has included data for rimegepant and eptinezumab in the relevant NMAs;
- the EAG has a preference for efficacy analyses (MMD-related outcomes) performed in the overall migraine population for EM and CM, whereas the company prefers NMAs within the 3+ TF subgroup for these outcomes in EM, and the EAG's preferred NMA model (i.e. FE or RE analyses with or without adjustment for baseline risk) differs to the company's for many outcomes (see Section 3.4 and Key Issues 2 and 3 in Table 3 and Table 4);
- based on the point estimates from the EAG's preferred analyses in EM, the EAG considers that atogepant may be associated with [redacted] other treatments in terms of MMD-related efficacy outcomes and HRQoL, or that there is only a [redacted] comparator treatments, with no major concerns about differences in discontinuation or TEAEs. However, uncertainty with regards to this exists based on 95% CrIs from the NMAs (see Section 3.4.3);
- for CM, point estimates for MMD-related efficacy outcomes and HRQoL were generally [redacted] compared to within the EM population, with many point estimates [redacted] comparator treatments rather than atogepant, although the differences for CFB outcomes were fairly small and may not be clinically meaningful. However, for most outcomes uncertainty exists for all comparators based on 95% CrIs from the NMAs. While some [redacted] comparator treatments were identified for the ≥30% MMD reduction outcome, the EAG notes the limitations of this analysis given an FE analysis was preferred by the EAG due to limited data, which may mean

CrIs are inappropriately narrow. There are no major concerns about differences between treatments in terms of discontinuation and TEAEs (see Section 3.4.3);

- the EAG considers the results from the NMAs to be the best available evidence on which to base decisions about the relative clinical effectiveness of atogepant vs other treatments, but notes that limitations remain in terms of clinical and methodological heterogeneity of studies included and the applicability of the EAG's preferred analyses to the 3+ TF migraine population (see Key Issues 2 and 4 in Table 3 and Table 5). The EAG considers that while overall migraine population analyses may represent a deviation from the decision problem population, the robustness of the NMAs and the results obtained from them are improved as a result.

3.5 Conclusions of the clinical effectiveness section

Evidence for atogepant in the population specified in the decision problem (3+ TF) is available for EM and CM populations from ELEVATE and PROGRESS RCTs (Section 3.3), respectively. Evidence from these studies was considered to be at some risk of bias (see Section 3.2) but similar issues were identified for some comparator studies used in NMAs. The EAG notes that both trials exclude patients with >4 treatment failures, which the experts advising the EAG note is unfortunate given this is a patient group seen in clinical practice (Section 2.3.1).

Given that the EAG prefers NMAs performed within the overall migraine population for EM and CM (Section 3.4.1), it notes that ADVANCE and CGP-MD-01 RCTs for EM are also of relevance. The results presented in Section 3.3 indicate that across the three EM RCTs and single CM RCT for atogepant, atogepant appears to lead to benefits in terms of efficacy and HRQoL compared to placebo, some of which are [redacted]. While for EM the extent of the differences varies across the three studies, they are consistent in that point estimates suggest benefits for atogepant. For EM and CM, results were often [redacted] for atogepant in the 3+ TF subgroup compared to the overall trial population, although they did not always [redacted] in PROGRESS potentially due to the reduced sample size and lack of stratification at randomisation for this factor.

While the EAG's preference for NMAs within the overall migraine population in EM and CM (also the company's preference for the CM population) represents a deviation from the decision problem in

terms of population as the NMAs include data that are not specific to the 3+ TF population (see Key Issue 2 in Table 3), the EAG's clinical experts consider the baseline characteristics of the overall trial populations from ELEVATE and PROGRESS to be a reasonable representation of the UK 3+ TF population, with no major differences expected in these characteristics compared with the 3+ TF population. The EAG also considers the overall migraine population NMAs to be more robust given it avoids issues with lack of stratification for prior treatment history and allows the inclusion of more data. For some outcomes in each population, the EAG has a preference for an alternative NMA model compared to the company (i.e. RE adjusted instead of RE unadjusted in most cases; see Key Issue 3 in Table 4).

Conclusions from the NMA results are summarised in Section 3.4.6; the NMAs are not without their limitations (Section 3.4.4; see Key Issue 4 in Table 5) but the EAG considers them to be reasonable for decision-making. The results suggest that atogepant may have [redacted] in EM or [redacted], with the results being more mixed for CM (many differences may be considered [redacted] but differences for ≥30% and ≥50% MMD reduction outcomes are more notable for some comparators). The EAG notes that these conclusions are based on point estimates and that uncertainty remains for most NMAs given results were [redacted]. The EAG has included rimegepant and eptinezumab as additional comparators, as discussed in Sections 2.2.1, 2.3.3 and 3.4.5 (see Key Issue 1 in Table 2).

4 Cost effectiveness

The company's deterministic base case results for episodic migraine (EM) are given in Table 26. In the company's base case EM model results, the monoclonal antibodies (mAbs) are associated with higher costs and similar quality-adjusted life years (QALYs) compared to atogepant. Based on willingness-to-pay (WTP) thresholds of £20,000 or £30,000 per QALY, atogepant could be considered cost-effective compared to each mAb as the incremental cost-effectiveness ratios (ICERs) are above these WTP thresholds and the incremental net health benefits (NHBs) are positive.

The company's deterministic base case results for chronic migraine (CM) are given in Table 27. In the company's base case CM model results, the mAbs are associated with higher costs and marginally higher QALYs compared to atogepant. Based on WTP thresholds of £20,000 or £30,000 per QALY, atogepant could be considered cost-effective compared to each mAb as the ICERs are above these WTP thresholds and the incremental NHBs are positive.

Table 26. Company's pairwise deterministic base case results (EM)

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)	Inc. NHB (£20,000/ QALY WTP threshold)	Inc. NHB (£30,000/ QALY WTP threshold)
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Galcanezumab 120mg once monthly	£33,666	13.69	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Erenumab 140mg once monthly	£28,299	13.68	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Fremanezumab 225mg once monthly	£31,383	13.74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-

Fremanezumab 675mg once every three months	£32,976	13.75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*SW quadrant ICER (atogepant is cheaper and less effective than the comparator)

Abbreviations: EM, episodic migraine; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

Table 27. Company's pairwise deterministic base case results (CM)

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)	Inc. NHB (£20,000/ QALY WTP threshold)	Inc. NHB (£30,000/ QALY WTP threshold)
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Galcanezumab 120mg once monthly	£47,490	10.86	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Erenumab 140mg once monthly	£39,404	10.87	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Fremanezumab 225mg once monthly	£40,991	10.86	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Fremanezumab 675mg once every three months	£41,222	10.86	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*SW quadrant ICER (atogepant is cheaper and less effective than the comparator)

Abbreviations: CM, chronic migraine; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

4.1 EAG comment on the company's review of cost effectiveness evidence

The company carried out three separate systematic literature reviews (SLRs), to identify existing:

- Economic evaluations for the prevention of migraines;
- Health-related quality of life (HRQoL) evidence (health state utility values [HSUVs]) in the prevention of migraines; and
- Cost and resource use evidence in the prevention of migraines conducted in the UK.

Searches were initially run in August 2020 and were last updated in November 2022 for the economic evaluation and HRQoL evidence. Searches for cost and resource use were originally conducted on in January 2022 and last updated in November 2022. A summary of the External Assessment Group's (EAG's) critique of the methods implemented by the company to identify relevant evidence is presented in Table 28. Due to time constraints, the EAG was unable to replicate the company's searches and appraisal of identified abstracts.

Table 28. EAG's critique of company's systematic literature review (migraine prevention)

SLR step	Section of CS in which methods are reported			EAG assessment of robustness of methods
	Cost effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Data sources	Section 1 of Appendix H	Section 1 of Appendix I	Section of Appendix J	Electronic databases included: MEDLINE, MEDLINE In-Process, Embase, econLit and HTAD and NHS EED (searched simultaneously through the CRD platform). The company also searched conference proceedings, HTA websites and grey literature sources.
Search terms	Table 46-59 Section 2.5 of Appendix H	Table 71-80 Section 1.5 of Appendix I	Table 88-97 Section of Appendix J	**Appropriate.** For all applicable searches the search terms to capture economic studies are based on the validated SIGN filter set.
Inclusion criteria	Table 60 in Section of Appendix H	Table 81 in Section of Appendix I	Table 98 in Section of Appendix J	**Appropriate.** For the economic evaluations review, the company could have considered rimegepant and eptinezumab NICE final scope. The EAG also notes that the company could have been more specific regarding the inclusion criteria in the HRQoL review to identify QoL measures. The company stated "Any HSUVs" were included but do not provide a comprehensive list of what this includes or excludes.

				For example, at present it is not clear if a study that used MSQ values directly would be excluded or included; all studies included that use MSQ are mapped to EQ-5D.
Screening	Section 4 Appendix H	Section 3 Appendix I	Section 3 Appendix J	**Appropriate.**
Data extraction	Table 64 in Section 5 of Appendix H	Table 84 in Section 5 of Appendix I	Table 103 in Section 4 of Appendix J	**Appropriate.** For the economic evaluations review, 39 unique studies from 46 publications were extracted. For the HRQoL review, 44 unique studies were extracted. For the cost and resource use studies, 16 were extracted.
QA of included studies	Table 68 and 70 in Section 5 of Appendix H	No QA only assessment of appropriateness for cost-effectiveness evaluation	No QA only assessment of appropriateness for cost-effectiveness evaluation	**Appropriate.**

Abbreviations: AWMSG, All Wales Medicines Strategy Group; CADTH, Canadian Agency for Drugs and Technologies in Health; CEA, cost-effectiveness analysis; CRD, University of York's Centre for Reviews and Dissemination; CS, company submission; EAG, External Assessment Group; HRQoL, health-related quality of life; HSUVs, health state utility values; HTA, Health Technology Assessment; HTAD, Health Technology Assessment Database; MSQ, Migraine Specific Questionnaire; NCPE, National Centre for Pharmacoeconomics; NHS EED, National Health Service Economic Evaluation Database; NICE, National Institute for Health and Care Excellence; QA, quality assessment; ScHARRHUD, University of Sheffield School of Health and Related Research Health Utilities Database; SIGN, Scottish Intercollegiate Guidelines Network; SLR, systematic literature review; SMC, Scottish Medicines Consortium.

The EAG notes that eight cost-effectiveness studies for EM and six for CM considered the UK NHS perspective. The EAG notes that the company states that a Scottish NHS perspective is aligned to decision making in England for EM health technology assessment (HTA) studies but states that this perspective does not align with English decision making for CM HTA studies.

Three were National Institute for Health and Care Excellence (NICE) technology appraisals (TAs) in EM (TA764/TA631, TA659 and TA682)[8-10] and four were NICE TAs in CM (TA260, TA764/TA631, TA659 and TA682)[1]. The EAG notes that the NICE submission for rimegepant (TA906)[2] and eptinezumab (TA871)[3] were not included. The semi-Markov model structure described by the galcanezumab (TA659) was adopted by the company. The key differences between these modelling assumptions and those used in the other NICE submissions are discussed further in Section 4.2.4. Across all the health economic studies, the most common time horizon used was 10-years, with a range of 1- to 3-month cycles.

Of the 20 extracted and unique EM HRQoL studies, six reported migraine-specific quality of life questionnaire (MSQ) mapped to EQ-5D values, one collected data from the Health Utilities Index (HUI)-3, one used exclusively SF-36D and 12 report EQ-5D values directly. Of the 22 extracted and unique EM HRQoL studies, seven reported MSQ mapped to EQ-5D values, 12 report EQ-5D values directly and the remaining used alternate elicitation methods. These studies were not used to inform the base case as the company elicited MSQv2 data from the key clinical trials of atogepant (ELEVATE and PROGRESS). Please refer to Section 4.2.9 for further details on the HRQoL data applied in the model.

The company considered the cost and resource use data from the galcanezumab and erenumab appraisals to be the most appropriate source for informing the economic analysis. Please refer to Section 4.2.10 for further details on the cost and resource use data applied in the model.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 29 summarises the EAG's appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base-case analysis, with reference to the NICE final scope outlined in Section 2.3.

Table 29. NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes.
Perspective on costs	NHS and PSS	Yes.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes.
Synthesis of evidence on health effects	Based on systematic review	Yes.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-	Health effects were expressed in QALYs. The EQ-5D does not appear to be appropriate to

	5D is the preferred measure of HRQoL in adults.	measure HRQoL in this population as patients may not have a migraine when they complete the EQ-5D. The MSQ is preferred as it has a 4-week recall period. Study BHV3000-305 included MSQv2 responses from patients which the company mapped to EQ-5D utilities.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes.
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Yes. MSQv2 was mapped to EQ-5D-3L utilities using a validated algorithm developed by Gillard *et al.* 2012,[60] which uses a UK valuation set.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	The company utilised HCRU estimates accepted in previous NICE appraisals in migraine prevention (TA631/TA764 and TA682), these estimates were obtained from the NHWS. Unit costs were derived from the BNF, PSSRU and NHS References Costs.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes.

Abbreviations: BNF, British National Formulary; EAG, External Assessment Group; HCRU, healthcare resource use; HRQoL, health-related quality of life; HSUVs, health state utility values; MSQ, Migraine Specific Questionnaire; NHS, national health service; NHWS, National Health and Wellness Survey; PSS, personal social services; QALY, quality adjusted life year

4.2.2 Population

The population considered in the NICE final scope consists of adults with migraine who have discontinued/failed on at least 3 oral preventative drug treatments (3+TF). The company focuses on two specific patient populations within this, “episodic migraine” (EM) and “chronic migraine” (CM). EM includes patients who have at least four migraine days per month but fewer than 15 headache

days per month whereas CM includes all patients with ≥15 headache days per month and ≥8 migraine days per month.

The proposed target populations is in line with the NICE final scope and marketing authorisation.[11] The company's target population is also consistent with the BASH guideline[61] and recent NICE recommendations for the comparator treatments (monoclonal antibody [mAb] calcitonin gene-related peptide [CGRP] antagonists – erenumab 140 mg [TA682], galcanezumab [TA659] and fremanezumab [TA631/TA764]).[8-10]

The company used clinical effectiveness data for atogepant from the ADVANCE[26] or ELEVATE[28] study for the EM population and the PROGRESS[25] study for the CM population to inform the economic analysis. The results of a network meta-analysis (NMA) were used to inform comparator treatment outcomes relative to atogepant.

The ADVANCE study included the total EM patient population with [redacted] in the atogepant 60 mg arm and [redacted] in the placebo group. ELEVATE focused on EM patients with 2 to 4 previous preventative treatment failures (TF) and contained a subgroup based on 3+ TF, in line with the target population laid out in the NICE final scope.[11] Within this 3+ TF subgroup of ELEVATE, [redacted] patients were in the placebo arm and [redacted] in the atogepant 60 mg arm. The PROGRESS study included the total CM patient population with 246 in the placebo arm and 256 in the atogepant arm. There was a subgroup of patients with 3+ TF in this trial but with only [redacted] in the atogepant arm and [redacted] in the placebo it was not seen as sufficiently powered to obtain accurate efficacy estimates for these patients. As a result, the base case CM data for atogepant is based on a population that differs from the NICE final scope. Baseline characteristics that can be used in the model are listed in Table 30, with the ADVANCE data representing an optional scenario and the data from ELEVATE and PROGRESS representing the base case for the EM and CM populations, respectively.

Table 30. Baseline characteristics for populations used in economic model

Characteristic	EM (overall mITT) ADVANCE	EM (3+ TF mITT) ELEVATE	CM (overall mITT) PROGRESS
Age, mean	***	***	42.1
Proportion female, %	***	***	87.5%
Pooled baseline MMDs (SD)	***	***	***
Pooled baseline monthly acute MUDs (SD)	***	***	***

4.2.2.1 EAG comment

As previously stated in section 3.4.1, the EAG considers the overall modified intention to treat (mITT) is a more appropriate population to use in the EM arm of the model. This is due to a lack of available 3+ TF data for comparator randomised controlled trials (RCTs) used in the NMA. Therefore, the EAG base case uses the overall mITT population from ADVANCE.

4.2.3 Interventions and comparators

4.2.3.1 Intervention

The economic analysis investigates the cost-effectiveness of atogepant (Aquipta™; AbbVie) 60 mg every day; a small molecule, orally administered CGRP antagonist. As per the SmPC, atogepant is indicated for the prophylaxis treatment of EM and CM patients. UK marketing authorisation has been granted and covers adults with ≥4 monthly migraine days (MMDs) and in whom ≥3 prior oral preventive treatments have failed.[4]

The intervention has a list price of £463.68 per 28-tablet pack. The company have applied a confidential patient access scheme (PAS) discount of [redacted] bringing the cost per pack down to [redacted]. The company have also noted in the submission that atogepant has potential for use in primary care. The EAG notes that the pharmaceutical price regulation scheme[62] states that treatments used in primary care are unlikely to be able to apply a PAS.

4.2.3.2 Comparators

The comparators listed in the NICE final scope are:

- Erenumab;
- Galcanezumab;
- Fremanezumab;
- Botulinum toxin type A (BoNT/A , in CM only);
- Eptinezumab (subject to NICE evaluation); and,
- Rimegepant (subject to NICE evaluation)

Although rimegepant and eptinezumab have both received approval from NICE for use in routine commissioning, the company excluded these as comparators. The company have provided three key justifications for this decision:

1. The low predicted market share for 2023 of the respective treatments; up to [redacted] for rimegepant and [redacted] for eptinezumab,[13] in the relevant population (see section 4.2.2), along with clinical expert opinion suggests these treatments are not part of established care in the UK.
2. The populations these treatments target are not fully aligned with atogepant. Rimegepant is restricted to EM patients only and eptinezumab will likely be reserved for patients with severe migraine attacks, or have difficulty administering other mAb treatments, due to its intravenous (IV) administration.
3. The requirement for IV administration further limits the population eligible for treatment due to lack of access to suitable hospital facilities.
4. While eptinezumab and rimegepant are recommended by NICE, these recommendations had not been published at the time of scoping (the EAG notes that they were, however, listed in the final scope subject to NICE evaluation).

Despite this, in response to a clarification request the company have provided limited efficacy data comparing atogepant to eptinezumab and rimegepant, this is included in section 3.4.5 and 4.2.6.

In addition, the company excludes BoNT/A from their base case analysis, including it as a scenario only. This decision was made as the treatment is predicted to decline following the introduction mAbs and they state that this is in line with TA871.

Two regimens of fremanezumab are recommended by NICE: 225 mg monthly and 675 mg every three months (quarterly).[10] These were included in the company's NMA and economic analysis. For erenumab, the modelled dose reflected the dose recommended by NICE in TA682;[8] 140 mg every 4 weeks. For galcanezumab, the modelled dose reflected the dose recommended in the BNF (120 mg monthly dose after a 240 mg initial loading dose), which aligns with clinical trial evidence informing TA659.[9] The EAG also notes that these doses reflect the clinical trials informing the NMA.

4.2.3.3 EAG comment

The EAG disagrees with the decision to exclude rimegepant and eptinezumab. Firstly, the market share estimates are based on an assumption that [redacted]. This assumption is sourced

from the resource impact template uploaded for fremanezumab, which has been removed from the NICE website. This template has been superseded by the resource template for rimegepant and does not contain this assumption. According to the data provided by the company [redacted] out of [redacted] patients ([redacted]) are expected to receive rimegepant in 2023, which represents a significant uptake considering the treatment was approved in May and is only available for EM. The EAG clinical experts predict a notable uptake in rimegepant, although not much change is expected with the use of eptinezumab. A slow or limited uptake does not seem like a reasonable justification for excluding a treatment; if the medication is in the final scope, has NICE approval and can be provided to the same patient population.

In addition, a treatment being a comparator to only a subgroup of the intended patients does not exclude it from being used as a comparator, as evidenced by BoNT/A featuring as a comparator in prior submissions for eptinezumab, erenumab, galcanezumab, and fremanezumab.

As a result, the EAG has attempted to incorporate a scenario utilising rimegepant and eptinezumab as comparators.

The EAG also disagrees with the company's claim that BoNT/A is not a relevant treatment comparator for atogepant and that this decision is in line with TA871. The EAG could not find evidence that BoNT/A was not considered a relevant comparator in the NICE appraisal for eptinezumab as it appears to have been included in base case results and it is mentioned in the FAD as one of the 4 currently available treatment options (for CM)[21, 63].

Aside from the exclusion of these treatments, the EAG considers the comparators included in the economic analysis to be appropriate.

