NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Atogepant for treating migraine [ID6615]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

COST COMPARISON APPRAISAL

Atogepant for treating migraine [ID6615]

Contents:

The following documents are made available to stakeholders:

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

1. **Company submission** from AbbVie:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submission** from:
   a. The Migraine Trust
   b. Association of British Neurologists
   c. British Association for the study of Headache
   d. UK Clinical Pharmacy Association

4. **Expert personal perspectives** from:
   a. Dr Callum Duncan – clinical expert, nominated by British Association for the Study of Headache
   b. Mrs Olga Tanda – clinical expert, nominated by UK Clinical Pharmacy Association
   c. Debbie Shipley – patient expert, nominated by The Migraine Trust
   d. Oscar Harvey – patient expert, nominated by The Migraine Trust

5. **External Assessment Report** prepared by BMJ Technology Assessment Group

6. **External Assessment Group response to factual accuracy check of EAR**

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

Cost-comparison appraisal

Atogepant for treating migraine [ID6615]

Company evidence submission

January 2026

File name	Version	Contains confidential information	Date
ID6615_Atogepant in Migraine_Company Submission [noCON]	V1.2	Yes	15th May 2026

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) when a cost-comparison case is made as part of the single technology appraisal process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the single technology appraisal: cost-comparison, user guide for company evidence submission template.

This submission must not be longer than 100 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

Companies making evidence submissions to NICE should also refer to the https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation.

In this template any information that should be provided in an appendix is listed in a box.

Highlighting in the template (excluding the contents list)

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.

To delete grey highlighted text, click anywhere within the text and press 'delete'.

Grey highlighted text in the footer does not work as an automatic form field, but serves the same purpose – as prompt text to show where you need to fill in relevant details. Replace the text highlighted in [grey] in the footer with appropriate text. (To change the footer, double click over the footer text. Double click back in the main body text when you have finished.)

Use of artificial intelligence (AI) in this submission

A NICE position statement sets out our view on the use of AI methods in the generation and reporting of evidence considered by its evaluation programmes.

To your knowledge:

1. Has AI been used in the generation of data or research presented in this submission?

Yes – Information from the full articles included in the clinical systematic literature review (SLR) was extracted through the use of artificial intelligence (AI) data queries, with the exception of confidential or paywalled studies which were extracted manually by an investigator.

2. Has AI been used in the reporting or synthesis of research presented in this evidence submission?

No – AI has not been used in the reporting or synthesis of research presented in this evidence submission.

3. Please indicate where AI was used, any potential risks with its use and what steps were taken to address these risks.

Potential risks of using AI for data extraction include inaccuracy and errors through misinterpretation or missing critical information, introduction of bias from AI training data or algorithms, and hallucinations and generation of unsupported information by producing plausible but fabricated details not found in source material.

These risks were mitigated by having all extracted data independently validated for completeness and accuracy by a human investigator, as well as reading through the comments generated by AI post-extraction for any assumptions made or references used.

4. Please indicate the level of human oversight for these uses.

Any discrepancies were resolved and reviewed by a second, human investigator, as needed.

Extracted data which required plot digitisation (i.e., figures without values for endpoints of interest) or calculation (ex., n and N provided but no percentage) were reviewed and validated for additional quality assurance.

Contents

List of Tables

List of Figures

Abbreviations

Abbreviation	Definition
AEs	Adverse events
AI	Artificial intelligence
BASH	British Association for the Study of Headache
BMI	Body mass index
BNF	British National Formulary
BSC	Best supportive care
CfB	Change from baseline
CFS	Cognitive Function Scale
CGRP	Calcitonin gene-related peptide
CI	Confidence interval
CrI	Credible interval
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Cardiovascular
CYP3A4	Cytochrome P450 3A4
DB	Double-blind
DIC	Deviance information criterion
DSU	Decision Support Unit
EAG	External Assessment Group
ECG	Electrocardiogram
EQ-5D-5L	EuroQol 5-Dimension 5-Level
EU	European Union
FDS	Functional Disability Scale
FE	Fixed effect
GBD	Global Burden of Disease
GLMM	Generalized linear mixed model
GP	General practitioner
HRQoL	Health-related quality of life
HSUV	Health state utility value
ITT	Intention-to-treat
LS	Least squares
MAAP	Market Access Analysis Plan
MBS	Most bothersome symptom
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MIDAS	Migraine Disability Assessment
MMDs	Monthly migraine days
MMRM	Mixed model for repeated measures
MOH	Medication-overuse headache