4.2.4 Modelling approach and model structure

The company developed a *de novo* cost-effectiveness model in Microsoft Excel® to evaluate the incremental cost-utility of atogepant versus erenumab, fremanezumab, and galcanezumab, in adults with EM and CM, with BoNT/A added as an additional comparator scenario for adults with CM. The model is a semi-Markov most similar to the NICE submission for galcanezumab (TA659).[64] The model has a 28-day cycle which means 3 cycles precede the 12-week assessment period. There are six health states, two of the health states are defined by their position prior to response assessment and three are defined by their position post response assessment with one death state. The model

structure is presented in Figure 2. The model also includes a health state for background mortality; however, this does not differ across treatment arms.

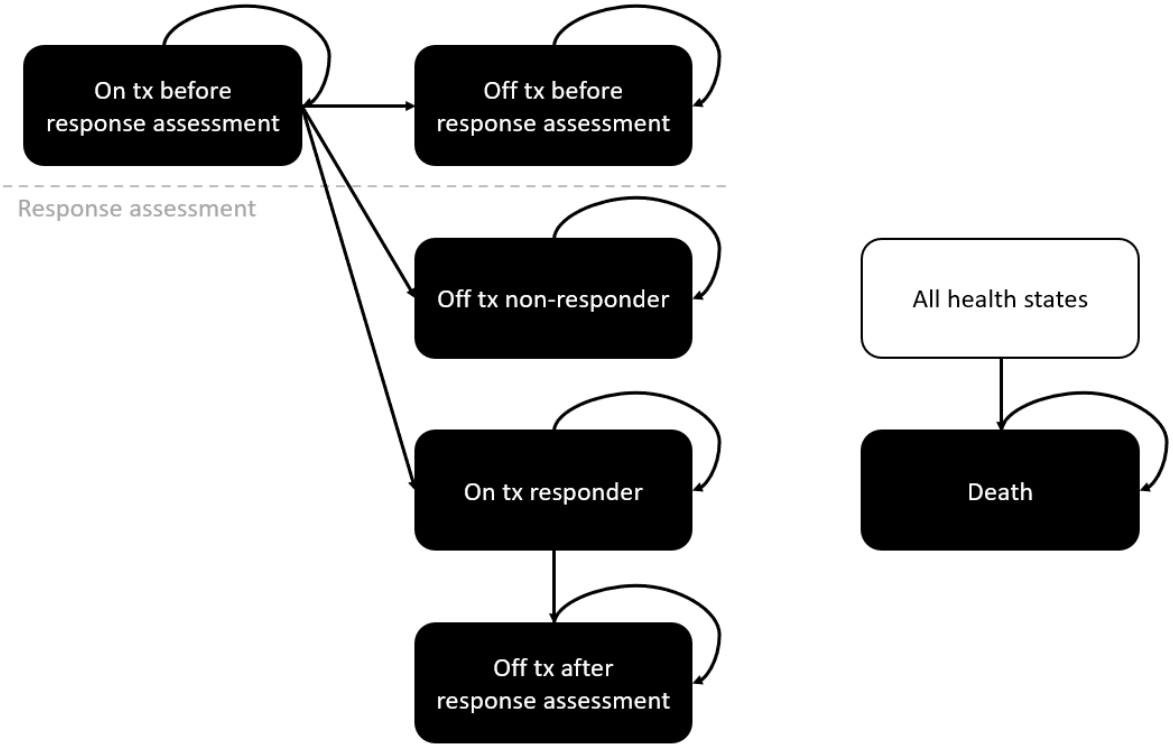
Assessment period

At the start of the model, patients initiate treatment on atogepant, erenumab, fremanezumab, galcanezumab or botulinum toxin type A (CM only) for a period of 12 weeks. This on treatment initiation state is "On tx before response assessment". Patients can discontinue in the cycles prior to the response assessment to "Off tx before response assessment" in which a patient will remain until death. For patients still on treatment, response is then assessed after the 12-week trial period (or 24-week period for BoNT/A) and defined as a ≥50% (for EM) and ≥30% (for CM) MMD reduction from baseline (see Section 4.2.6).

Post-assessment period

Non-responders immediately discontinue treatment at 12 weeks, consistent with previous NICE appraisals in migraine prevention (TA764/TA631, TA659 and TA682). Non-responders enter the Markov model in the off-treatment non-responder health state and responders continue treatment and enter the Markov model in the on-treatment responder health state. Patients who discontinue after this will enter the Off tx after response assessment health state. Utility for these health states is determined by average MMDs assumed to be distributed using a Poisson distribution.

Figure 2. Overview of the semi-Markov model for migraine prevention (reproduced from Figure 24 of the CS)



4.2.4.1 EAG comment

The EAG considers the company's model structure and modelling approach to be generally in line with those accepted in previous NICE appraisals in migraine prevention (TA764/TA631, TA659 and TA682).

A significant difference in the treatment waning assumption when compared to most prior submissions was identified and this is outlined in Table 31, based on committee preferences reported in the final guidance (note that the eptinezumab appraisal is excluded from the table as it was approved based on a cost-comparison).

Table 31. Treatment waning assumptions in previous NICE migraine prevention technology appraisals accepted at the final committee meetings

TA	Non-responders to BSC	Responders to BSC	Non-responders to active treatment at 12-weeks	Responders to active treatment who stay on treatment	Responders to active treatment who discontinue treatment
Company	NA	NA	Return to baseline MMDs immediately	Treatment effect maintained	Return to baseline MMDs immediately

Rimegepant TA906	NA	NA	Wane back to baseline MMDs over 12 months	Treatment effect maintained	Wane back to baseline MMDs over 12 months
Erenumab TA682 (FAD Section 3.17 and 3.21)	Return to baseline MMDs immediately	Return to baseline MMDs at the end of year 1 immediately	Return to baseline MMDs immediately	Treatment effect maintained	Return to baseline MMDs immediately
Fremanezumab TA764/TA631 (FAD Section 3.16)	Return to baseline MMDs immediately*	Wane back to baseline MMDs over 12 months	Wane back to baseline MMDs over 12 months	Treatment effect maintained	Return to baseline MMDs immediately*
Galcanezumab TA659 (Technical report, Issue 5)	Return to baseline MMDs immediately*	Wane back to baseline MMDs over 12 months	Wane back to baseline MMDs over 12 months (treatment-specific waning)*	Treatment effect maintained	Wane back to baseline MMDs over 12 months (treatment-specific waning)

*This assumption is not explicitly stated but could be inferred

Abbreviations: ACM, appraisal committee meeting; BSC, best supportive care; FAD, final appraisal determination; MMDs, monthly migraine days; NA, not applicable; NICE, National Institute for Health and Care Excellence; TAs, technology appraisals

As highlighted in Table 31, the company's assumptions regarding reversions to baseline MMD is in line with erenumab, in which its exclusion was a conservative assumption when comparing the treatment to BSC. In all other previous submissions, the reversion to baseline takes 12 months. This approach favours the more effective treatment. It may also be in line with fremanezumab, though it is not clear from the text in TA764/TA631.

As a result, the EAG requested the company provide scenario analysis assuming a 12-month gradual loss of treatment benefit and explain their rationale for the immediate reversion to baseline. The company provided this analysis but stated that there is no evidence available to show a placebo effect persists following treatment discontinuation, indicating this case was argued in the fremanezumab submission. The company note that the model includes an assumption that placebo responders in the "MMDs" input sheet retain their 'treatment effect'. In addition, they claim that the assumption of immediate reversion to baseline MMDs following discontinuation of active treatments is a conservative assumption.

Immediate reversion to baseline is conservative when comparing active treatment comparators such as atogepant or erenumab to BSC, but the impact of the same assumption when the comparator is another active treatment is uncertain. In the scenario analysis results provided by the company, the only recorded change in NHB was a 0.01 reduction when comparing atogepant to fremanezumab

(225mg) in EM. The company's assumption that placebo response is maintained would be conservative, but this does not impact results since BSC is not a comparator treatment.

The company is correct that the committee decided against including a continued treatment response following discontinuation in the fremanezumab appraisal (TA764/TA631). Furthermore, figure 1 in Vernieri *et al.* 2021[65] suggests benefits from discontinuing CGRP treatments are lost relatively quickly. Patients who discontinue mAbs experience a ≥50% response rate decline to 31.9% in EM and 34.3% in CM at the 2-month follow-up, from a peak of 73.3% and 60.6% whilst on treatment. A multicentre observational study on erenumab discontinuation, Schiano di Cola *et al.* 2021,[66] reaffirms this conclusion, although it remains uncertain whether this assumption is also true for atogepant and/or rimegepant.

As a result, the EAG will only incorporate post discontinuation treatment effect waning used in TA906 and TA659 as a scenario. This scenario compared to the base case is illustrated in Table 32. Note that although a user defined transition period may be inputted as "0 cycles" the model applies a minimum 1 cycle transition period.

Table 32. Health state transition period EAG and company

Health state	Base case MMD assumptions		Company transition period	TA906 and TA659 scenario transition period
	Start	End		
On treatment before response assessment	Pooled baseline MMDs	Pooled baseline MMDs	3 cycles (12 weeks)	3 cycles (12 weeks)
Off treatment before response assessment	Treatment-specific non-responder MMDs[a]	Pooled baseline MMDs	0 cycles (4 weeks)	13 cycles (1 year)
Off treatment non-responder	Treatment-specific non-responder MMDs	Pooled baseline MMDs	0 cycles (4 weeks)	13 cycles (1 year)
On treatment responder	Treatment-specific responder MMDs	Treatment-specific responder MMDs	18 cycles (72 weeks)	18 cycles (72 weeks)'
Off treatment after response assessment	Treatment-specific responder MMDs	Pooled baseline MMDs	0 cycles (4 weeks)	13 cycles (1 year)
Death	None		NA	NA

Abbreviations: IV: intravenous; MMD: monthly migraine day; NA: not applicable; SC: subcutaneous; TA: technology appraisal.

In addition, this scenario will also be included in a combined scenario that attempts to match the assumptions used in TA906. The modelling assumptions in this submission depart from prior

submissions in a number of key areas. To provide a consistent comparison with prior assessments a scenario has been created that matches the assumptions of the most recent submission in this area (TA906).

4.2.5 Perspective, time horizon and discounting

The model was conducted from the perspective of the UK NHS and Personal Social Services (PSS), in line with the NICE reference case.

The time horizon of the model was 60 years. Based on a starting age of 41.7-43.5 years (depending on if the EM or CM population is selected), patients would be over 100 years old at the end of the time horizon, meaning the time horizon is effectively lifetime.

The cycle length in the model was 28 days to align with the schedule of MMD reporting in the randomised control trials. A simple half cycle correction, taking the average of the two consecutive cycles, was applied to the model trace.

Finally, an annual discount rate of 3.5% was applied to both costs and benefits, in line with the NICE reference case.

4.2.5.1 EAG comment

In previous submissions for galcanezumab and rimegepant, it has been identified that women are predominately impacted by migraine and prevalence is significantly reduced after menopause, making a lifetime time horizon potentially inappropriate. However, given the high rates of discontinuation across all treatment arms this is likely to have minimal impact. At the end of the 20-year time horizon, less than 0.1% of patients remain on atogepant.

4.2.6 Treatment effectiveness

4.2.6.1 Assessment period discontinuation

The treatment effect is modelled according to the proportion of patients achieving a 50% reduction in MMD from baseline for EM or a 30% reduction MMD for CM, consistent with previous NICE appraisals in migraine prevention (TA764/TA631, TA659 and TA682). The probabilities for achieving response or discontinuing prior to the assessment period were derived from an NMA and results were expressed in terms of odds ratios (ORs) and/or hazard ratios (HRs).

The HRs obtained from the NMA and used to inform discontinuation prior to response assessment in the model, are summarised in Table 32. The NMA results used to establish treatment response are shown in Table 34. Atogepant was used as the baseline treatment in the economic analysis (i.e., the treatment ORs are compared to atogepant).

Table 33. Hazard ratios for discontinuation before response assessment (reproduced from table 18 of CQ)

	EM		CM	
	HR (95% CrI)	Probability of disc.	HR (95% CrI)	Probability of disc.
Atogepant 60 mg once daily (reference)	[redacted]	[redacted]	[redacted]	[redacted]
Galcanezumab 120 mg once monthly *	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg once every four weeks	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 225 mg once monthly †	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]	[redacted]	[redacted]

*Galcanezumab regimen is a 240 mg loading dose followed by 120 mg once a month. † Fremanezumab regimen is 675 mg initial dose followed by 225 mg once a month. *this was marked as once monthly in CS but has been updated to match dosing schedule used in the model.

Abbreviations: CM: chronic migraine; CrI: credible interval; CS: company submission; disc.: discontinuation; EM: episodic migraine; HR: hazard ratio.

Table 34. Hazard ratios for response and corresponding probabilities applied in the base case (reproduced from table 41 and 42 of CS)

Treatment	Random-effects model (EM)		Random-effects model (CM)	
	OR (95% CrI)	Response probability	OR (95% CrI)	Response probability
Atogepant 60 mg	1	46.2%	1	59.0%
Galcanezumab 120 mg	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 225 mg	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 675 mg*	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CM: chronic migraine; CrI, credible interval; CS: company submission; EM: episodic migraine; OR, odds ratio (treatment vs atogepant)

4.2.6.2 *Monthly migraine day (MMD) distributions*

Health-state related QoL in the model was determined by MMDs. When a patient transitions to a new health state, in order to represent waning, a mean MMD is applied to the start and end of the transition to that health state. These transitions are represented in Table 35. The mean MMD for the start is applied in the joining cycle and the mean MMD for the end, in the company's base case, is applied in the subsequent cycle (though the option is available to extend this transition period). Treatment-specific non-responder MMDs were assumed equal across all active treatments.

Table 35. MMD assumptions made per health state (preproduced from table 43 of CS)

Health state	Base case MMD assumptions	
	Start	End
On treatment before response assessment	Pooled baseline MMDs	Pooled baseline MMDs
Off treatment before response assessment	Treatment-specific non-responder MMDs	Pooled baseline MMDs
Off treatment non-responder	Treatment-specific non-responder MMDs	Pooled baseline MMDs
On treatment responder	Treatment-specific responder MMDs	Treatment-specific responder MMDs
Off treatment after response assessment	Treatment-specific responder MMDs	Pooled baseline MMDs
Death	None	

Abbreviations: CS, company submission; MMD, monthly migraine days.

A Poisson distribution is used in conjunction with mean MMD in order to establish the distribution of MMDs for a patient. The utility formula laid out in section 4.2.9 is then used to convert this to HRQoL values for a health state. Treatment specific change from baseline (CFB) values derived from the NMA are shown in Table 36, these values were used to obtain treatment specific MMDs for the comparator treatments.

Table 36. Change from baseline in mean MMDs across the 12-week treatment period to atogepant and relevant comparators in EM and CM

	EM (RE)		CM (RE)	
	Median CFB (95% CrI)	Mean MMDs	Median CFB (95% CrI)	Mean MMDs
Atogepant 60 mg once daily (reference)	***	***	***	***
Galcanezumab 120 mg once monthly	***	***	***	***
Erenumab 140 mg once every four weeks	***	***	***	***
Fremanezumab 225 mg once monthly	***	***	***	***

Fremanezumab 675 mg once every three months	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EM: episodic migraine; CM: chronic migraine; CFB: change from baseline; CrI: credible interval; EM: episodic migraine; MMDs: monthly migraine days; OR: odds ratio; RE: random effects

To prevent clinically implausible MMD results arising from the NMA, the company added a restriction that prevented mean MMDs for treatment responders falling below 1. This was further explained by the company, at clarification, that without this limitation galcanezumab responders in EM would have negative MMDs or 100% of these patients would have 0 MMDs if the restriction was set to 0.

4.2.6.3 Long-term discontinuation

Following the 12-week assessment patients remain at risk of discontinuation. During the clarification stage the company provided further details on how this was calculated. This was based on LTS-302 in EM. Patients on atogepant remained on treatment a mean time of 291.6 days with 173 patients discontinued and 546 total patients. Using the 28 day cycle length the company used the below formula to calculate long term discontinuation (applied to EM and CM and all treatment arms):

$$Rate\ per\ day = {-\ln\left(1-\frac{173}{546}\right)}/{291.6}$$

$$Rate\ per\ cycle = 1 - e^{(-Rate\ per\ day \times 28)} = 3.59\%$$

4.2.6.4 EAG comment

As previously noted in section 3.4 the EAG seeks to update, alter and add to the NMA values used in the model. To recap, these updates include:

- Add rimegepant and eptinezumab as part of the preferred base case (the EAG reran NMAs to include data for rimegepant and eptinezumab);
- Use the total mITT population for efficacy outcomes for both EM and CM (as opposed to the 3+ TF population for EM patients);
- Preference for random effects (RE) adjusted analysis for CFB MMDs and ≥50% reduction in MMDs in CM, and fixed effects (FE) unadjusted analysis for ≥30% reduction in MMDs in CM;
- Preference in EM for the RE adjusted analysis for CFB in MMDs, ≥50% reduction in MMDs, CFB in acute medication use days (MUDs) and discontinuation.

Table 37. Relative effect of atogepant 60 mg once daily vs comparators for MMD outcomes – EAG- and company-preferred analyses

Atogepant 60 mg once daily vs	Company-preferred NMA	EAG-preferred NMA
EM CFB in MMD, MD (95% CrI)		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
Rimegepant 75 mg every other day	-	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]
EM ≥50% reduction in MMDs, OR (95% CrI)		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
Rimegepant 75 mg every other day	-	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]
EM, discontinuation pre assessment period HR (95% CrIs)		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
Rimegepant 75 mg every other day	-	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]
CM CFB in MMD, MD (95% CrI)		

Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
BoNT/A	[redacted]	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]
CM ≥30% reduction in MMDs, OR (95% CrI) - company base case		
Erenumab 140 mg once monthly	[redacted]*	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
BoNT/A	[redacted]*	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]
CM ≥50% reduction in MMDs, OR (95% CrI)		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
BoNT/A	[redacted]	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]
CM, discontinuation pre assessment period HR (95% CrIs)		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]

Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
BoNT/A	[redacted]	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]

*Obtained using conversion factors

Abbreviations: BoNT/A, botulinum toxin type A; CFB, change from baseline; CM, chronic migraine; CrI, credible interval; CQ, clarification question; CS, company submission; EAG, External Assessment Group; EM, episodic migraine; HR, hazard ratio; MD, mean difference; MMD, monthly migraine days; NMA, network meta-analysis; OR, odds ratio; RE, random effects;

The EAG disagreed with the company's clinically plausible limit of 1 MMD. While it is evidently true that negative MMDs are implausible, it is not reasonable to use unexpected results from the NMA to justify an arbitrary limit. Furthermore, in the EAG base case analysis, using updated/preferred NMA results, the responder MMDs do not result in the same issue of 100% of patients having 0 MMDs, with the lowest mean responder MMDs in EM being 0.014 and 0.4555 for fremanezumab 225mg and 675mg, respectively.

In the most recent submission for this therapy area (TA906), MMD of responders and non-responders was assumed conditionally independent of treatment (i.e., MMD was solely dependent on responder status, treatment was not a relevant factor). There is some justification for making the same assumption given that CFB in MMD for all treatments in EM and CM is not statistically significant; however if this standard was consistently applied it would also disqualify most other efficacy inputs. Given this, the EAG has only included this as a scenario around the EAG base case and utilised it in a scenario that consistently utilizes the same assumptions as TA906.

The EAG's clinical experts advised that a lower rate of discontinuation would be expected in CM due to the higher rate of severity of the disease. In addition, the company's method of calculating this rate appears flawed as this calculation assumes approximately 173 patients will discontinue every 291.6 days in order to obtain a rate of discontinuation. However, given 291.6 is the mean time to discontinuation and 173 is the total number of patients that discontinue this is an implausible assumption. A more plausible assumption would be that half of 173 patients discontinued at 291.6 days, although this would involve assuming equivalence between the median patient discontinuing treatment and the mean time on treatment. In addition, the average treatment duration value is limited due to the cut off time of the study meaning that this places an arbitrary limit on how high

treatment duration can be, biasing the outcome. As a result, the long-term discontinuation rate from TA659 (0.44% per cycle)[64], provided by the company as a scenario, appears the most appropriate for use in the EAG base case. Note that whilst the company states this value is sourced from TA682, this appears to be an error as the 12 week discontinuation rate used in the erenumab submission was 2.38%[8].

4.2.7 Adverse events

The company did not directly include adverse events in the model given no patients experienced serious adverse events (Grade ≥3) in the phase III treatment studies (ELEVATE, PROGRESS and ADVANCE) and they have not been incorporated into previous submissions (TA260, TA659, TA682, TA764, TA871, TA906). The company also considered this to be a conservative assumption given the potential for injection site reactions, constipation and hypersensitivity reactions with mAbs.

However, the company have indirectly included AE disutility associated with injections by attaching a utility decrement for SC (subcutaneous) or IM (intramuscular) administration from Matza *et al*. 2019.[67] A disutility of 0.011 for SC and 0.0735 for IM was applied. The paper included utility for migraine patients and members of the general population taking oral treatments (propranolol, topiramate, and amitriptyline), receiving 31-39 injections once every 3 months (representing BoNT/A) and receiving 1 injection per month (representing mAb treatments). The average difference in utility, for migraine patients and general population patients, between the oral treatment and the injectables is what was used to derive the disutility. Utility was derived via interviewers completing a time-trade-off (TTO) task.

4.2.7.1 EAG comment

The EAG heard from its clinical experts that they were unaware of any specific serious adverse events associated with atogepant. The EAG accepts that it is likely a conservative assumption to exclude AEs, although the Matza *et al*. 2019 source effectively incorporates any injection-related disutility.

The EAG does not consider that the Matza paper represents an appropriate source for administration related disutility. The utility difference between 1 injection per month and oral medication was not statistically significant and a disutility associated with injection was not incorporated into the rimegepant appraisal (TA906).[2] This would suggest use of this disutility for SC

administration has not been sufficiently demonstrated and is inconsistent with the most recent/comparable NICE submission.

Furthermore, the paper did not use EQ-5D utility from patients actively receiving treatment. Utilities were instead elicited, from migraine sufferers and the general population, using a TTO task with a 10-year time horizon and health state vignettes described to interviewees. Given this, it is unclear whether the 0.0735 utility decrement derived for botulinum toxin type A is comparable to a 0.0735 decline in EQ-5D utility score.

4.2.8 Mortality

In both EM and CM, the company only included all-cause mortality, as per prior NICE TAs in migraine prevention (TA906, TA764, TA659 and TA682). To further support this approach, the company referred to a published meta-analysis, which found no association between migraine and all-cause mortality.[68]

The company obtained all-cause general population mortality from UK national life tables provided by the Office for National Statistics (ONS). Data from Years 2018 to 2020 were used to inform the model. These probabilities were age and sex adjusted according to the baseline patient characteristics in the atogepant studies. The life years gained in all company model runs was [redacted] years in EM and [redacted] years in CM.

4.2.8.1 EAG comment

The EAG found that the life table values used in the model differ to the qx, lx and dx column in the latest release of the ONS life tables (2018-20). The difference between the values is minor, as shown in Table 38, Table 39 and Table 40, but it is unclear where the company derived their general population mortality values since their inputs do not match any of the values within any of the last three ONS releases. The EAG base case uses the updated life tables to match the latest ONS data. The life years gained in all model runs remained [redacted] years in EM but decreased marginally to [redacted] years in CM following this change.

Table 38. ONS lifetables 2018-20 qx versus company inputs

Age	ONS national life table 2018-20		Company mortality input	
	Male	Female	Male	Female
0	0.004224	0.003503	0.004244	0.003519
1	0.000229	0.000214	0.000231	0.000211

2	0.000127	0.000114	0.000128	0.000113
3	0.000102	0.000095	0.000099	0.000093
4	0.000086	0.000064	0.000090	0.000061
5	0.000074	0.000074	0.000077	0.000079
6	0.000085	0.000071	0.000081	0.000069
7	0.000067	0.000055	0.000068	0.000051
8	0.000069	0.000058	0.000065	0.000053
9	0.000060	0.000051	0.000062	0.000056
10	0.000078	0.000066	0.000073	0.000065
Abbreviations: ONS; Office of National Statistics.				

Table 39. ONS lifetables 2018-20 lx versus company inputs

Age	ONS national life table 2018-20		Company mortality input	
	Male	Female	Male	Female
0	100000	100000	100000	100000
1	99578	99650	99576	99648
2	99555	99628	99553	99627
3	99542	99617	99540	99616
4	99532	99608	99530	99607
5	99524	99601	99521	99601
6	99516	99594	99513	99593
7	99508	99587	99505	99586
8	99501	99581	99499	99581
9	99494	99576	99492	99576
10	99488	99570	99486	99570
Abbreviations: ONS; Office of National Statistics.				

Table 40. ONS lifetables 2018-20 dx versus company inputs

Age	ONS national life table 2018-20		Company mortality input	
	Male	Female	Male	Female
0	422	350	424	352
1	23	21	23	21
2	13	11	13	11
3	10	9	10	9
4	9	6	9	6
5	7	7	8	8
6	8	7	8	7

7	7	5	7	5
8	7	6	6	5
9	6	5	6	6
10	8	7	7	7

Abbreviations: ONS; Office of National Statistics.

4.2.9 Health-related quality of life

The company used a mapping regression from Gillard *et* al. 2012 to convert MSQ v2.1 values from the placebo and atogepant arms of the ELEVATE and PROGRESS trials to EQ-5D values. These individual patient data (IPD) EQ-5D utility values was then regressed against MMD and response for the EM and CM groups separately in order to obtain the regression shown in Table 41.

Table 41. Regression models for mapped EQ-5D-3L utility (copy of table 47 in CS)

MMDs and treatment	EM		CM	
	Coeff	SE	Coeff	SE
Intercept	***	***	***	***
MMD	***	***	***	***
Response	***	***	***	***

Abbreviations: CM: chronic migraine; Coeff: coefficient; EM: episodic migraine; MMD: monthly migraine days; SE: standard error.

With MMDs derived for each health state, as described in section 4.2.6.2, along with this regression applied, the company obtained HRQoL values for each health state/treatment.

Age-related utility decrements were included in the prevention model based on the algorithms reported in Health Survey for England (HSE) 2014 data[69].

4.2.9.1 EAG comment

During the clarification stage, the company was asked to rerun the regression using "on treatment" in place of "response" to match the previous submission TA906 and avoid issues of multicollinearity. The company stated that it was not possible to dynamically define treatment status this way, as it would require recalculating mean monthly migraine days for time periods were taking atogepant versus after they discontinued . Given that "on treatment" is likely to be aligned with responder status the EAG expects the absence of this regression will have minimal impact.

In scenarios that include eptinezumab, where a treatment disutility is applied for other treatments, a 0.005 disutility is used for each IV administration, in line with TA871 NICE submission[3].

4.2.10 Resource use and costs

The company has proposed a confidential patient access scheme (PAS) discount of approximately [redacted] on the list price, and all results presented in this report are inclusive of the discount. Confidential PAS discounts are available for fremanezumab, erenumab, galcanezumab, and eptinezumab. Furthermore, there is a CMU (Confidential Medicines Unit) price available for BoNT/A.

As such, the EAG has produced a confidential appendix to the EAG report. Analyses in the confidential appendix include the company base case results, scenario analyses and EAG base case and scenario analyses.

4.2.10.1 Drug acquisition and administration costs

Treatment costs and dosages are provided in Table 42. The 28-day ongoing treatment cost is an approximate average of the per cycle costs applied in the model since the model applies cost of treatments only in cycles where a new pack/dose was required. Fremanezumab, for example, is administered once monthly (as opposed to once every four weeks if it were once per cycle), meaning that the full cost per pack is applied from cycles 0 to 11 but no cost is applied in cycle 12.

No administration cost is associated with atogepant since it is administered orally. All mAb treatments have an initial cost in the first cycle for SC administration, following this it is assumed that 10% of patients who have issues self-administering will incur this cost every cycle. The cost for SC administration is £21.50 based on 30 minutes of Band 5 nurse time from the PSSRU 2022.[70] The administration cost for multiple intramuscular (IM) injections (required for BoNT/A) is £226.41 per appointment, based on the cost of a consultant lead neurology service for non-admitted face-to-face follow-up attendance.[71]

Table 42. Treatment costs for prevention (adapted from Table 49 of the CS)

Treatment	Dose	Cost per pack or vial	28-day initial treatment cost	28-day ongoing treatment cost
Atogepant	60mg once daily	List price £463.68 [redacted]	£463.68 [redacted]	£463.68 [redacted]
Erenumab	140 mg once every four weeks	£386.50	£386.50	£386.50
Fremanezumab	225 mg once monthly	£450.00	£450.00*	£414.00
Fremanezumab	675 mg once every three months	£1,350	£1,350	£414.00
Galcanezumab	120 mg once monthly with 240 mg initial dose	£450.00	£900.00*	£414.00
Botulinum toxin type A (CM only)	155–195 U (200 U assumed in the model as vial sharing is assumed not feasible) once every 12 weeks	£276.40	£276.40	£92.13

Abbreviations: CM, chronic migraine; CS, company submission; U, units

In addition to the intervention and comparator, acute medications are also costed for based on the trial results and the results from the NMA. The trial provides a baseline value for MUD (medication use days) for atogepant of [redacted] in CM and [redacted] in EM. This is then utilised in conjunction with the relative effects from the NMA to estimate MUDs for the comparators. As previously noted, the NMA has been updated to include rimegepant and eptinezumab; the updated results for MUD alongside the company base case are shown Table 43 and the acute medication costs and usage rates shown in Table 44. Due to a lack of available data, rimegepant was assumed to have equal MUD to atogepant.

Table 43. Relative effect of atogepant 60 mg once daily vs comparators for MUD outcomes – EAG- and company-preferred analyses

Atogepant 60 mg once daily vs	Company-preferred NMA	EAG-preferred NMA
CFB in acute MUDs, MD (95% CrI)		
Erenumab 140 mg once monthly	-	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
Rimegepant 75 mg every other day	-	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]
CM CFB in acute MUDs, MD (95% CrI)		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
BoNT/A	[redacted]	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]

*95% CrI assumed

Outputs from the NMAs are means for the CFB outcome. Bold values indicate statistically significant differences.

Abbreviations: BoNT/A, botulinum toxin type A; CFB, change from baseline; CM, chronic migraine; CrI, credible interval; EAG, External Assessment Group; EM, episodic migraine; MD, mean difference; MUDs, medication use days; NMA, network meta-analysis.

Table 44.Acute medication use costs (reproduced from table 53 in the CS)

Acute Medication	Recommended dosing		Unit costs		Maximum daily cost	Patients receiving acute medication (%)
	Dose	Maximum frequency	Cost per pack	Pack size		
Ibuprofen	400 mg	Three times per day	£3.25	84 tablets	£0.12	***
Thomapyrin N®	One sachet	Three times per day	£6.61[a]	6 sachets	£3.31	***
Sumatriptan	50 mg	Six times per day	£1.03	6 tablets	£1.03	***
Paracetamol	1,000 mg	Four times per day	£0.22	32 tablets	£0.05	***

Abbreviations: CS, company submission; U, units

Commercial arrangements are available for most of the comparators. Table 45 shows the source of commercial arrangement that has been used for each treatment in the confidential appendix. The results from Figure 3 to Figure 11, Table 52 to Table 55 and Table 60 to Table 63 from sections 5 and 6 have been replicated in the confidential appendix using confidential commercial arrangements. In addition, Table 56 and Table 57 have been replicated in the same way, with additional scenarios provided by the company at CQs added.

Table 45. Source of prices for confidential appendix.

Treatment	Formulation	Source
Atogepant	60mg 28 tablets	PAS
Galcanezumab	120 mg/1 ml solution for injection	PAS
Erenumab	140 mg/1 ml solution for injection	PAS
Fremanezumab	225 mg/1.5 ml solution for injection	PAS
Fremanezumab	675 mg/4.5 ml solution for injection	PAS
Eptinezumab	100 mg/mL	PAS
Rimegepant	75mg 8 tablets	List price
Botulinum toxin type A	200 units	CMU
Ibuprofen	400 mg 84 tablets	eMIT

Thomapyrin N® - company used price of aspirin with metoclopramide as a proxy	900 mg/10 mg 6 sachets	
Sumatriptan	50 mg 6 tablets	eMIT
Paracetamol	500 mg 32 tablets (company) 500 mg 100 tablets (EAG)	eMIT
Abbreviations: BNF, British national formulary; CMU, confidential medicines unit; eMIT, electronic market information tool; PAS, Patient access scheme,		

4.2.10.2 Treatment monitoring costs

All mAb patients are costed for a headache specialist visit in the first cycle, while atogepant has a 50:50 split between a headache specialist or a general neurologist visit. Clinical follow up visits are assumed to occur in primary care for atogepant and by a general neurologist for the mAbs. These professionals' unit costs are shown in Table 46.

Table 46. Monitoring unit costs

Resource	Unit cost
Headache specialist	£226.41
General neurologist	£184.23
General practitioner	£41.00

4.2.10.3 Health care resource use cost per migraine

The company states that health care resource use is taken from the National Health and Wellness Survey (NHWS) data as published in Vo *et al.* 2018[72]. However, the original data source appears to be NHWS data on file analysed as part of the erenumab submission (shown in table 58 and 59 of the original TA682 submission) [8,].

Nevertheless, this matches the dataset used in multiple recent submissions (rimegepant, erenumab fremanezumab, galcanezumab)[2, 8, 10, 64], the resource use can be seen listed in Table 47. These resource use values are then multiplied by the costs listed in Table 48.

Table 47. HCRU data from the NHWS (reproduced from table 51 in the CS)

Number of MMDs	Resource use per MMD				
	GP visit	A&E visit	Hospitalisation	Nurse specialist visit	Neurologist visit
0	0.202	0.030	0.023	0.063	0.003
1–3	0.288	0.067	0.042	0.102	0.015

4–7	0.413	0.058	0.040	0.175	0.013
8	0.553	0.092	0.040	0.048	0.038
9–14	0.553	0.092	0.052	0.048	0.038
15–28	0.585	0.117	0.052	0.127	0.073

Abbreviations: A&E, accident and emergency; GP, general practitioner; MMD, monthly migraine days, NHWS, National Health and Wellness Survey.

Table 48. Disease management unit costs (reproduced from table 52 in the CS)

Medical resource	Unit cost	Description
GP visits	£41.00	Based on contact lasting 9.22 minutes, including direct care staff costs, carbon emissions, and qualification costs
A&E visits	£236.69	VB08Z: Emergency Medicine, Category 2 Investigation with Category 1 Treatment. (Total HRGs)
Hospitalisation	£449.52	AA31E: Headache, Migraine or Cerebrospinal Fluid Leak, with CC Score 0–6. Day case (DC)
Nurse specialist visits	£43.00	60-minute appointment with a Band 5 community-based nurse at an hourly rate of £37.00
Neurologist visit	£184.23	WF01A: follow-up attendance – single professional. Neurology (service Code 400). Outpatient procedures

Abbreviations: A&E, accident and emergency; CS, company submission; GP, general practitioner; HRG, healthcare resource group.

4.2.10.4 EAG comment

As stated in section 4.2.3, the EAG considers that rimegepant and eptinezumab should be included in the analysis. The costs for these treatments used in the EAG analysis are listed in Table 49 and are sourced from the British national formulary (BNF)[73].

Table 49. Treatment costs of additional comparators

Treatment	Dose	Cost per pack or vial	28-day initial treatment cost	28-day ongoing treatment cost
Rimegepant	75mg every other day	£103.20	£361.20	£361.20
Eptinezumab	100mg once every 12 weeks	£1,350	£1,350	£450

Rimegepant is administered orally, therefore it has no administration cost. Eptinezumab is administered via intravenous (IV) injection, which requires a professional in every instance. The cost used for this was £174.04, taken from the eptinezumab NICE submission[3].

There is no specific source for the percentage of patients who have difficulty self-administering, although EAG's clinical experts agreed with the company that approximately 10% seemed reasonable. The sensitivity of the results to this assumption has been explored in EAG scenario analyses using 5% and 15% in section 6.2.

For acute medication costs, the company did not use the latest available eMIT costs. As a result, the EAG have updated the acute medication costs using the eMIT data from July 2022 to December 2022, as shown in Table 50. There has since been an update to eMIT costs released on the 5th of October 2023, though since this was released after the company submission this has not been used.

Table 50.Acute medication use costs update using eMIT

Acute Medication	CS strength	CS pack size	CS Pack cost	EAG strength	EAG pack size	EAG pack cost	EAG source
Ibuprofen	400 mg	84 tablets	£3.25	400 mg	84 tablets	£1.10	eMIT
Thomapyrin N*	One sachet	6 sachets	£6.61*	900mg/10 mg	6 tablets	£6.61*	BNF: List price for Migramax
Sumatriptan	50 mg	6 tablets	£1.03	50 mg	6 tablets	£0.79	eMIT
Paracetamol	500 mg	32 tablets	£0.22	500 mg	100 tablets	£0.88	eMIT

*Company used price of aspirin with metoclopramide as a proxy
Abbreviations: BNF, British National Formulary; CS, company submission; EAG, External Assessment Group; eMIT, electronic market information tool.

Given HCRU includes neurologist and GP visits, there is a potential issue of double counting by incorporating monitoring costs. In addition, the EAG's clinical experts expected that as it is a new treatment a period of time would be required when it was exclusively monitored by specialist care before any transfer of care could be possible to primary care. This is in line with previous expectations for monitoring of rimegepant explained in TA906. In addition, the company has additional savings from including 50% of atogepant patients as being prescribed in primary care. Since the company intends to apply for a confidential PAS this would not be possible, as treatments that are eligible for a PAS must be prescribed in secondary care.

The EAG has opted to exclude monitoring costs in line with the most recent submission for rimegepant (TA906) and to avoid the potential issue of double counting. Health state costs include neurologist and GP visits and there is no indication from the source that these rates of resource use excluded monitoring.

In the eptinezumab submission (TA871), the submitting company presented an analysis of the updated NHWS survey results to apply in their model for informing resource use rates by MMD. The source of these data was a report commissioned by the company and has not been published; however, the annual resource use by MMD frequency was made publicly available in the committee papers for TA871. These values, adjusted to per cycle rates, are shown in Table 51.

Table 51. per cycle HCRU data from the TA871

Number of MMDs	Resource use per MMD					
	GP visit	A&E visit	Hospitalisation	Nurse specialist visit	Neurologist visit	Psychiatrist visits
0	0.000	0.000	0.000	0.000	0.000	0.000
1–3	0.057	0.020	0.010	0.008	0.006	0.008
4–7	0.058	0.023	0.012	0.011	0.008	0.011
8–14	0.059	0.023	0.014	0.009	0.012	0.009
15–28	0.064	0.027	0.016	0.014	0.018	0.014

Abbreviations: A&E, accident and emergency; GP, general practitioner; MMD, monthly migraine days, NHWS, National Health and Wellness Survey.

Given this is the most recent available data, these rates of resource use would be the most appropriate values to inform the model. However, since the per cycle resource values appear to differ significantly from those used in previous submissions and the EAG cannot access and verify the original source, this has been provided as an additional scenario analysis around the EAG base case.

5 Cost effectiveness results

5.1 Company's base case results

5.1.1 Deterministic results

Table 52 and Table 53 shows the company's deterministic base case for episodic migraine (EM) and chronic migraine (CM), comparing each of the three monoclonal antibodies (mAbs) to atogepant. As shown in Table 52, mAbs are associated with higher costs and similar quality-adjusted life years (QALYs). Based on willingness-to-pay (WTP) thresholds of £20,000 or £30,000 per QALY, atogepant could be considered cost-effective compared to each mAb as the incremental cost-effectiveness ratios (ICERs) are above these WTP thresholds and the incremental net health benefits (NHBs) are positive. The company made minor corrections to the network meta-analyses (NMAs) following clarification questions which resulted in the updated model results presented in this section.

Table 52. Company's pairwise deterministic base case results (EM)

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)	Inc. NHB (£20,000/ QALY WTP threshold)	Inc. NHB (£30,000/ QALY WTP threshold)
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Galcanezumab 120mg once monthly	£33,647	13.69	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Erenumab 140mg once monthly	£28,260	13.68	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Fremanezumab 225mg once monthly	£31,394	13.74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant 60mg once daily	[redacted]	[redacted]					

Fremanezumab 675mg once every three months	£32,980	13.75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*SW quadrant ICER (atogepant is cheaper and less effective than the comparator)

Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

Table 53. Company's pairwise deterministic base case results (CM)

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)	Inc. NHB (£20,000/ QALY WTP threshold)	Inc. NHB (£30,000/ QALY WTP threshold)
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Galcanezumab 120mg once monthly	£47,530	10.87	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Erenumab 140mg once monthly	£39,510	10.87	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Fremanezumab 225mg once monthly	£40,993	10.86	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Fremanezumab 675mg once monthly	£41,220	10.86	[redacted]	[redacted]†	[redacted]	[redacted]	[redacted]

*SW quadrant ICER

†Value of [redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

5.1.2 *Probabilistic results*

The company performed probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around base case results. Generally, probabilities were varied using a normal distribution unless it was necessary to constrain the variation (i.e. if a value couldn't be negative or exceed 1).