MQoLQ	Migraine Quality of Life Questionnaire
MUD	Medication use day
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NRI	Non-responder imputation
NSAID	Non-steroidal anti-inflammatory drug
OATP	Organic anion-transporting polypeptide
OBS	Observed
OL	Open-label
ONS	Office for National Statistics
OR	Odds ratio
PAS	Patient Access Scheme
PGIC	Patient Global Impression of Change
PICO	Population, Intervention, Comparator, Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcome
PSSM	Patient Satisfaction with Study Medication
PSSRU	Personal Social Services Research Unit
PT	Preferred term
QD	Once daily
QTcF	Corrected QT interval
RCT	Randomised controlled trial
RE	Random effects
RoB	Risk of bias
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SOC	System organ class
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TEM	Treatment effect modifier
TSD	Technical Support Document
UK	United Kingdom
ULN	Upper limit of normal
USA	United States of America
VAS	Visual analogue scale
VAT	Value-added tax
VP	Vague prior
WHO	World Health Organization

Executive summary

Background

Atogepant is an orally administered calcitonin gene-related peptide (CGRP) receptor antagonist which was recommended by NICE (TA973) in 2024 as a preventive migraine treatment.[1]

This submission focuses on atogepant as an acute treatment of migraine. Although the anticipated marketing authorisation is expected to be broad for acute migraine, this submission focuses on a subset of this, aligned to current NHS clinical practice and clinical feedback. Specifically, for the acute treatment of migraine in adults who have either:[2]

- Tried at least two triptans and they did not work well enough, or
- Have contraindications or intolerance to triptans, and have tried non-steroidal non-inflammatory drugs (NSAID) and paracetamol without adequate response

This is fully aligned with the population for which rimegepant for the treatment of migraine has received a positive recommendation by NICE (TA919).[3]

There remains an unmet need in patients who are suboptimally treated, and as a result, these patients experience a myriad of symptoms and burdens, including substantial disability, medication overuse headaches, impact on work productivity, and caregiver burden.[4, 5]

This assessment demonstrates that atogepant can offer a new, well tolerated acute treatment option for underserved migraine patients that delivers equivalent efficacy and safety to rimegepant at a lower cost.

Disease overview

Migraine is a prevalent neurological disorder that causes recurrent, disabling headache attacks lasting between four and 72 hours and affects about one in seven people globally.[6-8] A leading cause of disability, migraine severely impacts individuals to lead a normal life, affecting their mental wellbeing, daily activities, and working lives.[9]

Approximately 10 million individuals in the UK suffer from migraine,[10] contributing to extensive healthcare resource use, including high rates of general practitioner (GP) appointments, hospital admissions and accident and emergency (A&E) visits, with annual NHS costs of around £150 million.[11-13] Additionally, migraine significantly reduces work productivity, leading to tens of millions of lost workdays and at least £6 billion in economic losses annually.[11, 14]

Current treatment pathway

Acute treatment of migraine aims to stop the attack or reduce the severity of the headache and other associated symptoms. Guidelines from NICE (CG150) and the British Association for the Study of Headache (BASH) recommend simple analgesics (i.e., ibuprofen) or a triptan as monotherapies or in combination for the acute treatment of migraine.[15, 16]

However, these treatment options are frequently inadequate, with up to half of patients experiencing poor symptom control, leading to increased disability, progression risk, and healthcare resource use.[17] Many patients are inadequately managed with triptans and are unable to use these treatments due to intolerable side effects or contraindications to triptans.[18] Moreover, more than half of patients discontinue treatment with triptans, often due to

insufficient efficacy, adverse effects, or safety concerns.[19, 20] The only currently available treatment option in this population is rimegepant, which highlights the need for an alternative, effective and well tolerated treatment option.

Clinical expert opinion indicated that atogepant would be used within the NHS as an acute treatment option for patients with migraine in whom at least two triptans have been tried and they did not work well enough, or triptans were contraindicated or not tolerated.[21] This is fully aligned with the population for which rimegepant has received a positive recommendation by NICE (TA919).[3]

Clinical efficacy of atogepant

Atogepant is a once daily, as needed, oral treatment which provides effective and sustained pain relief, in addition to other clinically important benefits for patients with migraine.[2] The efficacy of atogepant is supported by results from the ECLIPSE trial, a Phase 3 placebo-controlled randomised controlled trial (RCT), which showed atogepant to be associated with statistically significant improvements that are clinically meaningful compared to placebo in pain freedom at 2 hours, most bothersome symptom (MBS) freedom at 2 hours, pain relief at 2 hours, sustained pain relief between 2 to 24 hours, rescue medication use within 24 hours as well as most of the remaining secondary endpoints.[22, 23]

Beyond pain, patients experienced meaningful enhancements in health-related quality of life (HRQoL) and functioning at 24 hours compared to placebo, including greater gains in EuroQoL 5-dimensions, 5 levels (EQ-5D-5L) and visual analogue scale (VAS) scores, higher medication satisfaction (patient satisfaction with study medication [PSSM] at 2 and 24 hours), and improved Migraine Quality of Life Questionnaire (MQoLQ) domain scores for work functioning, social functioning, energy/vitality, feelings/concerns, and migraine symptoms.[22, 23]

Safety of atogepant

Atogepant demonstrated an acceptable safety and tolerability profile for the acute treatment of migraine over the 24-week treatment period with no new safety signals.[22, 23]

Comparative efficacy & safety

In the absence of direct head-to-head data for the comparative efficacy and safety of atogepant versus rimegepant, network meta-analyses (NMAs) were conducted. These results show point estimates [redacted] across a range of endpoints (including [redacted] demonstrating that the efficacy and safety of atogepant and rimegepant are comparable. Differences in outcomes between the two treatments were not statistically significant.

In the absence of direct comparison studies, this evidence supports the assumption that atogepant offers similar clinical benefits to rimegepant.

Cost-comparison

Given the similarity in mechanism of action and mode of administration, position in the treatment pathway, relevant patient population and similarity of efficacy and safety profiles of atogepant and rimegepant, a cost-comparison analysis was performed.

Results of the cost comparison model show that atogepant was cost saving versus rimegepant of £[redacted] per patient in the base case analysis with savings realised due to the lower atogepant drug acquisition costs. Scenario analyses were conducted and these results demonstrated the

model is robust to uncertainty in model parameters and alternative assumptions, such as differences in time horizon and pack sizes.

Conclusion

This submission demonstrates that using atogepant as an acute migraine medication in the relevant patient population is expected to generate cost savings compared to rimegepant. Atogepant offers a clinically equivalent efficacy and safety profile with a similar mechanism of action and mode of administration to rimegepant. The NMA has shown no statistically significant differences between the treatments, and the conclusion of similar efficacy and safety between atogepant and rimegepant was supported by clinical experts. The cost-comparison analysis highlights that atogepant achieves cost savings primarily due to lower drug acquisition costs, providing a drug that delivers the same outcomes in acute migraine patients at a lower cost to the NHS.

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

1.1 *Decision problem*

Population

Atogepant is an orally administered CGRP receptor antagonist that is anticipated to be licensed for the acute treatment of migraine with or without aura in adults. In accordance with clinical expert feedback, atogepant is intended for use in adults within a subset of this anticipated marketing authorisation. This subset is for the acute treatment of migraine in adults who have either:[2]

- Tried at least two triptans and they did not work well enough, or
- Have contraindications or intolerance to triptans, and have tried NSAIDs and paracetamol without adequate response

This is fully aligned with the population for which rimegepant for the treatment of migraine has received a positive recommendation by NICE (TA919).[3]

Comparator

Rimegepant is the only relevant comparator for this appraisal for the following reasons:

- In the population of interest, patients will have used triptans and NSAIDs in earlier lines of treatment and found them to be not effective, or are otherwise not suitable. Therefore, patients would not be given triptans or NSAIDs at this line of therapy, so they are not relevant comparators.
- Rimegepant represents established UK clinical practice in the proposed target population, as determined by five UK clinical experts at an advisory board, who further confirmed that no other treatments are licensed or used in practice in this population.[21]
- Atogepant and rimegepant have a similar mechanism of action and mode of administration, and are expected to be licensed in the same population for this indication. As such, clinical experts would consider atogepant as an alternative to rimegepant in this patient population.[21]

There is a significant unmet need in this patient population. During the TA919 appraisal, it was recognised that these patients had no approved treatment options and as a result experience substantial disability, medicine overuse headaches, impact on work productivity and caregiver burden.[3] Suboptimal acute treatment may increase the risk of disease progression, with those with very poor acute treatment efficacy having more than a two-fold increased risk of disease progression to chronic migraine.[3] This unmet need still remains given there is now only one approved treatment option in this patient population, highlighting the need for an alternative, effective and well tolerated treatment option for these patients; it is anticipated that clinicians would use atogepant as an alternative to rimegepant.

Consequently rimegepant is the only comparator in this population.

The results of the NMAs (Section 3.9) comparing atogepant and rimegepant show no clinically meaningful differences, including in the primary endpoint of pain freedom at two hours and safety

endpoint of “any AEs”, suggesting equivalence in delivery of health benefits. A total of five clinical experts and two economic experts consulted during individual consultations and an advisory board confirmed that based on the results presented, they would conclude that atogepant and rimegepant have similar efficacy and safety profiles.[21]

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 (with or without aura)	Acute treatment of migraine with or without aura in adults who have either: • Tried at least two triptans and they did not work well enough, or • Have contraindications or intolerance to triptans, and have tried NSAIDs and paracetamol without adequate response	The acute management of migraine in the UK is informed by NICE clinical guidelines (CG150) and guidelines published by the British Association for the Study of Headache (2019).[15, 16] At present, first- and second-line therapy consists of treatments such as simple analgesics (i.e., ibuprofen, aspirin or paracetamol) or a triptan (with or without an NSAID). If NSAIDs, paracetamol and at least two triptans have been tried and they did not work well enough, or triptans were contraindicated or not tolerated, the only treatment available that is recommended by NICE is rimegepant (TA919);[3] further details on the clinical care pathway are discussed in Section 1.3.3. Further rationale on unmet need in this population is included in Section 1.1 above.
Intervention	Atogepant	Atogepant (60 mg) as needed, once daily	N/A – In line with final scope
Comparator(s)	• Rimegepant • Paracetamol, with or without an anti-emetic • An NSAID (such as aspirin, ibuprofen, diclofenac or naproxen), with or without an anti-emetic • An oral or non-oral triptan (such as sumatriptan, zolmitriptan, rizatriptan, almotriptan or eletriptan), with or without an anti-emetic • Paracetamol with an oral or non-oral triptan, with or	Rimegepant (75 mg) as needed, once daily	As noted above, the population in which clinicians are expected to use atogepant for the acute treatment of patients with migraine is in those who have received prior treatment with at least two triptans and they did not work well enough, or triptans were contraindicated or not tolerated and NSAIDs and paracetamol did not work well enough. In this population, atogepant would be considered as an alternative to rimegepant (as recommended in TA919).[3] It should be noted that atogepant also has a similar mechanism of action (CGRP inhibition) and a similar oral mode of administration to rimegepant. The results of the NMAs (discussed in Section 3.9) produced [redacted], demonstrating equivalence. As atogepant is intended for use after triptans and other simple analgesics and anti-emetics have been exhausted,