The PSA results provided by the company, arising from 1,000 simulations, are reproduced in Table 54. The External Assessment Group (EAG) considers these results to be similar to the company's deterministic results.

Table 54. Company's revised probabilistic base case results (EM)

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)	Inc. NHB (£20,000/ QALY WTP threshold)	Inc. NHB (£30,000/ QALY WTP threshold)
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Galcanezumab 120mg once monthly	£33,714	13.69	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Erenumab 140mg once monthly	£28,277	13.67	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Fremanezumab 225mg once monthly	£31,466	13.73	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Fremanezumab 675mg once every three months	£33,047	13.74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*SW quadrant ICER (atogepant is cheaper and less effective than the comparator)

Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

Table 55. Company's revised probabilistic base case results (CM)

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)	Inc. NHB (£20,000/ QALY WTP threshold)	Inc. NHB (£30,000/ QALY WTP threshold)
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Galcanezumab 120mg once monthly	£47,569	10.87	[redacted]	[redacted]	1,314,438*	0.66	0.44
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Erenumab 140mg once monthly	£39,452	10.88	[redacted]	[redacted]	420,750*	0.25	0.16
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Fremanezumab 225mg once monthly	£40,919	10.87	[redacted]	[redacted]	1,255,618*	0.33	0.22
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Fremanezumab 675mg once monthly	£41,180	10.86	[redacted]	[redacted]	-50,434,768	0.35	0.23

*SW quadrant ICER (atogepant is cheaper and less effective than the comparator)

†Value of [redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

5.1.3 *One-way sensitivity analysis*

The company carried out one-way sensitivity analyses (OWSAs) to assess the impact of varying the key parameters between the upper and lower 95% credible intervals or confidence intervals of the mean value. The tornado plot figures presented by the company in the company submission (CS; figures 38-45) were not correctly updated, resulting in many of the lower/upper bound NHB results exceeding the chart axis range. In addition, the model has since been updated following clarification. As a result the EAG have rerun the OWSA for EM and CM and present the results in Figure 3 to

Figure 10.These plots include the 10 most influential parameters resulting from the OWSA, comparing each mAb and botulinum toxin type A (BoNT/A) with atogepant. The ICER was most sensitive to unit cost of treatments, response rates and discontinuation.

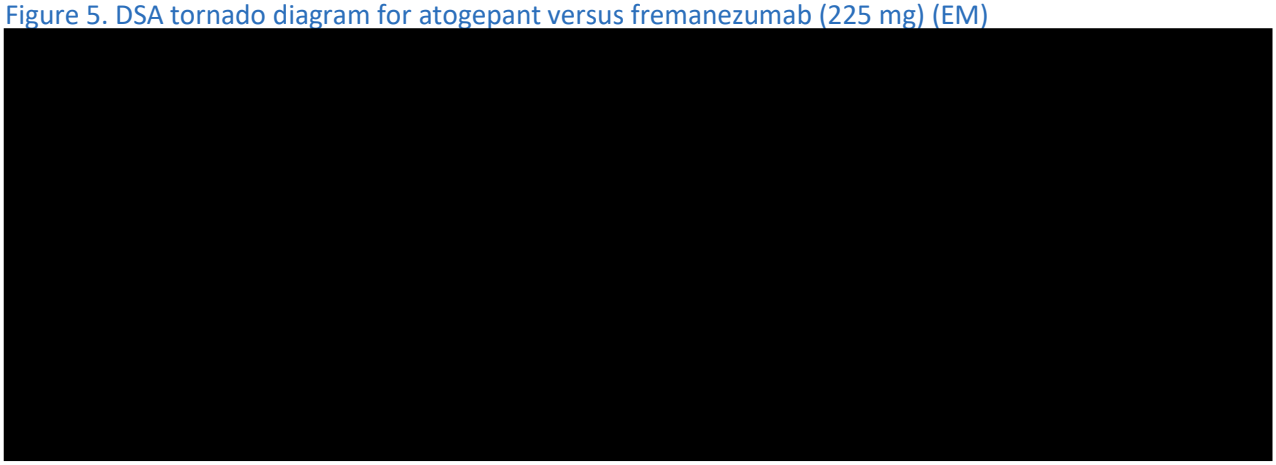
Figure 3. DSA tornado diagram for atogepant versus erenumab (140 mg) (EM)

Abbreviations: DSA: deterministic sensitivity analysis; EM: episodic migraine.

Figure 4. DSA tornado diagram for atogepant versus galcanezumab (120 mg) (EM)

Abbreviations: DSA: deterministic sensitivity analysis; EM: episodic migraine.

Figure 5. DSA tornado diagram for atogepant versus fremanezumab (225 mg) (EM)



Abbreviations: DSA: deterministic sensitivity analysis; EM: episodic migraine.

Figure 6. DSA tornado diagram for atogepant versus fremanezumab (675 mg) (EM)

Abbreviations: DSA: deterministic sensitivity analysis; EM: episodic migraine.

Figure 7. DSA tornado diagram for atogepant versus erenumab (140 mg) (CM)

Abbreviations: CM: chronic migraine; DSA: deterministic sensitivity analysis.

Figure 8. DSA tornado diagram for atogepant versus galcanezumab (120 mg) (CM)

Abbreviations: CM: chronic migraine; DSA: deterministic sensitivity analysis.

Figure 9. DSA tornado diagram for atogepant versus fremanezumab (225 mg) (CM)

Abbreviations: CM: chronic migraine; DSA: deterministic sensitivity analysis.

Figure 10.DSA tornado diagram for atogepant versus fremanezumab (675 mg) (CM)

Abbreviations: CM: chronic migraine; DSA: deterministic sensitivity analysis.

Figure 11. DSA tornado diagram for atogepant versus BoNT/A (CM)

Abbreviations: CM: chronic migraine; DSA: deterministic sensitivity analysis.

5.1.4 Scenario analysis

The company undertook a series of scenario analyses to assess the impact of applying alternative assumptions to key model parameters. The scenarios run by the company are presented in Table 56 and Table 57. The largest decrease in the NHB (favoring the mAbs) was observed for using an alternate responder definition of ≥50% response definition for CM and exclusion of disutility associated with administration for EM, although in both cases atogepant could still be considered cost-effective at £20,000 and £30,000 WTP thresholds.

Table 56. Scenario analyses (EM) – atogepant PAS price (deterministic results) (reproduced from table 35 in company CQ response)

#	Description	Galcanezumab (120 mg)			Erenumab (140 mg)			Fremanezumab (225 mg)			Fremanezumab (675 mg)		
		Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]
Base Case		[redacted]	[redacted]	0.26	[redacted]	[redacted]	0.10	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.19
1	Missing NMA data equal to average mAb	[redacted]	[redacted]	0.26	[redacted]	[redacted]	0.10	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.19
2	Consider natural history of migraine	[redacted]	[redacted]	0.26	[redacted]	[redacted]	0.10	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.19
3a	Discontinuation before response assessment assumed to be a one-off probability at the response assessment timepoint	[redacted]	[redacted]	0.27	[redacted]	[redacted]	0.10	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.19
3b	Discontinuation after response assessment informed by alternative value	[redacted]	[redacted]	0.98	[redacted]	[redacted]	0.37	[redacted]	[redacted]	0.59	[redacted]	[redacted]	0.75
3c	Long-term discontinuation based on	[redacted]	[redacted]	0.39	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.22	[redacted]	[redacted]	0.29

	fremanezumab (1.95% per cycle)												
3d	Long-term discontinuation based on galcanezumab (0.79% per cycle)	[redacted]	[redacted]	0.70	[redacted]	[redacted]	0.27	[redacted]	[redacted]	0.42	[redacted]	[redacted]	0.53
4	Use of regression model 2 for utilities	[redacted]	[redacted]	0.26	[redacted]	[redacted]	0.09	[redacted]	[redacted]	0.16	[redacted]	[redacted]	0.20
5	Exclusion of disutility associated with SC or IM administration routes	[redacted]	[redacted]	0.26	[redacted]	[redacted]	0.09	[redacted]	[redacted]	0.13	[redacted]	[redacted]	0.17
6a	Monitoring costs 1	[redacted]	[redacted]	0.26	[redacted]	[redacted]	0.09	[redacted]	[redacted]	0.14	[redacted]	[redacted]	0.18
6b	Monitoring costs 2	[redacted]	[redacted]	0.27	[redacted]	[redacted]	0.11	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.20
7	EM overall population	[redacted]	[redacted]	0.42	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.18	[redacted]	[redacted]	0.20
8	Use of trial-observed MMD distributions	[redacted]	[redacted]	**0.27**	[redacted]	[redacted]	**0.10**	[redacted]	[redacted]	**0.16**	[redacted]	[redacted]	**0.19**
9	Assuming a gradual loss of benefit over 1 year	[redacted]	[redacted]	**0.26**	[redacted]	[redacted]	**0.10**	[redacted]	[redacted]	**0.14**	[redacted]	[redacted]	**0.19**
10	All treatments have equal MMD distributions for	[redacted]	[redacted]	**0.27**	[redacted]	[redacted]	**0.10**	[redacted]	[redacted]	**0.16**	[redacted]	[redacted]	**0.19**

	responders (based on atogepant data)												
11	HRQoL regression based on MMDs alone	[redacted]	[redacted]	**0.25**	[redacted]	[redacted]	**0.09**	[redacted]	[redacted]	**0.15**	[redacted]	[redacted]	**0.21**

*NHB calculated at a WTP threshold of £30,000. Note: Baseline risk-adjusted analyses were removed given that the NMA exploring ≥50% reduction in MMDs following baseline risk-adjustment did not converge (per CS appendices Table 26).
Abbreviations: CGRP: calcitonin gene-related peptide; EM: episodic migraine; mAbs: monoclonal antibodies; NMA: network meta-analysis; PAS: patient access scheme; SC: subcutaneous; TA: technology appraisal; tx: treatment.

Table 57. Scenario analyses (CM) – atogepant PAS price (deterministic results) (reproduced from table 36 in company CQ response)

#	Description	Galcanezumab (120 mg)			Erenumab (140 mg)			Fremanezumab (225 mg)			Fremanezumab (675 mg)		
		Inc. costs (£)	Inc. QALYs	NHB (QALYs) [a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs) [a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs) [a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs) [a]
Base Case		[redacted]	[redacted]	0.43	[redacted]	[redacted]	0.16	[redacted]	[redacted]	0.22	[redacted]	[redacted]	0.23
12	Missing NMA data equal to average mAb	[redacted]	[redacted]	0.43	[redacted]	[redacted]	0.18	[redacted]	[redacted]	0.22	[redacted]	[redacted]	0.23
13	Consider natural history of migraine	[redacted]	[redacted]	0.43	[redacted]	[redacted]	0.16	[redacted]	[redacted]	0.22	[redacted]	[redacted]	0.24
14a	Discontinuation before response assessment assumed to be a one-off probability at the response assessment timepoint	[redacted]	[redacted]	0.43	[redacted]	[redacted]	0.16	[redacted]	[redacted]	0.22	[redacted]	[redacted]	0.23

14b	Discontinuation after response assessment informed by alternative value	[redacted]	[redacted]	1.85	[redacted]	[redacted]	0.70	[redacted]	[redacted]	0.96	[redacted]	[redacted]	0.97
14c	Long-term discontinuation based on fremanezumab (1.95% per cycle)	[redacted]	[redacted]	**0.68**	[redacted]	[redacted]	**0.26**	[redacted]	[redacted]	**0.35**	[redacted]	[redacted]	**0.36**
14d	Long-term discontinuation based on galcanezumab (0.79% per cycle)	[redacted]	[redacted]	**1.30**	[redacted]	[redacted]	**0.49**	[redacted]	[redacted]	**0.67**	[redacted]	[redacted]	**0.68**
15	Use of regression model 2 for utilities	[redacted]	[redacted]	0.44	[redacted]	[redacted]	0.17	[redacted]	[redacted]	0.23	[redacted]	[redacted]	0.24
16	Exclusion of disutility associated with SC or IM administration routes	[redacted]	[redacted]	0.42	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.20	[redacted]	[redacted]	0.22
17	≥50% response definition	[redacted]	[redacted]	0.34	[redacted]	[redacted]	0.11	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.17
18a	Monitoring costs 1	[redacted]	[redacted]	0.43	[redacted]	[redacted]	0.16	[redacted]	[redacted]	0.21	[redacted]	[redacted]	0.23
18b	Monitoring costs 2	[redacted]	[redacted]	0.44	[redacted]	[redacted]	0.17	[redacted]	[redacted]	0.23	[redacted]	[redacted]	0.24
19	Use of trial-observed MMD distributions	[redacted]	[redacted]	0.44	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.18	[redacted]	[redacted]	0.20

20	Assuming a gradual loss of benefit over 1 year	[redacted]	[redacted]	0.43	[redacted]	[redacted]	0.16	[redacted]	[redacted]	0.22	[redacted]	[redacted]	0.23
21	All treatments have equal MMD distributions for responders (based on atogepant data)	[redacted]	[redacted]	0.44	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.18	[redacted]	[redacted]	0.20
22	HRQoL regression based on MMDs alone	[redacted]	[redacted]	0.44	[redacted]	[redacted]	0.17	[redacted]	[redacted]	0.24	[redacted]	[redacted]	0.25

*NHB calculated at a WTP threshold of £30,000. Note: Baseline risk-adjusted analyses were removed as per the response to clarification question A5.
Abbreviations: CGRP: calcitonin gene-related peptide; EM: episodic migraine; mAbs: monoclonal antibodies; NMA: network meta-analysis; PAS: patient access scheme; SC: subcutaneous; TA: technology appraisal; tx: treatment.

5.2 Model validation and face validity check

In the CS, the company stated that expert clinical validation was sought throughout the model development in order to validate key inputs. In addition, technical validation was undertaken by an independent modelling team. Further, extreme value testing has been performed to investigate and ensure robustness of model behaviours for wide range of input parameter values.

The EAG considers that the company's model validation and face validity checks were generally extensive and robust.

6 Additional economic analysis undertaken by the EAG

6.1 Model corrections

The External Assessment Group (EAG) identified one error in the model. As explained in Section 4.2.8, the most recent life tables uploaded to the Office for National Statistics (ONS) website (2021) do not appear to match the table in the company submitted model. As such, the EAG has updated the life tables to match the latest ONS release. This was the only correction applied to the model. Corrected vs original model results for episodic migraine (EM) are shown in Table 58 and chronic migraine (CM) is shown in Table 59.

Table 58. Company's revised deterministic base case results (EM)

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)	Inc. NHB (£20,000/ QALY WTP threshold)	Inc. NHB (£30,000/ QALY WTP threshold)
Original company base case							
Atogepant 60mg once daily	[redacted]	[redacted]	–	–	–	–	–
Galcanezumab 120mg once monthly	33,647	13.69	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140mg once monthly	28,260	13.68	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 225mg once monthly	31,394	13.74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 675mg once every three months	32,980	13.75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated company base case							
Atogepant 60mg once daily	[redacted]	[redacted]	–	–	–	–	–
Galcanezumab 120mg once monthly	£33,954	13.92	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140mg once monthly	£26,805	13.91	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 225mg once monthly	£30,233	13.97	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 675mg once every three months	£31,554	13.99	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*SW quadrant ICER (atogepant is cheaper and less effective than the comparator)

Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

Table 59. Company's revised deterministic base case results (CM)

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)	Inc. NHB (£20,000/ QALY WTP threshold)	Inc. NHB (£30,000/ QALY WTP threshold)
Original company base case							
Atogepant 60mg once daily	[redacted]	[redacted]	–	–	–	–	–
Galcanezumab 120mg once monthly	£47,530	10.87	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140mg once monthly	£39,510	10.87	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 225mg once monthly	£40,993	10.86	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 675mg once every three months	£41,220	10.86	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BoNT/A	£34,107	10.743	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated company base case							
Atogepant 60mg once daily	[redacted]	[redacted]	–	–	–	–	–
Galcanezumab 120mg once monthly	£47,428	10.83	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140mg once monthly	£39,409	10.84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 225mg once monthly	£40,892	10.83	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 675mg once every three months	£41,119	10.82	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BoNT/A	£34,007	10.712	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*SW quadrant ICER (atogepant is cheaper and less effective than the comparator)

[redacted]

Abbreviations: BoNT/A, botulinum toxin type A; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

6.2 EAG scenario analysis

In section 4 of this report, the EAG identified changes to the model that would be preferred or warrant further exploration. These scenarios were each explored individually and included:

1. Removal of monitoring costs 4.2.10.4;
2. Removal of injection related disutility 4.2.7.1;
3. Alternate long-term discontinuation source from TA659 (0.44%) 4.2.6.3;
4. 12-month waning post disc treatment 4.2.4.1;
5. Updated National Health and Wellness Survey (NHWS) resource use values 4.2.10.4;
6. No monthly migraine day (MMD) reduction difference in responders between treatments 4.2.6.4;
7. Responder MMD restricted to 0, EM only 4.2.6.4;
8. 5% of patients require assistance in administering subcutaneous (SC) injection
9. 15% of patients require assistance in administering SC injection
10. Updates to the network meta-analyses (NMAs) - Using modified intention to treat (mITT) population for EM, addition of rimegepant and eptinezumab, alternate use of random effects/fixed effects (RE/FE) and adjusted/unadjusted where justified 4.2.6.4;
11. Assumptions to match TA906 (combination of scenario 1, 2, 4, 6, 7 and 10).

Results for these scenarios are shown in Table 60 for EM and Table 61 for CM.

Table 60. Results of the EAG's scenario analyses (episodic migraine)

Results per patient	Epti (7)	Rim (6)	Ere (5)	Gal (4)	Fre (3)	Fre (2)	Ato (1)	Incremental value					
								(1-7)	(1-6)	(1-5)	(1-4)	(1-3)	(1-2)
Company corrected base case													
Total costs	NA	NA	£28,183	£33,571	£32,904	£31,318	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	NA	13.64	13.65	13.71	13.70	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Removal of monitoring costs													
Total costs	NA	NA	£27,393	£32,739	£31,771	£30,280	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	NA	13.64	13.65	13.71	13.70	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Removal of injection related disutility													
Total costs	NA	NA	£28,183	£33,571	£32,904	£31,318	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	NA	13.65	13.66	13.72	13.71	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
12-month waning post-discontinuation in line with rimegepant submission													
Total costs	NA	NA	£28,147	£33,509	£32,832	£31,247	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	NA	13.64	13.67	13.72	13.71	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]

ICER (£/QALY)								NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Health care resource use utilising updated NHWS from eptinezumab submission													
Total costs	NA	NA	£13,162	£20,357	£18,063	£16,715	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	NA	13.91	13.92	13.99	13.97	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
No MMD reduction difference for responders between treatments													
Total costs	NA	NA	£26,742	£33,954	£31,725	£30,358	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	NA	13.91	13.92	13.97	13.96	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Responder MMD restricted to 0													
Total costs	NA	NA	£26,805	£33,777	£31,551	£30,068	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	NA	13.91	13.93	13.99	13.98	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
5% of patients require assistance in administering subcutaneous (SC) injection													
Total costs	NA	NA	£26,792	£33,940	£31,547	£30,214	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	NA	13.91	13.92	13.99	13.97	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
15% of patients require assistance in administering subcutaneous (SC) injection													

Total costs	NA	NA	£26,817	£33,967	£31,561	£30,252	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	NA	13.91	13.92	13.99	13.97	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Updates to the NMA - Using MITT population for EM, addition of rimegepant and eptinezumab, alternate use of RE/FE and adjusted/unadjusted where justified.													
Total costs	£30,439	£24,202	£28,401	£36,709	£29,480	£29,114	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	13.94	13.94	13.94	13.94	13.95	13.95	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assumptions to match TA906													
Total costs	£29,198	£23,178	£27,250	£35,515	£28,380	£28,003	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	13.97	13.96	13.97	13.97	13.97	13.97	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* SW quadrant ICER (atogepant is cheaper and less effective than the comparator)

Abbreviations: BoT, botulinum toxin type A, Epti, eptinezumab; Ere, erenumab; Fre, fremanezumab; Gal, galcanezumab; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; Rim, rimegepant

Table 61. Results of the EAG's scenario analyses (chronic migraine)

Results per patient	Epti (7)	Bot (6)	Ere (5)	Gal (4)	Fre (3)	Fre (2)	Ato (1)	Incremental value					
								(1-7)	(1-6)	(1-5)	(1-4)	(1-3)	(1-2)
Company corrected base case													

Total costs	NA	£34,007	£39,409	£47,428	£41,119	£40,892	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	10.71	10.84	10.83	10.82	10.83	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)									[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Removal of monitoring costs													
Total costs	NA	£34,007	£38,228	£46,294	£39,902	£39,658	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	10.71	10.84	10.83	10.82	10.83	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Removal of injection related disutility													
Total costs	NA	£34,007	£39,409	£47,428	£41,119	£40,892	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	10.82	10.85	10.85	10.84	10.85	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12-month waning post-discontinuation in line with rimegepant submission													
Total costs	NA	£33,943	£39,335	£47,351	£41,058	£40,829	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	10.73	10.86	10.86	10.85	10.85	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health care resource use utilising updated NHWS from eptinezumab submission													
Total costs	NA	£14,976	£20,429	£28,462	£22,064	£21,850	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	10.71	10.84	10.83	10.82	10.83	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER (£/QALY)								NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No MMD reduction difference between treatments													
Total costs	NA	£34,016	£39,461	£47,492	£41,130	£40,932	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	10.71	10.83	10.82	10.82	10.82	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5% of patients require assistance in administering subcutaneous (SC) injection													
Total costs	NA	£34,007	£39,389	£47,410	£41,113	£40,872	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	10.71	10.84	10.83	10.82	10.83	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15% of patients require assistance in administering subcutaneous (SC) injection													
Total costs	NA	£34,007	£39,430	£47,446	£41,125	£40,913	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	10.71	10.84	10.83	10.82	10.83	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updates to the NMA - Using MITT population for EM, addition of rimegepant and eptinezumab, alternate use of RE/FE and adjusted/unadjusted where justified.													
Total costs	£41,837	£34,390	£39,778	£46,697	£41,646	£41,244	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	10.82	10.72	10.83	10.80	10.80	10.80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assumptions to match TA906													

Total costs	£40,681	£34,396	£38,514	£45,461	£40,239	£39,867	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	10.84	10.85	10.87	10.85	10.86	10.86	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* SW quadrant ICER (atogepant is cheaper and less effective than the comparator)

Abbreviations: BoT, botulinum toxin type A, Epti, eptinezumab; Ere, erenumab; Fre, fremanezumab; Gal, galcanezumab; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; Rim, rimegepant

6.3 EAG preferred assumptions

The EAG's preferred assumptions are listed in the bullet points below. Table 62 and Table 63 provides cumulative impact these assumptions have on the incremental cost-effectiveness ratio (ICER) for episodic migraine. The preferred assumptions are:

- Removal of monitoring costs 4.2.10.4;
- Removal of injection related disutility 4.2.7.1;
- Alternate long-term discontinuation source from TA659 (0.44%) 4.2.6.3;
- Responder MMD restricted to 0 (only impacts EM), 4.2.6.4;
- Acute medication costs updated, 4.2.10.4;
- Updates to the NMA - Using mITT population for EM, addition of rimegepant and eptinezumab, alternate use of RE/FE and adjusted/unadjusted where justified 4.2.6.4.