	without an anti-emetic • An NSAID with a triptan, with or without an anti-emetic • Best supportive care		these therapies are not considered relevant comparators to atogepant in this submission. Based on these considerations, rimegepant is considered the only relevant comparator to atogepant in the intended population.
Outcomes	The outcome measures to be considered include: • Reduction in headache pain (including freedom from pain) • Speed of onset • Freedom from most bothersome symptom • Reduction in nausea and vomiting • Reduction in hypersensitivity (e.g. light, sound, smell) • Regain of normal functioning • Prevention of recurrence • Use of rescue medication • Adverse effects of treatment • Health-related quality of life.	• Pain freedom • Pain relief • Sustained pain relief • Sustained pain freedom • Freedom from most bothersome symptom • Use of rescue medication • Ability to function normally • Absence of photophobia, phonophobia and nausea • Adverse effects • Health-related quality of life	In line with the NICE final scope.
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.	• A cost-comparison analysis has been conducted in Microsoft Excel to estimate the incremental costs of atogepant versus rimegepant. • The time horizon for assessing costs was set to 2 years, which is sufficiently long to capture the majority of costs associated with the use of atogepant. • Costs were considered from	N/A – in line with NICE reference case for a cost-comparison analysis.

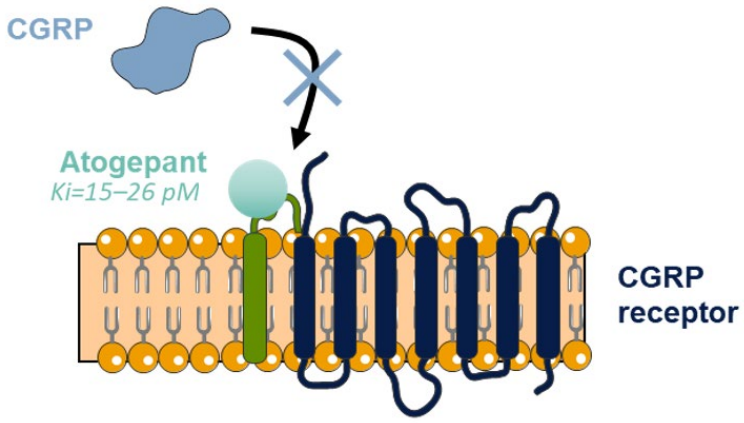
	Costs will be considered from an NHS and Personal Social Services perspective. The availability and cost of biosimilar and generic products should be taken into account.	an NHS and PSS perspective.	
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • Subgroups defined by migraine severity • People currently having treatment for the prevention of migraine • People for whom triptans do not work well enough, are contraindicated or not tolerated • Subgroups defined by the number of previous treatments • People with or who are at risk of medication overuse and developing associated symptoms including MOH • Subgroups defined by severity or number of headache days per month	This submission will focus on the acute treatment of patients with migraine who have had at least two prior triptans and they did not work well enough, or triptans were contraindicated or not tolerated. This is in line with the final recommended population for rimegepant.	The focus of this submission is patients who have had at least two prior triptans and they did not work well enough, or triptans were contraindicated or not tolerated. Therefore, separate subgroup analyses for this population, as requested in the final scope, are not required. Subgroup analyses defined by baseline headache severity (moderate or severe) and preventative migraine medication use were pre-specified and conducted in the ECLIPSE trial (Section 3.7). The results were broadly consistent with those observed for the mITT population in ECLIPSE, which informed the clinical effectiveness evidence in this submission. Therefore, it is not expected that the presence of these factors would influence outcomes, so subgroups for the economic analysis are not presented. Subgroup analyses by number of previous treatments or number of headache days per month were not pre-specified and data on participants at risk of developing MOH was not collected in ECLIPSE.

Abbreviations: MOH: medication overuse headache; NHS: National Health Service; NICE: National Institute of Health and Care Excellence; NSAID: non-steroidal anti-inflammatory drug; PSS: Personal Social Services.