Table 62. Results of the EAG's cumulative preferred assumptions (episodic migraine)

Results per patient	Epti (7)	Rim (6)	Ere (5)	Gal (4)	Fre (3)	Fre (2)	Ato (1)	Incremental value					
								(1-7)	(1-6)	(1-5)	(1-4)	(1-3)	(2-2)
Company corrected base case													
Total costs	NA	NA	£28,183	£33,571	£32,904	£31,318	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	NA	13.64	13.65	13.71	13.70	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Removal of monitoring costs													
Total costs	NA	NA	£27,393	£32,739	£31,771	£30,280	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	NA	13.64	13.65	13.71	13.70	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Removal of injection site disutility													
Total costs	NA	NA	£27,393	£32,739	£31,771	£30,280	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	NA	13.65	13.66	13.72	13.71	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Alternate LT disc source													

Total costs	NA	NA	£37,008	£57,481	£57,005	£51,125	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	NA	13.84	13.93	14.23	14.16	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Responder MMD restricted to 0													
Total costs	NA	NA	£37,008	£56,878	£57,005	£51,125	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	NA	13.84	13.95	14.23	14.16	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Updated acute medication costs													
Total costs	NA	NA	£36,808	£56,678	£56,822	£50,939	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	NA	13.84	13.95	14.23	14.16	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Updates to the NMA - Using MITT population for EM, addition of rimegepant and eptinezumab, alternate use of RE/FE and adjusted/unadjusted where justified.													
Total costs	£55,233	£30,790	£48,222	£83,849	£50,471	£49,737	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	14.40	14.35	14.46	14.45	14.50	14.52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*SW quadrant ICER (atogepant is cheaper and less effective than the comparator)

Abbreviations: BoT, botulinum toxin type A, Epti, eptinezumab; Ere, erenumab; Fre, fremanezumab; Gal, galcanezumab; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; Rim, rimegepant

Table 63. Results of the EAG's cumulative preferred assumptions (chronic migraine)

Results per patient	Epti (7)	Bot (6)	Ere (5)	Gal (4)	Fre (3)	Fre (2)	Ato (1)	Incremental value					
								(1-7)	(1-6)	(1-5)	(1-4)	(1-3)	(2-2)
Company corrected base case													
Total costs	NA	£34,007	£39,409	£47,428	£41,119	£40,892	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	10.71	10.84	10.83	10.82	10.83	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]†	[redacted]
ICER (£/QALY)								NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Removal of monitoring costs													
Total costs	NA	£34,007	£38,228	£46,294	£39,902	£39,658	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	10.71	10.84	10.83	10.82	10.83	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]†	[redacted]
ICER (£/QALY)								NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Removal of injection site disutility													
Total costs	NA	£34,007	£38,228	£46,294	£39,902	£39,658	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	10.82	10.85	10.85	10.84	10.85	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Alternate LT discontinuation source													
Total costs	NA	£41,681	£63,119	£97,385	£68,855	£69,467	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	11.47	11.64	11.62	11.58	11.61	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated acute medication costs													
Total costs	NA	£41,361	£62,818	£97,087	£68,546	£69,161	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	11.47	11.64	11.62	11.58	11.61	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updates to the NMA-Using MITT population for EM, addition of rimegepant and eptinezumab, alternate use of RE/FE and adjusted/unadjusted where justified.													
Total costs	£72,104	£43,366	£64,621	£93,493	£71,092	£70,872	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	11.53	11.57	11.59	11.45	11.46	11.49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*SW quadrant ICER (atogepant is cheaper and less effective than the comparator)

[redacted]Abbreviations: BoT, botulinum toxin type A, Epti, eptinezumab; Ere, erenumab; Fre, fremanezumab; Gal, galcanezumab; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; Rim, rimegepant

6.4 Conclusions of the cost effectiveness sections

As stated in section 4.2.10 fremanezumab, erenumab, galcanezumab, eptinezumab and BoNT/A all have confidential prices that have not been used in the analysis. Conclusions on comparisons to these treatments may differ when these alternate prices are applied. Rimegepant is the only comparator used which does not have a confidential price, therefore conclusions on cost-effectiveness of atogepant versus rimegepant will remain unchanged.

Overall, in the company's base case analysis, atogepant is significantly less expensive and approximately as effective as mAb comparators, leading to south-west quadrant ICERs of around [redacted] per quality-adjusted life year (QALY) for the next best mAb comparator in EM and around [redacted] per QALY in CM. BoNT/A was the only treatment that appeared to be less expensive than atogepant but atogepant could still be considered to be cost-effective with a North-East quadrant ICER of [redacted].

However, the inclusion of rimegepant by the EAG has shown it to be a critical comparator for atogepant in terms of cost-effectiveness. Atogepant could be considered cost-effective versus rimegepant at a willingness-to-pay-threshold (WTP) threshold of £30,000 but not at a cost-effectiveness threshold of £20,000, since rimegepant is less costly and less effective using the company base case for scenario analysis (EM only). In addition, the cumulative impact of EAG preferences has resulted in BoNT/A becoming a more cost-effective treatment for the treatment of CM, with a south-west quadrant ICER of [redacted]. However, given the small incremental cost and QALYs involved, and the large standard errors in the effectiveness derived from the NMA, this result comes with significant uncertainty. It should also be noted that the EAG's clinical experts have stated that BoNT/A is currently being used less frequently in favour of easier to administer treatments, although this may be just an issue of availability of services to provide BoNT/A.

The EAG considers the model structure and modelling assumptions to be generally appropriate and match other migraine prevention models submitted for appraisal by the National Institute for Health and Care Excellence (NICE). The EAG maintains that rimegepant and eptinezumab are relevant comparators currently approved by NICE and so should be included in analysis going forward.

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8 Appendices

8.1 Meta-analyses of atogepant RCTs in episodic migraine

In the company submission for episodic migraine (EM), the company focused on the subgroup from ELEVATE with ≥3 prior oral preventive treatment failures (3+ TF) given this is most aligned with the decision problem and it was stratified for at randomisation in this randomised controlled trial (RCT). The EAG considers this to be reasonable but, given the External Assessment Group (EAG)'s preference for network meta-analysis (NMAs) within the EM population is the overall migraine population analyses (see Section 3.4.1), the EAG presents meta-analyses of the three atogepant RCTs in EM here, including the overall modified intention to treat (mITT) populations from each (ELEVATE, ADVANCE and CGP-MD-01).

Random effects analyses have been used for all analyses, as indicated in the Forest plots below. This is because there was reason to suspect clinical heterogeneity across the studies given ELEVATE differs to ADVANCE and CGP-MD-01 in that it is specific to patients with EM and 2-4 prior treatment failures. This assumption appears to be supported by meta-analysed results for most outcomes based on statistically significant heterogeneity and or high (>60) I^2 values, or a notable difference in the direction of the point estimates, but results for change from baseline (CFB) in the emotional function subdomain of the migraine-specific quality of life questionnaire (MSQ-EF) are not supportive of this. As discussed in Section 3.3, the three RCTs are [redacted] for atogepant based on point estimates (apart from discontinuation and treatment-emergent adverse events [TEAEs]), but the results from ADVANCE and/or CGP-MD-01 indicate treatment differences that [redacted] (and for CGP-MD-01 are often [redacted]). Pooled results suggest [redacted] benefits for atogepant 60 mg once daily vs placebo for all outcomes (apart from discontinuation and TEAEs where rates are [redacted] for atogepant but [redacted]), although these are [redacted] compared with when the ELEVATE mITT population is considered alone.

Figure 12. CFB in MMD – meta-analysis of three EM RCTs

Abbreviations: atog, atogepant 60 mg; CFB, change from baseline; CI, confidence interval; EM, episodic migraine; IV, inverse variance; MMD, monthly migraine days; RCT, randomised controlled trial; SD, standard deviation.

Figure 13. ≥50% reduction in MMDs from baseline – meta-analysis of three EM RCTs

Abbreviations: atog, atogepant 60 mg; CI, confidence interval; EM, episodic migraine; M-H, Mantel–Haenszel; MMD, monthly migraine days; RCT, randomised controlled trial.

Figure 14. CFB in acute MUDs – meta-analysis of three EM RCTs

Abbreviations: atog, atogepant 60 mg; CFB, change from baseline; CI, confidence interval; EM, episodic migraine; IV, inverse variance; MUD, medication use days; RCT, randomised controlled trial; SD, standard deviation.

Figure 15. All-cause discontinuation – meta-analysis of three EM RCTs

Abbreviations: atog, atogepant 60 mg; CI, confidence interval; EM, episodic migraine; M-H, Mantel–Haenszel; RCT, randomised controlled trial.

Figure 16. CFB in MSQ-RFR – meta-analysis of three EM RCTs

Abbreviations: atog, atogepant 60 mg; CFB, change from baseline; CI, confidence interval; EM, episodic migraine; IV, inverse variance; MSQ-RFR, role function-restrictive subdomain of migraine-specific quality of life questionnaire; RCT, randomised controlled trial; SD, standard deviation.

Figure 17. CFB in MSQ-RFP – meta-analysis of three EM RCTs

Abbreviations: atog, atogepant 60 mg; CFB, change from baseline; CI, confidence interval; EM, episodic migraine; IV, inverse variance; MSQ-RFR, role function-preventive subdomain of migraine-specific quality of life questionnaire; RCT, randomised controlled trial; SD, standard deviation.

Figure 18. CFB in MSQ-EF – meta-analysis of three EM RCTs

Abbreviations: atog, atogepant 60 mg; CFB, change from baseline; CI, confidence interval; EM, episodic migraine; IV, inverse variance; MSQ-RFR, emotional function subdomain of migraine-specific quality of life questionnaire; RCT, randomised controlled trial; SD, standard deviation.

Figure 19. CFB in HIT-6 – meta-analysis of three EM RCTs

Abbreviations: atog, atogepant 60 mg; CFB, change from baseline; CI, confidence interval; EM, episodic migraine; HIT-6, Headache Impact Test-6; IV, inverse variance; RCT, randomised controlled trial; SD, standard deviation.

Figure 20. TEAEs – meta-analysis of three EM RCTs

Abbreviations: atog, atogepant 60 mg; CI, confidence interval; EM, episodic migraine; M-H, Mantel–Haenszel; RCT, randomised controlled trial; TEAEs, treatment-emergent adverse events.

8.2 Additional EAG NMA results

8.2.1 Episodic migraine – MMD-related outcomes in the overall migraine population

Results from the unadjusted random effects(RE) NMAs within the overall migraine population performed by the EAG for these outcomes are presented below in Table 64. The EAG notes that

these are very similar to the results presented by the company in Table 27 of the company submission (CS) for the RE unadjusted analyses in the overall migraine population for EM.

Table 64. Relative effect of atogepant 60 mg once daily vs comparators in EM for MMD outcomes – RE unadjusted analyses

Atogepant 60 mg once daily vs	RE unadjusted NMA results - EAG
CFB in MMD, MD (95% CrI)	
Erenumab 140 mg once monthly	[redacted]
Fremanezumab 225 mg once monthly	[redacted]
Fremanezumab 675 mg once every three months	[redacted]
Galcanezumab 120 mg once monthly	[redacted]
Rimegepant 75 mg every other day	[redacted]
Eptinezumab 100 mg once every three months	[redacted]
Eptinezumab 300 mg once every three months	[redacted]
≥50% reduction in MMDs, OR (95% CrI)	
Erenumab 140 mg once monthly	[redacted]
Fremanezumab 225 mg once monthly	[redacted]
Fremanezumab 675 mg once every three months	[redacted]
Galcanezumab 120 mg once monthly	[redacted]
Rimegepant 75 mg every other day	[redacted]
Eptinezumab 100 mg once every three months	[redacted]
Eptinezumab 300 mg once every three months	[redacted]
CFB in acute MUDs, MD (95% CrI)	
Erenumab 140 mg once monthly	[redacted]
Fremanezumab 225 mg once monthly	[redacted]
Fremanezumab 675 mg once every three months	[redacted]
Galcanezumab 120 mg once monthly	[redacted]
Rimegepant 75 mg every other day*	-

Eptinezumab 100 mg once every three months	[redacted]
Eptinezumab 300 mg once every three months	[redacted]

*rimegepant could not be included in the NMA for CFB in acute MUDs when rerun by the EAG given this outcome was not reported for the only available rimegepant study.

Outputs from the NMAs are means for the CFB outcome and median OR for the proportion with ≥50% reduction in MMD from baseline. Bold values indicate statistically significant differences.

Abbreviations: CFB, change from baseline; CrI, credible interval; EAG, External Assessment Group; EM, episodic migraine; MD, mean difference; MMD, monthly migraine days; MUDs, medication use days; NMA, network meta-analysis; OR, odds ratio; RE, random effects.

Some minor edits to NMA input data were made by the EAG for these outcomes, as outlined below in Table 65, but the EAG considers these have not had a large impact on the results of the NMAs given how similar the results are to the original results presented by the company. The most notable difference is for the comparison against fremanezumab 225 mg once monthly CFB in acute medication use days (MUDs), where the point estimate in the EAG-corrected NMAs is slightly smaller than that in Table 27 of the CS appendices.

Table 65. EAG corrections to NMA input data – MMD-related outcomes in EM overall migraine analyses

Study (arm; value corrected)	Value in company analysis	Correction made in EAG analysis
CFB in MMDs		
ADVANCE (placebo, mean [SE])	-2.50 (0.20)	-2.48 (0.21)
ADVANCE (atogepant 60 mg, SE)	0.20	0.206
ELEVATE (placebo, SE)	[redacted]	[redacted]
ELEVATE (atogepant 60 mg, SE)	[redacted]	[redacted]
≥50% reduction in MMDs		
EMPOwER (placebo, number of events)	149/330	148/330
CFB in acute MUDs		
CGP-MD-01 (atogepant 60 mg, SE)	[redacted]	[redacted]

ADVANCE (placebo, mean [SE])	-2.40 (0.2)	-2.35 (0.184)
ADVANCE (atogepant 60 mg, SE)	-3.90 (0.2)	-3.85 (0.180)
ELEVATE (placebo, SE)	[redacted]	[redacted]
ELEVATE (atogepant 60 mg, SE)	[redacted]	[redacted]
HALO EM (placebo, SE)	0.21	0.22
HALO EM (fremanezumab 225 mg, SE)	0.64	0.22

Abbreviations: CFB, change from baseline; EAG, External Assessment Group; EM, episodic migraine; MMD, monthly migraine days; MUDs, medication use days; NMA, network meta-analysis; SE, standard error.

8.2.2 *Chronic migraine – MMD-related outcomes in the overall migraine population*

Results from the unadjusted RE NMAs within the overall migraine population performed by the EAG for these outcomes in chronic migraine (CM) are presented below in Table 66. The EAG notes that these are very similar to the results presented by the company in Tables 30 and 116 of the CS appendices for the RE unadjusted analyses in the overall migraine population for CM.

Table 66. Relative effect of atogepant 60 mg once daily vs comparators in CM for MMD outcomes – RE unadjusted analyses

Atogepant 60 mg once daily vs	RE unadjusted NMA results - EAG
CFB in MMD, MD (95% CrI)	
Erenumab 140 mg once monthly	[redacted]
Fremanezumab 225 mg once monthly	[redacted]
Fremanezumab 675 mg once every three months	[redacted]
Galcanezumab 120 mg once monthly	[redacted]
BoNT/A	[redacted]
Eptinezumab 100 mg once every three months	[redacted]
Eptinezumab 300 mg once every three months	[redacted]

≥50% reduction in MMDs, OR (95% CrI)	
Erenumab 140 mg once monthly	[redacted]
Fremanezumab 225 mg once monthly	[redacted]
Fremanezumab 675 mg once every three months	[redacted]
Galcanezumab 120 mg once monthly	[redacted]
BoNT/A	[redacted]
Eptinezumab 100 mg once every three months	[redacted]
Eptinezumab 300 mg once every three months	[redacted]

Outputs from the NMAs are means for the CFB outcome and median OR for the proportion with ≥50% reduction in MMD from baseline. Bold values indicate statistically significant differences.

Abbreviations: BoNT/A, botulinum toxin type A; CFB, change from baseline; CM, chronic migraine; CrI, credible interval; EAG, External Assessment Group; MD, mean difference; MMD, monthly migraine days; NMA, network meta-analysis; OR, odds ratio; RE, random effects.

Some minor edits to NMA input data were made by the EAG for these outcomes, as outlined below in Table 67 below.

Table 67. EAG corrections to NMA input data – MMD-related outcomes in CM overall migraine analyses

Study (arm; value corrected)	Value in company analysis	Correction made in EAG analysis
CFB in MMDs		
N/A		
≥30% reduction in MMDs		
FOCUS (placebo, number of events)	32/167	27/167
FOCUS (fremanezumab 225 mg, number of events)	93/173	91/173
≥50% reduction in MMDs		
HALO CM data was initially said not to be available for this outcome but the EAG identified this and included it in the NMA. Included data were 67/371, 153/375 and 144/366 for placebo, fremanezumab 225 mg and fremanezumab 675 mg groups, respectively.		
CFB in acute MUDs		
CONQUER (galcanezumab 120 mg, mean difference vs placebo [SE])	-4.0 (0.714286)	-3.9 (0.73979592)

Abbreviations: CFB, change from baseline; CM, chronic migraine; EAG, External Assessment Group; NMA, network meta-analysis; MMD, monthly migraine days; MUDs, medication use days; N/A, not applicable; SE, standard error.

8.2.3 *Episodic and chronic migraine – discontinuation*

Alternative RE results from the EAG's analyses for the discontinuation outcome in each population (RE unadjusted for EM, RE adjusted for CM) are presented in Table 68 below. The EAG's results for the RE unadjusted discontinuation NMA in EM are very similar to those preferred by the company in Section 3.4.3.2. The adjusted RE results for CM are very similar to those obtained by the EAG (and company) for the RE unadjusted analysis. The EAG did not make any changes to data analysed for the discontinuation NMAs, other than to add eptinezumab and rimegepant as comparators where applicable.

Table 68. Relative effect of atogepant 60 mg once daily vs comparators in EM and CM for discontinuation (cloglog analyses) – alternative analyses

Atogepant 60 mg once daily vs	Alternative analysis (RE unadjusted for EM, RE adjusted for CM)
EM, HR (95% CrIs)	
Erenumab 140 mg once monthly	[redacted]
Fremanezumab 225 mg once monthly	[redacted]
Fremanezumab 675 mg once every three months	[redacted]
Galcanezumab 120 mg once monthly	[redacted]
Rimegepant 75 mg every other day	[redacted]
Eptinezumab 100 mg once every three months	[redacted]
Eptinezumab 300 mg once every three months	[redacted]
CM, HR (95% CrIs)	
Erenumab 140 mg once monthly	[redacted]
Fremanezumab 225 mg once monthly	[redacted]
Fremanezumab 675 mg once every three months	[redacted]
Galcanezumab 120 mg once monthly	[redacted]
BoNT/A	[redacted]
Eptinezumab 100 mg once every three months	[redacted]
Eptinezumab 300 mg once every three months	[redacted]

Outputs from these NMAs are mean HRs. Bold values indicate statistically significant differences.

Abbreviations: BoNT/A, botulinum toxin type A; CM, chronic migraine; CrI, credible interval; EM, episodic migraine; HR, hazard ratio; RE, random effects.

8.3 Company's quality assessment of comparator studies

Table 69. Company's risk of bias assessment of comparator studies included in the NMAs – adapted from Tables 33 and 34 of the CS appendices

Study name Author (reference)	Was randomisation adequate?	Was allocation adequately concealed?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there unexpected imbalances in dropouts between groups?	Were any outcomes measured but not reported?	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
EM							
PERSIST (Hu 2022)	Yes	Yes	Yes	Yes	No	No	Yes
Sakai 2021	Yes	Yes	Yes	Yes	No	No	Yes
EMPOwER (Wang 2021)	Yes	Yes	Yes	Yes	No	No	Yes
BHV3000-305 (Croop 2021)	Yes	Yes	Yes	Yes	No	No	Yes
Sakai 2020	Yes	Yes	Yes	Yes	No	No	Yes
Sakai 2019	Yes	Yes	Yes	Yes	No	No	Yes
PROMISE-1 (Ashina 2020)	Yes	Unclear	Yes	Yes	No	No	Yes
CONQUER (Mulleners 2020)	Yes	Yes	Yes	Yes	No	No	Yes

FOCUS (Ferrari 2019)	Yes	Yes	Yes	Yes	No	No	Yes
LIBERTY (Reuter 2018)	Yes	Yes	Yes	Yes	No	No	Yes
HALO EM (Dodick 2018)	Yes	Yes	Yes	Yes	No	No	Yes
EVOLVE-2 (Skljarevski 2018)	Yes	Yes	Yes	Yes	No	No	Yes
EVOLVE-1 (Stauffer 2018)	Yes	Yes	Yes	Yes	No	No	No
STRIVE (Goadsby 2017)	Yes	Yes	Yes	Yes	No	No	Yes
Bigal 2015	Yes	Yes	Yes	Yes	No	No	Yes
CM							
Sakai 2021	Yes	Yes	Yes	Yes	No	No	Yes
PROMISE-2 (Lipton 2020)	Yes	Yes	Yes	Yes	No	No	Yes
CONQUER (Mulleners 2020)	Yes	Yes	Yes	Yes	No	No	Yes
Dodick 2019	Yes	Yes	Yes	Yes	No	No	Yes
FOCUS (Ferrari 2019)	Yes	Yes	Yes	Yes	No	No	Yes
REGAIN (Detke 2018)	Yes	Yes	Yes	Yes	No	No	Yes
HALO-CM (Silberstein 2017)	Yes	Yes	Yes	Yes	No	No	Yes
Tepper 2017	Yes	Yes	Yes	Yes	No	No	Yes
Bigal 2015	Yes	Yes	Yes	Yes	No	No	Yes

PREEMPT-1 (Aurora 2010)	Yes	Yes	Yes	Yes	No	No	Yes
PREEMPT-2 (Diener 2010)	Yes	Yes	Yes	Yes	No	No	Yes

Abbreviations: CM, chronic migraine; CS, company submission; EM, episodic migraine; ITT, intention to treat; NMA, network meta-analysis.

8.4 Data extraction tables for rimegepant and eptinezumab

The data extracted and included in relevant NMAs for rimegepant and eptinezumab comparators are presented below. A full systematic literature review (SLR) was not performed by the EAG to identify relevant rimegepant and eptinezumab studies given time constraints, but the EAG reviewed the relevant NICE appraisals for included studies (TA906 and TA871) and also the excluded studies lists provided within the CS and in response to clarification question A10, as the company's SLR covered rimegepant and eptinezumab. To identify secondary publications for each study, the EAG reviewed ClinicalTrials.gov using the clinical trial number. In some cases, data for an outcome was identified and extracted from ClinicalTrials.gov.

8.4.1 *Episodic migraine*

Table 70. Data extraction table for rimegepant and eptinezumab in EM – efficacy outcomes

Study name	Treatments	Time-point (weeks)	CFB in MMDs		CFB in MUDs		≥50% reduction in MMDs	
			N	Mean (SE)	N	Mean (SE)	n	N
PROMISE-1 (eptinezumab once every three months)[53]	Placebo	1-12	222	-3.2 (0.21)	222	-0.4 (0.09)	83 (37.4%)	222
	Eptinezumab 100 mg		221	-3.9 (0.21); difference vs placebo: -0.69 (-1.25 to -0.12)	221	-0.9 (0.13)	110 (49.8%)	221
	Eptinezumab 300 mg		222	-4.3 (0.20); difference vs placebo: -1.11 (-1.68 to -0.54)	222	-0.8 (0.12)	125 (56.3%)	222
BHV3000-305 (rimegepant every other day)[17]	Placebo	1-12 and 9-12 (1-12 used in NMA)	347	1-12: -2.7 (0.20); 9-12: -3.5 (0.26)	NR		144 (41.0%)	347
	Rimegepant 75 mg		348	1-12: -3.6 (0.20); 9-12: -4.3 (0.23)			171 (49.0%)	348

Abbreviations: CFB, change from baseline; EM, episodic migraine; MMD, monthly migraine days; MUDs, medication use days; NMA, network meta-analysis; NR, not reported; SE, standard error.

Table 71. Data extraction table for rimegepant and eptinezumab in EM – HRQoL outcomes

Study name	Treatments	Time-point (weeks)	CFB in MSQ-RFR		CFB in MSQ-RFP		CFB in MSQ-EF		CFB in HIT-6	
			N	Difference (SE) vs placebo	N	Difference (SE) vs placebo	N	Difference (SE) vs placebo	N	Difference (SE) vs placebo
	Placebo	N/A	NR		NR		NR		NR	

PROMISE-1 (eptinezumab once every three months)[53]	Eptinezumab 100 mg						
	Eptinezumab 300 mg						
BHV3000-305 (rimegepant every other day)[17]	Placebo	12 weeks	266	-	NR	NR	NR
	Rimegepant 75 mg		269	3.5 (0.2 to 6.7, SE 1.66), p=0.036			

Abbreviations: CFB, change from baseline; EM, episodic migraine; HIT-6, Headache Impact Test-6; HRQoL, health-related quality of life; MSQ, migraine-specific quality of life questionnaire; MSQ-EF, emotional function subdomain of MSQ; MSQ-RFP, role function-preventive subdomain of MSQ; MSQ-RFR, role function-restrictive subdomain of MSQ; N/A, not applicable; NR, not reported; SE, standard error.

Table 72. Data extraction table for rimegepant and eptinezumab in EM – discontinuation and TEAEs

Study name	Treatments	Time-point (weeks)	All-cause discontinuation	TEAEs
PROMISE-1 (eptinezumab once every three months)[53]	Placebo	12 weeks	20/225	132/222
	Eptinezumab 100 mg		13/225	141/223
	Eptinezumab 300 mg		11/224	129/224
BHV3000-305 (rimegepant every other day)[17]	Placebo	12 weeks	64/374	133/371
	Rimegepant 75 mg		57/373	133/370

Abbreviations: EM, episodic migraine; TEAEs, treatment-emergent adverse events.

8.4.2 *Chronic migraine*

Table 73. Data extraction table for eptinezumab in CM – efficacy outcomes

Study name	Treatments	Time-point (weeks)	CFB in MMDs		CFB in MUDs		≥30% reduction in MMDs		≥50% reduction in MMDs	
			N	Mean (SE)	N	Mean (SE)	n	N	n	N
PROMISE-2 (eptinezumab once every three months)[57]	Placebo	1-12	366	-5.6 (NR)	366	-1.9 (0.22)	NR		144 (39.3%)	366
	Eptinezumab 100 mg		356	-7.7 (NR); difference vs placebo: -2.0 (-2.9 to -1.2, SE 0.43)	356	-3.3 (0.26); difference vs placebo: -1.2 (-1.7 to -0.6, SE 0.28)			205 (57.6%)	356
	Eptinezumab 300 mg		350	-8.2 (NR); difference vs placebo: -2.6 (-3.4 to -1.7, SE 0.43)	350	-3.5 (0.25); difference vs placebo: -1.4 (-1.9 to -0.9, SE 0.26)			215 (61.4%)	350
Dodick 2019 (NCT02275117; eptinezumab once every three months)[58]	Placebo	1-12	116	-5.6 (0.61)	NR		NR		47 (40.5%)	116
	Eptinezumab 100 mg		118	-7.7 (0.64)					65 (55.1%)	118
	Eptinezumab 300 mg		114	-8.2 (0.66)					65 (57.0%)	114

Abbreviations: CFB, change from baseline; CM, chronic migraine; MMD, monthly migraine days; MUDs, medication use days; NR, not reported; SE, standard error.

Table 74. Data extraction table for eptinezumab in CM – HRQoL outcomes

Study name	Treatments	Time-point (weeks)	CFB in MSQ-RFR		CFB in MSQ-RFP		CFB in MSQ-EF		CFB in HIT-6	
			N	Difference (SE) vs placebo	N	Difference (SE) vs placebo	N	Difference (SE) vs placebo	N	Difference (SE) vs placebo
PROMISE-2 (eptinezumab once every three months)[57]	Placebo	12 weeks	NR		NR		NR		366	-4.6 (NR) for arm
	Eptinezumab 100 mg								356	-1.7 (-2.8 to -0.7, SE 0.54); -6.9 (NR) for arm
	Eptinezumab 300 mg								350	-2.9 (-3.9 to -1.8, SE 0.56); -8.6 (NR) for arm
Dodick 2019 (NCT02275117; eptinezumab once every three months)[58]	Placebo	12 weeks	NR		NR		NR		110	-5.8 (0.71) for arm
	Eptinezumab 100 mg								107	-1.1 (1.01); -6.9 (0.72) for arm
	Eptinezumab 300 mg								106	-4.2 (1.08); -10.0 (0.82) for arm

Abbreviations: CFB, change from baseline; CM, chronic migraine; HIT-6, Headache Impact Test-6; HRQoL, health-related quality of life; MSQ, migraine-specific quality of life questionnaire; MSQ-EF, emotional function subdomain of MSQ; MSQ-RFP, role function-preventive subdomain of MSQ; MSQ-RFR, role function-restrictive subdomain of MSQ; NR, not reported; SE, standard error.

Table 75. Data extraction table for eptinezumab in CM – discontinuation and TEAEs

Study name	Treatments	Time-point (weeks)	All-cause discontinuation	TEAEs
PROMISE-2 (eptinezumab once every three months)[57]	Placebo	12 weeks discontinuation; 32 weeks TEAEs	19/375	171/366
	Eptinezumab 100 mg		23/372	155/356
	Eptinezumab 300 mg		30/374	182/350

Dodick 2019 (NCT02275117; eptinezumab once every three months)[58]	Placebo	12 weeks discontinuation; 49 weeks TEAEs	4/121	68/121
	Eptinezumab 100 mg		4/122	70/122
	Eptinezumab 300 mg		2/121	77/121

Abbreviations: CM, chronic migraine; TEAEs, treatment-emergent adverse events.

Single Technology Appraisal

Atogepant for preventing migraine [ID5090]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Thursday 7 December** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Factual Inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 27 (Table 6) of the EAG report states: *"Furthermore, rimegepant, another oral treatment for prevention of migraine did not include any difference in monitoring costs, versus mAbs, in the previous submission."*	This statement should be removed.	As noted in the final appraisal determination of the NICE appraisal of rimegepant (TA906; Section 3.13), additional monitoring costs were included for CGRP mAbs to reflect the expectation that rimegepant could be monitored in primary care; monitoring was assumed to consist of a one-off starting visit and 3-month follow-up visit provided by a GP and a neurologist for rimegepant and comparators, respectively, as well as an additional referral GP visit for comparators. This statement is therefore incorrect and should be removed.[1]	In the original submission, the company excluded treatment specific monitoring costs, as stated in section 4.2.12.2.2 of the original EAG report. Following ACM1 the company added a one-off initiation and a 3-month follow-up cost for a GP (£39.23 per visit) for rimegepant and a neurologist for initiation/follow-up in the comparator mAbs (£194.24 per visit). A single GP visit referral cost was also added to the mAb treatments. The follow-up cost was a one-off cost and was not applied continuously. The ERG did not accept these costing changes as rimegepant may require referral/initial monitoring by a specialist. In the FAD following ACM2 the committee "concluded that currently it [rimegepant]

			would most likely be started by a specialist"[1] The EAG accepts that the sentence may imply no difference in monitoring was ever included. As a result of this the text has been updated to: *"Furthermore, rimegepant, another oral treatment for prevention of migraine did not include any difference in monitoring costs, versus mAbs, in the final model base case accepted by committee."*
Page 27 (Table 7) of the EAG report states: *"The EAG would require evidence from a source that used UK data, EQ-5D utility and showed a statistically significant difference in utility."*	In isolation, this statement may be subject to misinterpretation of the UK-based vignette study data that was employed as a source for the injection-related disutility values used in the model; given that it may misleadingly imply that UK-based data was not provided, EQ-5D utility is the only acceptable source of evidence, and no significant differences were identified between an oral and injectable route of administration in the provided data.	This statement mischaracterises a study used to justify the injection-related disutility used in the model and is factually incorrect. It also does not reflect available NICE guidance on the topic.	The description of the issue has been edited. The additional evidence required remains unchanged. The additional proposed amendments are not factual inaccuracies. No change required.

	For completeness, accuracy, and clarity, this statement should be revised to reflect that: 1. The study data provided is UK-based 2. While EQ-5D data are typically preferable, NICE technical support document 11 indicates that in the absence of EQ-5D data, vignette studies can be used to derive a utility value.[2] The hierarchy of preferred HRQoL methods in the NICE manual for health technology evaluation also states that vignettes can be used if EQ-5D are not appropriate;[3] Matza *et al.* (2019) makes explicit reference to this guidance,[4] and why the use of vignettes are appropriate to estimate disutility associated with route of administration, which has not been acknowledged in the EAG report: *"However, the NICE guide also acknowledges that the EQ-5D is not suitable for every situation, and other utility assessment methods may be used when the EQ-5D is not "appropriate." The current study is an example of a situation where*		

	an alternative utility assessment method seemed appropriate. Although generic instruments like the EQ-5D have some items that could possibly be affected by treatment process attributes (e.g., the EQ-5D usual activities item), none of the items specifically target attributes like route of administration. Furthermore, generic instruments cannot isolate the utility impact of a single AE because indices of overall health status would be influenced by symptoms related to the disease as well as the AE." Accordingly, prior NICE appraisals of interventions in migraine indicate that EQ-5D itself is not an appropriate instrument to estimate utilities in the treatment of patients with migraine, requiring the mapping of patient-level MSQ v2.1 data to EQ-5D-3L scores as performed in the present company submission. 3. Statistically significant utility differences were found between oral treatments and procedures that involved 31–39 injections once every three months in this study. In addition, the EAG		

	acknowledge earlier in their report that lack of statistical significance does not justify the exclusion of a clinically meaningful difference in HRQoL, with many efficacy endpoints used in the economic model not showing statistical significance between atogepant and comparators.		
Page 32 (Paragraph 4) of the EAG report states: *"The company also excludes eptinezumab and rimegepant as comparators in this appraisal given they have only recently been recommended and that it does not consider them to be part of established clinical practice yet, citing low market share in the 3+TF group."*	An additional consideration should be added here, as follows: *"The company also excludes eptinezumab and rimegepant as comparators in this appraisal given they have only recently been recommended* ***with NICE recommendations not published at the time of scoping;*** *and that it does not consider them to be part of established clinical practice yet* ***nor do they anticipate them to become established practice at the point of committee decision****, citing low market share in the 3+TF group****, which is further supported by clinical expert opinion elicited by the company.****"*	This statement is missing an important consideration outlined in Section B.1.1 of the CS.	The EAG has made the suggested changes.
Page 46 (Paragraph 2) of the EAG report states:	The statement should be amended as follows:	This statement is missing an important consideration outlined in the company	The EAG has incorporated the data from IQVIA™ into this paragraph.

"The company does not consider BoNT/A to be a relevant comparator in CM given feedback from clinical experts consulted that patients often choose mAbs due to extensive waiting lists for BoNT/A and the need to travel to clinics that administer this treatment."	*"The company does not consider BoNT/A to be a relevant comparator in CM given feedback from clinical experts consulted that patients often choose mAbs due to extensive waiting lists for BoNT/A and the need to travel to clinics that administer this treatment.* ***This is further supported by IQVIA™ in-hospital pharmacy dispensing data, as referenced by company in its response to Clarification Question B1, which indicates that between H2 2022 and H1 2023, erenumab, fremanezumab, and galcanezumab accounted for [redacted] of new (i.e. incident) fourth-line patients receiving treatment with a subcutaneous CGRP mAb or botulinum toxin type A across the UK.[5]"***	response to Clarification Question B1.	
Page 46 (Paragraph 3) of the EAG report states: *"In terms of the eptinezumab appraisal, while the EAG acknowledges that BoNT/A is not mentioned in the final guidance document,[21] it was included in the CS as can be seen from the committee papers. The EAG is unsure of the reason for this but*	The statement should be amended to include the additional context that botulinum toxin type A was not considered in the cost comparison that ultimately informed the NICE recommendation for eptinezumab.	Whilst botulinum toxin type A is included in the CS for eptinezumab, only the CGRP mAbs were considered relevant comparators in the cost comparison submission (as reported in Appendix M of the CS) that was ultimately used for decision-making. This is noted in the published recommendation for eptinezumab which states "*A*	Not a factual inaccuracy. No change required.

does not consider its omission from the final guidance document to be an adequate reason for it to be excluded from this STA, particularly given the feedback obtained from the EAG's clinical experts (see Key Issue 1 in Table 2)."		*cost comparison suggests that eptinezumab has similar costs and overall health benefits to erenumab, fremanezumab and galcanezumab*".[6]	
Page 47 (Paragraph 2) of the EAG report states: *"The company notes that eptinezumab may be reserved for patients with severe migraine attacks or those unable to self-administer mAbs subcutaneously based on clinical expert feedback as part of the eptinezumab appraisal. The EAG could not locate this statement within the eptinezumab appraisal documentation…"*	The statement should be amended as follows: *"The company notes that eptinezumab may be reserved for patients with severe migraine attacks or those unable to self-administer mAbs subcutaneously based on clinical expert feedback as part of the eptinezumab appraisal (**Section 3.2 of the final draft guidance for eptinezumab)**…."*	The company can confirm that this statement can be found in Section 3.2 of the eptinezumab final draft guidance document.[6]	The EAG has made the suggested changes.
Page 110 (Paragraph 1) of the EAG report provides three key justifications for the decision to exclude rimegepant and	The following key reason was omitted and should be added to this list *"While eptinezumab and rimegepant are recommended by NICE, these*	At the time of scoping for this appraisal, recommendations for eptinezumab and rimegepant were not	The EAG has made the suggested changes.

eptinezumab as comparators.	*recommendations had not been published at the time of scoping"*	published and this should be reflected within the report.	
Page 113 (Paragraph 1) of the EAG report states: "For patients still on treatment, response is then assessed after the 12-week trial period and defined as a ≥50% (for EM) and ≥30% (for CM) MMD reduction from baseline (see Section 4.2.6)."	The statement should be amended as follows: *"For patients still on treatment, response is then assessed after the 12-week trial period* ***(or 24-week period for BoNT/A)*** *and defined as a ≥50% (for EM) and ≥30% (for CM) MMD reduction from baseline (see Section 4.2.6)."*	Response is assessed at 24-weeks for botulinum toxin type A and the report should accurately reflect this.	The EAG has made the suggested changes.
Page 116 (Table 32) of the EAG report states that the company transition period for 'On treatment responder' health state is '0 cycles (4 weeks)'	This value should be updated to '18 cycles (72 weeks)'.	This value is incorrect as per the submitted model, however this duration does not impact the model results as start and end MMDs are unchanged.	The EAG has made the suggested changes.
Page 116 (Paragraph 5) of the EAG report states: "*Finally, an annual discount rate of 3.5% was applied to both costs and benefits, in line with the NICE reference case. In scenario analysis, an annual discount rate of 1.5% was applied.*"	This statement is incorrect and should be amended as follows: "*Finally, an annual discount rate of 3.5% was applied to both costs and benefits, in line with the NICE reference case.*"	A scenario analysis in which an annual discount rate of 1.5% was applied, was not performed in the CS.	The EAG has made the suggested changes.

Page 119 (Paragraph 2) of the EAG report states: *"To prevent clinically implausible MMD results arising from the NMA, the company added a restriction that prevented mean MMDs for any treatment falling below 1."*	This statement is incorrect and should be amended as follows: *"To prevent clinically implausible MMD results arising from the NMA, the company added a restriction that prevented mean MMDs for* ***treatment responders*** *falling below 1."*	The MMD minimum cap is only applied to treatment responders rather than for any treatment as the text implies.	The EAG has made the suggested changes.
Page 124 of the EAG report (Paragraph 6 states: *"The life years gained in all company model runs was [redacted] years."*	The statement should be revised as follows: *"The life years gained in all company model runs was [redacted] years in EM and [redacted] years in CM."*	The number of life years gained in company model runs differed between EM and CM.	The EAG has made the suggested changes.
Page 127 (Paragraph 3) of the EAG report states: *"Age-related utility decrements were included in the prevention model based on the algorithms reported in Ara and Brazier 2010."*	The statement should be revised as follows: *"Age-related utility decrements were included in the prevention model based on the latest Health Survey for England (HSE) data."*	This statement should be updated to reflect that the most recent Health Survey for England (HSE) data.	The EAG has made the suggested changes.
Page 133 of the EAG report (Table 50)	The per cycle HCRU data in Table 50 do not match those published in TA871 and should be revised to match those	The per cycle HCRU data used by the EAG in their version of the model are in	The rates published in table 42 of the committee paper are annual and have been

	presented in TA871 and used by the EAG in their version of the model.[6]	line with those detailed in the TA871 Committee Papers.[6]	adjusted to match per cycle rates. The following statement has been added: These values, adjusted to per cycle rates, are shown in **Error! Reference source not found.**.
Page 27 (Table 6) of the EAG report states: *"The company suggests monitoring costs will be lower for atogepant since prescriptions/monitoring can be provided 50:50 by specialists/GP to atogepant patients"* Page 31 (Paragraph 4) of the EAG report states: *"The company suggests that as an oral treatment, atogepant may be more likely to be prescribed by secondary care general neurologists and in primary care."*	Statements indicating that atogepant cost-savings related to primary care are dependent on a GP's ability to prescribe atogepant are not true, given that a GP may perform monitoring follow-up visits following secondary care initiation and prescribing.	The company apologise for any confusion caused and can confirm that the base case presented and the associated NHS resource savings and efficiencies are not reliant on atogepant being prescribed by a GP. Instead, the base case considers that follow-up appointments could be conducted in primary care by GPs, while treatment is initiated by either a headache specialist or a general neurologist (50:50). A scenario analysis is presented in the company submission in which atogepant is initiated in	The EAG has made the suggested changes. In TA906 the submitting company did update their base case, at ACM2, to include rimegepant initiated in primary care, with the justification that since there is no commercial arrangement for rimegepant it can be used in all settings. Not only does this not apply for atogepant (since a commercial arrangement is included), but the committee concluded that rimegepant would be initiated in secondary care due to its positioning in the treatment pathway. The committee were further advised that

Page 132 (Paragraph 4) of the EAG report states: *"In addition, the company's justification for lower monitoring costs for atogepant appears to be linked to the expectation that atogepant is likely to be prescribed in primary care."*		primary care. This is in line with the prior NICE appraisal of rimegepant (TA906),[1] and highlights the future potential of atogepant prescribing as the NHS aims to realise efficiencies within its organisation and improve access to medicines across primary and secondary care. In the base case, all SC CGRP mAbs are initiated by a headache specialist, while follow-up appointments are again conducted by a headache specialist.	rimegepant could possibly be provided by a GP, but within a shared care agreement or with advice and guidance from a specialist (indicating continued specialist involvement). In addition, it was indicated that this arrangement was subject to the GP's discretion and could be terminated leaving the patient purely in specialist care.

Typographical Errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Pages 29, 148, 149, 152, 158 of the EAG report (Tables 11, 57, 58, 59, 61) report the company's revised deterministic base case results for EM and CM while applying the footnote denoting a South West (SW) quadrant ICER inconsistently.	In line with the tables presented in the Clarification Question response (Tables 28, 31) and the EAG's own analyses, the footnote denoting a SW quadrant ICER should be correctly applied throughout the report.	Typographical error	The EAG has made the suggested changes.
Page 45 of the EAG report (Paragraph 5) states: *"Furthermore, the PROGRESS trial in CM allowed concomitant use of another preventive migraine treatment; the EAG's clinical experts note that while this is fairly uncommon, it may sometimes be done in clinical practice and can improve outcomes. The EAG notes that this was more common in the [redacted] arm ([redacted]% vs [redacted]%)."*	This statement should be revised as follows: *Furthermore, the PROGRESS trial in CM allowed concomitant use of another preventive migraine treatment; the EAG's clinical experts note that while this is fairly uncommon, it may sometimes be done in clinical practice and can improve outcomes. The EAG notes that this was more common in the [redacted] arm ([redacted]% vs [redacted]%)."*	Typographical error	The EAG has made the suggested changes. However, the EAG notes that the original values were those reported in Table 8 of the CS. It notes that the amended value appears to be for the mITT population rather than ITT and has also amended the percentage for the atogepant 60 mg arm in line with this (now [redacted]%).

Page 81 of the EAG report (Paragraph 2) states: *"As data for erenumab are not available within the 3+ TF population for CFB in acute MUDs, the company used a conversion factor (see response to CQ B5) to obtain an estimate for this comparator that could be used in the economic model (atogepant vs erenumab: median CFB [redacted]."*	The statement should be revised as follows: *"As data for erenumab are not available within the 3+ TF population for CFB in acute MUDs, the company used a conversion factor (see response to CQ B5) to obtain an estimate for this comparator that could be used in the economic model (atogepant vs erenumab: median CFB [redacted]."*	Typographical error	Not a factual inaccuracy. Table 46 of the CS is said to present the results of each mAb vs atogepant. On page 81, the EAG reverses this by comparing atogepant to erenumab, meaning the median CFB and CrI have been inverted.
Page 82 of the EAG report (Table 20) reports the following values under the "Company-preferred NMA" column: [redacted]	The values should be revised as follows: [redacted]	Typographical error	Not a factual inaccuracy. The values presented in Table 20 directly match those presented in Table 25 of the CS where atogepant is compared to comparators. The EAG acknowledges that Table 44 of the CS presents the values highlighted here by the company; however, this is when atogepant is used as the reference treatment (rather than the comparator being the reference treatment as in EAG table 20) and the values, therefore, are inverted.

Page 85 of the EAG report (Table 21) reports the following values under the "Company-preferred NMA" column: "[redacted]"	The values should be revised as follows: "[redacted]"	Typographical error	Not a factual inaccuracy. The values presented in Table 21 directly match those presented in Table 25 of the CS (and Table 116 of the CS appendices for botulinum toxin type A) where atogepant is compared to comparators. The EAG acknowledges that Table 44 of the CS presents the values highlighted here by the company; however, this is when atogepant is used as the reference treatment (rather than the comparator being the reference treatment as in EAG table 21) and the values, therefore, are inverted.
Page 103 of the EAG report (Table 26) states the following: "*Fremanezumab 225mg once every three months*"	The statement should be revised as follows: "*Fremanezumab 225mg* ***once monthly***"	Typographical error	The EAG has made the suggested changes.
Page 104 of the EAG report (Table 27) states the following: "*Fremanezumab 225mg once every three months*"	The statement should be revised as follows: "*Fremanezumab 225mg* ***once monthly***"	Typographical error	The EAG has made the suggested changes.

Page 104 of the EAG report (Table 27) reports the following total costs value for fremanezumab 225 mg: "[redacted]"	The value should be revised as follows: "[redacted]"	Typographical error	The EAG has made the suggested changes..
Page 104 of the EAG report (Table 27) reports the following total costs value fremanezumab 675 mg once every three months: "[redacted]"	The value should be revised as follows: "[redacted]"	Typographical error	The EAG has made the suggested changes.
Page 111 of the EAG report (point 1) states the following: *"The low predicted market share for 2023 of the respective treatments; up to [redacted] for rimegepant and [redacted] for eptinezumab[13], in the relevant population (see section 4.2.2), along with clinical expert opinion suggests these treatments are not part of established care in the UK."*	The statement should revised as follows: *"The low predicted market share for 2023 of the respective treatments; up to [redacted] for rimegepant and [redacted] for eptinezumab[13], in the relevant population (see section 4.2.2), along with clinical expert opinion suggests these treatments are not part of established care in the UK."*	Typographical error	Not a factual inaccuracy. On review of the Clarivate™ Market Forecast Assumptions reference (2020), the [redacted]% figure is mentioned for rimegepant. The EAG has amended text in the EAG report that had assigned [redacted]% to eptinezumab (page 47).
Page 121 of the EAG report (Table 37) reports the following values under the	The values should be revised as follows: "[redacted]"	Typographical error	Not a factual inaccuracy. The values presented in Table 37 directly match those

"Company-preferred NMA" column: "[redacted]"	[redacted]"		presented in Table 25 of the CS where atogepant is compared to comparators. The EAG acknowledges that Table 44 of the CS presents the values highlighted here by the company; however, this is when atogepant is used as the reference treatment (rather than the comparator being the reference treatment as in EAG table 20) and the values, therefore, are inverted.
Page 127 of the EAG report (Paragraph 4) states: *"The company stated that this was not possible as the company claimed it was not possible to dynamically define treatment status this way would require recalculating mean."*	The statement should be revised as this appears to be an incomplete sentence.	Typographical error	Sentence edited to read as follows: *"The company stated that it was not possible to dynamically define treatment status this way, as it would require recalculating mean monthly migraine days for time periods were taking atogepant versus after they discontinued."*
Page 132 of the EAG report (Table 49) reports the following column titles:	The column titles should be revised to the following: *"CS strength*	Typographical error	The EAG has made the suggested changes.

"CS dose *(…)* *EAG dose"*	*(…)* *EAG strength"*		
Pages 134, 148 of the EAG report (Tables 51, 57) report the following incremental QALYs value for atogepant 60 mg once daily vs erenumab 140 mg once monthly: "[redacted]"	The value should be revised as follows: "[redacted]"	Typographical error	Not a factual inaccuracy. The company is mistaken, erenumab incremental QALYs to 2 D.P are [redacted] as to 4 D.P this value is [redacted].
Page 134 of the EAG report (Table 51) reports the following ICER value for atogepant 60 mg once daily vs fremanezumab 225 mg once monthly: "[redacted]"	The value should be revised as follows: "[redacted]"	Typographical error	The EAG has made the suggested changes.
Page 134, 149 of the EAG report (Tables 51, 57) report the following incremental QALYs value for atogepant 60 mg once daily vs fremanezumab 675 mg once every three months: "[redacted]"	The value should be revised as follows: "[redacted]"	Typographical error	Not a factual inaccuracy. The company is mistaken, fremanezumab 675 mg incremental QALYs to 2 D.P are [redacted] as to 4 D.P this value is [redacted].

Page 134 of the EAG report (Table 51) reports the following ICER value for atogepant 60 mg once daily vs fremanezumab 675 mg once every three months: "[redacted]"	The value should be revised as follows: "[redacted]"	Typographical error	The EAG has made the suggested changes.
Page 135 of the EAG report (Table 52) reports the following incremental costs value for atogepant 60 mg once daily vs galcanezumab 120 mg once monthly: [redacted]	The value should be revised as follows: [redacted]	Typographical error	The EAG has made the suggested changes.
Page 135 of the EAG report (Table 52) reports the following incremental costs value for atogepant 60 mg once daily vs erenumab 140 mg once monthly: [redacted]	The value should be revised as follows: [redacted]	Typographical error	The EAG has made the suggested changes.
Page 135 of the EAG report (Table 52) reports the following incremental costs value for atogepant 60 mg once daily vs	The value should be revised as follows: [redacted]	Typographical error	The EAG has made the suggested changes.

fremanezumab 225 mg once monthly: [redacted]			
Page 135 of the EAG report (Table 52) reports the following incremental costs value for atogepant 60 mg once daily vs fremanezumab 675 mg once every three months: [redacted]	The value should be revised as follows: [redacted]	Typographical error	The EAG has made the suggested changes.
Page 158/159 of the EAG report (Table 61) reports the results of two scenario analyses: '*Alternate LT disc source*' and '*Responder MMD restricted to 0'*	The results of these scenarios should be checked and updated if incorrect.	The results of the two scenarios appear to be identical, please can the EAG check and confirm whether this is the case or whether one set of results are reported incorrectly.	Not a factual inaccuracy. The results are not identical, QALYs for galcanezumab differ. This is the only output effected because galcanezumab is the only treatment which had a responder MMD that would go below 1, were there no responder MMD limit.

Highlighting Issues

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG comment
Pages 29, 30 of the EAG report (Tables 10, 11)	It is unclear whether the results presented in Tables 10, 11 are using the list or PAS price for atogepant. In the absence of this information, ICER values should be marked as commercial in confidence.	All instances of *"[redacted]"* in both tables	All results in the report use the PAS price for atogepant, therefore all instances of the ICER where "[redacted]" is the result have been marked as confidential.
Page 58 of the EAG report (Table 14)	Unpublished data concerning dropouts in the PROGRESS study should be marked as commercial in confidence.	***No*** *(from ITT population, similar in atogepant 60 mg and placebo groups – [redacted]% vs [redacted]%)* *Unclear if similar was true for the 3+ TF subgroup*	The EAG has made the suggested changes.
Page 124 of the EAG report (Paragraph 6)	Unpublished life years gained data relating to atogepant and its comparators should be marked as commercial in confidence.	*The life years gained in all company model runs was [redacted] years.*	The EAG has made the suggested changes.
Page 125 of the EAG report (Paragraph 1)	Unpublished life years gained data relating to atogepant and its comparators should be marked as commercial in confidence.	*The EAG base case uses the updated life tables to match the latest ONS data. The life years gained in all model runs remained [redacted] years following this change.*	The EAG has made the suggested changes.. Also updated the text to include LYG in CM: *"The life years gained in all model runs remained [redacted]*

			years in EM but decreased marginally to [redacted] *years in CM following this change".*
Page 129 of the EAG report (Paragraph 1)	Unpublished medication use day data for atogepant in EM and CM should be marked as commercial in confidence.	*The trial provides a baseline value for MUD (medication use days) for atogepant of* [redacted] *in CM and* [redacted] *in EM.*	The EAG has made the suggested changes.
Page 137 of the EAG report (Table 54; footnotes)	Unpublished incremental QALY data relation to atogepant and its comparators should be marked as commercial in confidence.	*†Value of* [redacted]	The EAG has made the suggested changes.

References

1. National Institute for Health and Care Excellence (NICE). Rimegepant for preventing migraine [TA906]. . Available from: https://www.nice.org.uk/guidance/ta906. Date accessed: Oct 23.
2. Brazier J, Rowen, D. NICE DSU Technical Support Document 11: Alternatives to EQ-5D for Generating Health State Utility Values. 2011. Date accessed.
3. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual. 2022. Available from: https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741. Date accessed: 6 April 2023.
4. 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**: 2359-72.
5. AbbVie Data on File [CONFIDENTIAL]. Clarivate™ Market Forecast Assumptions Migraine 2020.
6. National Institute for Health and Care Excellence. Eptinezumab for preventing migraine [TA871]. Available at: https://www.nice.org.uk/guidance/TA871 [Last accessed: 22/03/2023]. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10677. Date accessed: 20 October 2022.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Atogepant for preventing migraine [ID5090]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with migraine or caring for a patient with migraine. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Thursday 1 February.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with migraine

Table 1 About you, migraine, current treatments and equality

1. Your name	Steph Weatherley
2. Are you (please tick all that apply)	☒ A patient with migraine? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with migraine? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	The Migraine Trust
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:
6. What is your experience of living with migraine?	I have chronic migraine and chronic daily headache which was diagnosed in 2019. I have had migraine since childhood which has worsened over time.

If you are a carer (for someone with migraine) please share your experience of caring for them	
7a. What do you think of the current treatments and care available for migraine on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	**The current treatments have improved over the last few years and now that CGRP medications are available there are more options for those that do not get relief from migraine preventives available via the GP. From a personal perspective having to trial 3 preventive medications that are most likely not going to work is very depressing when you have migraine everyday that impacts your quality of life and mental health. I am disgusted with the NHS care for migraine sadly, it takes a very long time to see a neurologist. I also work on The Migraine Trusts helpline and spoke to someone that after being referred 2.5 years ago to a neurologist still has not had an appointment- there is no way that is acceptable. This then goes into the prescribing guidelines for many medications and for Atogepant and the more recently approved Rimegepant these really should be prescribable by a GP for acute treatment as waiting years to see a neurologist to access it is not acceptable. The CGRP type medications have made a large difference to those with migraine including myself. Atogepant offers a CGRP treatment that is not an injection which is beneficial for those with a needle phobia, or have not been able to tolerate the injectable CGRP. I am allergic to an ingredient in the CGRP injections therefore Atogepant would be an ideal alternative for me to try.** **I feel that my views are fairly similar to those of other people, including my colleagues at The migraine Trust, the patients I speak with every day and others I know with migraine. We all just wish that the accessibility was quicker and not so difficult for these treatments.**
8. If there are disadvantages for patients of current NHS treatments for migraine (for example, how they are given or taken, side effects of treatment, and any others) please describe these	The disadvantages are accessing the treatments and the criteria that needs to be met. The time to access treatments for migraine that work can be lengthy with at least 9-12 months with a GP and then waiting approx. another year to see a neurologist, jumping through the neurology red tape to access treatments can take another few months so altogether it can take approx. 2.5 years for someone to

	access better effective treatment. This time frame impacts their quality of life, Jobs, relationships and mental health. Most treatments are aimed at those 18-65, more are needed for children and those over 65. Many patients are not able to take triptan medications and Atogepant will offer an alternative that helps to reduce the risk of medication over use headache.
9a. If there are advantages of atogepant over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does atogepant help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	**Atogepant advantages are the ability to take it orally and not via an injection. If side effects occur that are not tolerable it can be stopped and leaves the body quicker, this can be useful for those with drug intolerances. It can also be useful for those over 65 that can not take triptan medications or other pain relief medications. There is Rimegepant, however Atogepant will offer a second alternative to try if Rimegepant is not tolerable or effective. It is shown that trying an alternative is successful for those that try different triptans and CGRP injections, there are 7 different types of triptan licensed, but only one gepant.** **Atogepant will help improve the quality-of-life impacting improvement in their mental health, jobs and families of those that have not had relief from their migraine with current treatments. It can be used as a preventive and acutely, and I feel it should be licensed for both purposes to broaden the options available.** **I consider the advantage of offering another treatment option the most important as offering another treatment option feeds into the improvements made in the second advantage listed. Atogepant overcomes the issue of not having a suitable acute treatment when triptans can not be taken or when a person has medication over use issues. It is also over comes the age restriction triptans have and the risk of stroke for those over 65.**

10. If there are disadvantages of atogepant over current treatments on the NHS please describe these. For example, are there any risks with atogepant? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I am not aware of any disadvantages over other treatment
11. Are there any groups of patients who might benefit more from atogepant or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Yes, those aged 65 and over, those that cannot take NSAIDS or other pain relief medications, those at risk of medication overuse headache and those that have a needle phobia or are non-responsive to injectable CGRP's will all benefit more. It will fill a GAP that restricts treatment of migraine for these groups. In am not aware of any groups that would not benefit.
12. Are there any potential equality issues that should be taken into account when considering migraine and atogepant? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	The age restrictions of other migraine medications cause an issue for those over 65. Atogepant will fill this equality gap and provide a safer treatment alternative with a reduced stroke risk for this age group.

13. Are there any other issues that you would like the committee to consider?	Please consider the prescribing guidance, as to who can prescribe this to patients. If licensed for acute use please allow this to be available to GP's as neurology services are under pressure, and being referred to neurology for an acute treatment will add pressure to this service and delay the patient from obtaining a treatment unnecessarily. Being available in primary care will speed up treatment for those struggling and relieve the neurology services.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Provides an acute treatment alternative for those aged 65 and over of unable to take pain relief medications.
- Provides a second alternative for patients to try if Rimegepant is not suitable or tolerated.
- Allow prescribing to take place in primary care to reduce strain on secondary care services.
- A suitable alternative for those with needle phobia, or allergies to the injectable CGRP medications
- Can help to improve quality of life, mental health, ability to work and relationships int hose migraine

Thank you for your time.

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Single Technology Appraisal

Atogepant for preventing migraine [ID5090]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **Thursday 1 February.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Part 1: Treating mirgraine and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Brendan Davies
2. Name of organisation	Midlands Regional Headache Clinic University Hospital of North Midlands Neurology Dept. **Also** Current Chaimran of British Association for the Study of Headache (BASH)
3. Job title or position	Consultant Neurologist, Clinical Lead Midlands Regional Headache Clinic
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with migraine? ☐ A specialist in the clinical evidence base for migraine or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for migraine?	1. To reduce the severity and frequency of symptoms (largely headache

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	With associated symptoms) involved in Migraine attacks and their day to day impact on function and ideally any associated symptoms other than headache that impact daily functioning 2. To have a sustained benefit over time with minimal treatment related adverse effects and good safety. 3. To work across the whole spectrum of migraine – i.e. episodic & chronic whether migraine with or without aura and in all age groups
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	This depends on Migraine classification – This International Headache Society 1. In **episodic migraine**: At least a 30-50% reduction in monthly migraine days within 6 months of starting therapy compared to pre-treatment. 2. In **chronic migraine**: At least a 30% reduction in monthly migraine days within 6 months of starting therapy compared to pre-treatment. 3. In patients with **chronic migraine with continuous pain**: A 30% reduction in the number of severe monthly migraine days (as opposed to just migraine days) within 6 months of starting therapy compared to pre-treatment. 4. As well as above reduction in the HIT-6 score (Headache impact test score) ideally to below 60 (in chronic Migraine) and definitely significant if below 56 dependent on pretreatment HIT-6 score. In patients with chronic migraine with continuous pain by at least 6 points on the HIT-6 score
10. In your view, is there an unmet need for patients and healthcare professionals in migraine?	Yes - effective easy to access, tolerable oral preventative medication for non-responders to oral 1st line preventative and acute medications
11. How is migraine currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals	NICE CG 150 – Now really out of date, needs extensive revisitation and not really fit for practice given new MHRA safety data emerging about the risk of using 1st line Topiramate for female migraine sufferers of child bearing age. The majority group who need prevention. BASH Headache Guidelines 2019

across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	SIGN 155 Migraine pharmacological management guidelines 2018 (& Revised 2023) It would add to the number of new therapy NICE approved therapy technologies that have better efficacy evidence and better tolerability data than currently recommended NICE CG 150 & other UK headache guidelines.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Yes As primary care providers may not be familiar with these drugs and disease mechanisms in migraine then the imitation or ideally recommendation for commencing therapy may originate from secondary care but ideally be subsequently provided/prescribed for imitation or ongoing therapy prescription from primary care. This drug could be recommended by an Neurologist or GPwSI headache interest if familiar with making the diagnosis of migraine and initiation and supervision of therapy for 2nd line drugs . No additional facilities, equipment needed but familiarity with the CGRP drug mechanisms, interactions and training for prescribers would be needed. If provided from secondary care, then awareness of the “Bluetec approval process” might be needed – If prescribed direct from primary care this would not be needed. This would be the same as for ANIT-CGRP monoclonal antibody therapies if prescribed from secondary care
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes The length of life is not affected by migraine therapies to my knowledge. Migraine is not a life threatening disorder but a “life affecting” disorder
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Not to my knowledge

15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Possibly easier as logistics of prescription and access may be quicker especially if available for initiation and initial prescription by primary care. Current long wait times to access specialised headache or even Neurology clinics currently long – Oral medication from primary care might obviate the need for onward referral if effective from primary care prescription and improve faster access to effective therapies. Monitoring of effectiveness response at 3 months (like all these new therapies) and thereafter is the main logistical NHS issue that also affects practical usage.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Ideally not and could be used as an alternative 1st line drug but if being considered 2nd line then probably the same as for recommended for anti-CGRP mono-clonal antibodies (failed on 3 prior evidenced based migraine preventive therapies) before NHS eligible. The EMA announcement & MHRA Topiramate issues in women of child bearing age bears consideration in this scenario
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Yes - Reduction is dysutilities due to: Less migraine related headache and functional impairment. Less need for triptan prescriptions as acute abortive therapy, less GP visits, Less secondary care visits (ED, outpatients) Less medication overuse problems with triptans Less indirect work related loss due to severe migraine
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition?	Yes – This technology may be better than the currently NICE approved Gepant for the following reasons: Patient adherence to a daily tablet is likely to be better rather than an alternate day tablet. The pharmacology (Plasma half-life) of this technology is scientifically more plausible (tablets given daily) than the alternate day Gepant previously approved by NICE which has the same half-life but is still given alternate days.

• Does the use of the technology address any particular unmet need of the patient population?	The technology has a varied dose regime allowing flexible options for use in a real-world scenario if needed. The daily, oral formulation has the potential to meet an unmet need for earlier easy therapy access and easy primary care or secondary care prescribing without a need for direct secondary care face to face review and even has the potential to engage/utilise new modern NHS digital remote assessment care systems
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Few side effects – Better tolerability with efficacy improves compliance and sustained benefit
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes mostly – There is a need for some more data in the Chronic migraine population that have failed more than 2 and less than 4 therapies. Episodic migraine – 50% responder rate at 1 month & 3 months & open label 12 months Chronic Migraine – 30% responder & 50% responder at 3 months +/- 12 months if available Rarely exacerbation or Raynaud's syndrome/phenomenon - very rare but also seen ion the Mabs real world data
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA919?	No
23. How do data on real-world experience compare with the trial data?	Not seen much published from the UK or Europe
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any	Not aware of any

potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

1. Novel effective **daily** (rather than alternate day) oral drug will improve oral adherence/compliance
2. Effectiveness demonstrated in migraine prevention naïve & failed 2-3+ oral therapy appropriate target UK migraine populations
3. Oral novel mechanism with good safety & efficacy potential to allow UK migraine patients easier early access to primary care prescription access.
4. Trial data supports good efficacy and tolerability but uncertain if better or as convenient as Anti-CGRP Monoclonal antibodies
5. Pharmacological shorter half-life offers potentially safer therapy option for those with significant vascular risk or prior events

Thank you for your time.

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For more information about how we process your personal data please see our privacy notice.

Supplementary Information Title: 3101-302-002 (LTS-302) long-term discontinuation data

Affiliate: UK

Business Owner Role: HTA Manager

Approved by: Medical Advisor

Date: 16th February 2024

Based on discontinuation data collected from the LTS 302 study, a Kaplan-Meier curve estimate indicates that the probability of discontinuation up to Day 367 was [redacted]% (open-label treatment period = 52 weeks; **Table 1**).

This was adjusted to a 28-day cycle length using the following formula:

- *Adjusted rate = 1 – (1 – unadjusted rate)^(cycle length (days) / study period (days))*
- *Adjusted rate = 1 – (1 – [redacted])^(28 / 367) = [redacted]%*

Table 1. Kaplan-Meier Product-Limit Survival Estimate

Days	Survival Probability	Failure Probability	Number Failed
367	[redacted]	[redacted]	[redacted]

The following clarifications to EAG questions are also provided:

1. Why does the data in this spreadsheet appear to differ from the previously provided: "3101-302-002 CSR Table 14.3-1.1"?

    a. The spreadsheet presents the probability of discontinuation as estimated by Kaplan-Meier methodology (i.e. time to discontinuation), which accounts for patients who specifically discontinued during the open-label treatment period. Patients who did not discontinue during the open label treatment period were censored.
    b. On the other hand, Table 14.3-1.1 presents treatment duration data based on the number of patients who remained on treatment at each specified timepoint (regardless of whether they eventually discontinued during the open-label treatment period; therefore including both non-censored and censored patients).
    c. Analysis of the discontinuation rate adjusted to a 28-day cycle length based on the number of patients remaining on treatment at Day ≥360 (LTS-302 CSR Table 14.3-1.1) produces similar results to that of the Kaplan-Meier methodology:

        - *Adjusted rate = 1 – (1 – unadjusted rate)^(cycle length (days) / study period (days))*
        - *Adjusted rate = 1 – (1 – [redacted])^(28 / 360) = [redacted]%*

2. Does the company have any further information on why patients were censored?
    a. Patients were censored if they did not discontinue prior to their final visit during the open-label treatment period, as it is therefore not possible to observe the true time point at which they discontinue.

3. What proportion of patients in the LTS 302 study were treatment naïve to atogepant prior to day 0?

    a. The LTS 302 study included a safety population of [redacted] patients who received at least 1 dose of study intervention. Among these, [redacted] ([redacted]%) were De Novo Participants (i.e. naïve to atogepant) and [redacted] were CGP-MD-01 completers, [redacted] of which completed CGP-MD-01 on the atogepant arm ([redacted]%).

4. Would using this study for long term discontinuation double count patients who had discontinued in the response assessment period (prior to 3 months on treatment)?

    a. The LTS 302 study includes De Novo participants and patients who completed the preceding CGP-MD-01 study. Therefore, patients who discontinued during the preceding CGP-MD-01 study were not included in the LTS 302 discontinuation calculation; so patients are not being double counted.

Atogepant for preventing migraine [ID5090]

Post-ACM response to discontinuation issue

March 2023

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 136175.

1 Review of updated discontinuation rate

1.1 Introduction

The External Assessment Group (EAG) produced this document in response to an updated long-term (LT) long-term discontinuation rate presented by the company at the appraisal committee meeting (ACM). The long-term discontinuation rate determines the per-cycle (28 day) rate of discontinuation from treatment following the 12-week assessment period. This LT rate of discontinuation is assumed to be the same for all treatments. An alternate, higher, treatment-specific, per cycle rate of discontinuation is used during the 12-week assessment period and a significant number of patients discontinue following response-assessment as they are deemed to be non-responders.

The LT discontinuation rate of [redacted]%, used in the original company submission, was found to be calculated erroneously. Therefore, the EAG opted to use a rate of 0.44% in line with TA682 and the company's scenario analysis.

Using the LT safety study for atogepant, LTS 302, the company found that the Kaplan-Meier curve provided an estimated discontinuation of [redacted]% up to day 367. Using the formula below the company found the per cycle rate of discontinuation to be [redacted]%.

Adjusted rate = 1 – (1 – unadjusted rate)^(cycle length (days) / study period (days))

1.2 EAG critique

The company provided survival data from LTS 302 showing failed and censored patients. From these data, the EAG was unable to reproduce the estimated discontinuation at day 367 of [redacted]%, instead estimating discontinuation at day 367 to be [redacted]%, taking into account censored patients. This leads to a marginally different per cycle rate of discontinuation of [redacted]%.

The EAG requested the company clarify what proportion of patients in the LTS 302 study were treatment naïve to atogepant. They stated that [redacted] were *de novo* participants, [redacted] were patients who completed CGP-MD-01 in the atogepant arm and the remainder were patients who completed CGP-MD-01 in the placebo arm. The EAG considers there to be an issue with using a study with so many *de novo* participants for LT discontinuation, as these patients will likely experience far higher rates of discontinuation in the first 3 months of treatment, which is already accounted for in the model.

The EAG recommends that the company use only discontinuations that occur after the first 84 days (3 model cycles) to model LT discontinuation. This avoids double counting the initial high rate of pre-assessment period discontinuation. The EAG attempted to calculate a figure for LT discontinuation using only failures that occurred between day 84 and day 367. This resulted in an estimated discontinuation rate for this 283-day period of [redacted]% and a per cycle discontinuation rate of [redacted]%. However, as the EAG were not able to replicate the company's [redacted]% per cycle discontinuation rate, producing a value of [redacted]%, any error in the EAGs replication attempt will have been duplicated in producing this new rate.

The results for the original EAG base case, company updated results and EAG updated preferred base case are shown in section 2. An appendix is provided alongside this document with results including confidential price discounts for all relevant treatments.

2 EAG analysis

The External Assessment Group (EAG) has presented the results of the EAG base case using:

1. 0.44% long-term (LT) discontinuation rate as used in original EAG base case.
2. [redacted]% LT discontinuation rate updated by the company.
3. [redacted]% LT discontinuation rate suggested by EAG, taking only discontinuations that occur after the first 84 days.

Results using the original company discontinuation rate have not been used as this has been accepted as being calculated erroneously. Table 1 shows the scenario analysis results for episodic migraine and

Table 2 shows the results for chronic migraine.

Table 1. Results of the EAG's scenario analyses (episodic migraine)

Results per patient	Epti (7)	Rim (6)	Ere (5)	Gal (4)	Fre (3)	Fre (2)	Ato (1)	Incremental value					
								(1-7)	(1-6)	(1-5)	(1-4)	(1-3)	(1-2)
EAG original base case (0.44% discontinuation)													
Total costs	£55,233	£30,790	£48,222	£83,849	£50,471	£49,737	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	14.40	14.35	14.46	14.45	14.50	14.52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company updated discontinuation rate ([redacted])													
Total costs	£30,878	£23,760	£28,498	£38,477	£29,559	£29,047	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	13.97	13.96	13.99	13.99	14.00	14.01	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG updated base case discontinuation rate ([redacted])													
Total costs	£32,695	£24,285	£29,970	£41,861	£31,119	£30,590	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	14.01	13.99	14.03	14.02	14.04	14.05	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*South-west quadrant ICER (atogepant is less expensive and less effective than the comparator)

†-0.004; ‡-0.005.

Abbreviations: Ato, atogepant; EAG, External Assessment Group; Epti, eptinezumab; Ere, erenumab; Fre, fremanezumab; Gal, galcanezumab; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; Rim, rimegepant

Table 2. Results of the EAG's scenario analyses (chronic migraine)

Results per patient	Epti (7)	Bot (6)	Ere (5)	Gal (4)	Fre (3)	Fre (2)	Ato (1)	Incremental value					
								(1-7)	(1-6)	(1-5)	(1-4)	(1-3)	(1-2)
EAG original base case (0.44% discontinuation)													
Total costs	£72,104	£43,366	£64,621	£93,493	£71,092	£70,872	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	11.53	11.57	11.59	11.45	11.46	11.49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company updated discontinuation rate ([redacted])													
Total costs	£42,345	£34,647	£39,888	£48,270	£41,999	£41,605	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	10.88	10.89	10.89	10.86	10.86	10.87	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG updated base case discontinuation rate ([redacted])													
Total costs	£44,571	£35,300	£41,738	£51,652	£44,176	£43,794	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	10.93	10.94	10.95	10.90	10.90	10.91	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*South-west quadrant ICER (atogepant is less expensive and less effective than the comparator)

Abbreviations: Ato, atogepant; Bot, botulinum toxin; EAG, External Assessment Group; Epti, eptinezumab; Ere, erenumab; Fre, fremanezumab; Gal, galcanezumab; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Atogepant for preventing migraine [ID5090]

Post-ACM response to updated PAS price

March 2023

Source of funding
This report was commissioned by the NIHR Evidence Synthesis Programme as project number 136175.

1 Review of updated discontinuation rate

1.1 Introduction

The External Assessment Group (EAG) produced this document in response to an updated discounted PAS price for atogepant. The PAS discount for atogepant has changed from [redacted]% to [redacted]% resulting in a discounted pack price change from £[redacted] to £[redacted].

2 EAG analysis

2.1 Deterministic results

The External Assessment Group (EAG) has produced analysis comparing the original company and EAG base case with and without the updated PAS price. Following additional data, provided post-ACM, the base case company discontinuation rate was updated to [redacted]% which has been used in the company base case model runs presented here. In response to the companies updated discontinuation data the EAG suggested a rate of [redacted]% which is presented as a scenario using the EAG base case assumptions. The following scenario analyses are presented in this document:

1. Post-ACM company base case ([redacted]% discontinuation);
2. Updated company base case using new PAS price ([redacted]% discontinuation);
3. Original EAG base case (0.44% discontinuation);
4. Updated EAG base case using new PAS price (0.44% discontinuation);
5. Updated EAG base case using new PAS price ([redacted]% discontinuation).
6. Updated EAG base case using new PAS price ([redacted]% discontinuation + MMD restricted to 1).

Table 1 shows the scenario analysis results for episodic migraine and

Table 2 shows the results for chronic migraine.

Table 1. Results of the EAG's scenario analyses (episodic migraine)

Results per patient	Epti (7)	Rim (6)	Ere (5)	Gal (4)	Fre (3)	Fre (2)	Ato (1)	Incremental value					
								(1-7)	(1-6)	(1-5)	(1-4)	(1-3)	(1-2)
Post-ACM company base case ([redacted]% discontinuation)													
Total costs	NA	NA	£27,820	£36,363	£33,629	£32,079	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	NA	13.93	13.95	14.03	14.01	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Updated company base case using new PAS price ([redacted]% discontinuation)													
Total costs	NA	NA	£27,820	£36,363	£33,629	£32,079	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	NA	13.93	13.95	14.03	14.01	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Original EAG base case (0.44% discontinuation)													
Total costs	£55,233	£30,790	£48,222	£83,849	£50,471	£49,737	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	14.40	14.35	14.46	14.45	14.50	14.52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated EAG base case using new PAS price (0.44% discontinuation)													
Total costs	£55,233	£30,790	£48,222	£83,849	£50,471	£49,737	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	14.40	14.35	14.46	14.45	14.50	14.52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER (£/QALY)								[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated EAG updated base case using new PAS price ([redacted]% discontinuation)													
Total costs	£32,695	£24,285	£29,970	£41,861	£31,119	£30,590	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	14.01	13.99	14.03	14.02	14.04	14.05	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated EAG updated base case using new PAS price ([redacted]% discontinuation + MMD restricted to 1)													
Total costs	£32,695	£24,285	£29,970	£41,861	£31,264	£30,928	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	14.01	13.99	14.03	14.02	14.03	14.03	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*South-west quadrant ICER (atogepant is less expensive and less effective than the comparator)

‡-0.005; ǂ0.002; §0.0001.

Abbreviations: Ato, atogepant; EAG, External Assessment Group; Epti, eptinezumab; Ere, erenumab; Fre, fremanezumab; Gal, galcanezumab; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; Rim, rimegepant

Table 2. Results of the EAG's scenario analyses (chronic migraine)

Results per patient	Epti (7)	Bot (6)	Ere (5)	Gal (4)	Fre (3)	Fre (2)	Ato (1)	Incremental value					
								(1-7)	(1-6)	(1-5)	(1-4)	(1-3)	(1-2)
Post-ACM company base case ([redacted]% discontinuation)													
Total costs	NA	£34,482	£41,112	£50,740	£43,084	£42,914	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

QALYs	NA	10.73	10.88	10.88	10.87	10.87	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated company base case using new PAS price ([redacted]% discontinuation)													
Total costs	NA	£34,482	£41,112	£50,740	£43,084	£42,914	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	10.73	10.88	10.88	10.87	10.87	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Original EAG base case (0.44% discontinuation)													
Total costs	£72,104	£43,366	£64,621	£93,493	£71,092	£70,872	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	11.53	11.57	11.59	11.45	11.46	11.49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated EAG base case using new PAS price (0.44% discontinuation)													
Total costs	£72,104	£43,366	£64,621	£93,493	£71,092	£70,872	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	11.53	11.57	11.59	11.45	11.46	11.49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated EAG updated base case using new PAS price ([redacted]% discontinuation)													
Total costs	£44,571	£35,300	£41,738	£51,652	£44,176	£43,794	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	10.93	10.94	10.95	10.90	10.90	10.91	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER (£/QALY)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*South-west quadrant ICER (atogepant is less expensive and less effective than the comparator)

†0.001; ‡0.0005; §-0.001.

Abbreviations: Ato, atogepant; Bot, botulinum toxin; EAG, External Assessment Group; Epti, eptinezumab; Ere, erenumab; Fre, fremanezumab; Gal, galcanezumab; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.