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	Calcitonin gene-related peptide (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.[2, 25] 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.[26-30] Atogepant is a selective, oral, small molecule, CGRP receptor antagonist that blocks the binding of the CGRP to its receptor, antagonising receptor function.[2, 31] ***Mechanism of action for atogepant***  **Source:** Goadsby, et al 2019.[30]
Marketing authorisation/CE mark status	The MHRA marketing authorisation for atogepant for the acute treatment of migraine with or without aura in adults was submitted on [redacted], and is anticipated in April 2026.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	This submission covers the acute treatment of migraine with or without aura in adults. Atogepant is also already indicated for prophylaxis of migraine in adults who have at least 4 migraine days per month.[32]
Method of administration and dosage	Atogepant is an oral tablet. The maximum dose per day for atogepant is 60 mg. For acute treatment of migraine as needed, the recommended dose is 60 mg.[2, a]
Additional tests or investigations	NA

List price and average cost of a course of treatment	The list price of atogepant is: • £25.78 per 2-pack of 60 mg tablets • £90.23 per 7-pack of 60 mg tablets • £182.16 per 28-pack of 60 mg tablets
Patient access scheme/commercial arrangement (if applicable)	No patient access scheme is applicable.

Footnotes: [a] Alongside atogepant 60 mg, the MHRA marketing authorisation for the 10 mg dose of atogepant is also anticipated to be extended to include the acute treatment of patients with migraine; this dosage is not covered by this submission. The 10 mg dose is anticipated to be licensed for use only 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. Atogepant 10 mg is currently available in the UK as packs of 28 tablets for the prevention of migraine. Following receipt of the licence extension of atogepant as an acute treatment of migraine, it is anticipated that atogepant 10 mg will also be made available in the UK in packs of 7 tablets.
Abbreviations: CGRP: calcitonin gene-related peptide; MHRA: Medicines and Healthcare products Regulatory Agency; NA: not applicable; PAS: patient access scheme.

1.3 *Health condition and position of the technology in the treatment pathway*

Summary of migraine

- Migraine is a common neurological disorder characterised by recurrent and debilitating headache attacks which last between four and 72 hours.[33] Worldwide, it is one of the most common neurological disorders, affecting around one in seven people, and is a leading cause of disability.[6, 9, 34]
- Migraine attacks are characterised by the onset of a migraine headache, which are frequently accompanied by symptoms such as sensitivity to light and sound, difficulty concentrating, and nausea.[35] These debilitating symptoms can severely impact the ability of people with migraine to lead a normal life, affecting their mental wellbeing, daily activities, and working lives.[12, 36-40]

Current treatment pathway and unmet need

- Acute treatment of migraine aims to stop migraine attacks, or reduce the severity of the headache and other associated symptoms.[41] Effective treatments are expected to induce a response after two hours.[16, 42]
- Initial treatment options include oral generic treatments such as analgesics and NSAIDs, as well as triptans, all of which have limited efficacy.[43,44]
- Triptans are a mainstay of early line acute treatment.[16, 44] However, many patients do not have adequate symptom relief because of lack of response to triptans, and triptans are not suitable for a considerable proportion of patients either due to intolerable side effects or safety concerns.[19, 45, 46]
- If NSAIDs, paracetamol and at least two triptans have been tried and they did not work well enough, or triptans were contraindicated or not tolerated, rimegepant (TA919) – an oral CGRP antagonist – is the only NICE-recommended treatment in this population.[3, 4]
- Therefore, there is an unmet need for an additional acute treatment option other than rimegepant for patients with migraine who are ineligible for triptans due to lack of response, contraindication or intolerability.

Place of atogepant in the treatment pathway

- In line with clinical expert feedback (n=5), atogepant for the acute treatment of migraine is intended for use within the NHS as an alternative to rimegepant for the same population, that is patients who have had at least two prior triptans and they did not work well enough, or for whom triptans were contraindicated or not tolerated.[21]
- Atogepant is an oral CGRP antagonist which has a similar efficacy and safety profile to rimegepant and provides effective pain relief in addition to other clinically important benefits.[21] Consequently, if atogepant is recommended it would offer a much-needed additional treatment option for patients in the UK who require acute treatment for migraine and who have tried at least two triptans that did not work well enough, or for whom triptans were contraindicated or not tolerated.

1.3.1 Disease overview

Migraine is a neurological disease characterised by recurrent, debilitating headaches of moderate to severe intensity that represents the second most common cause of disability worldwide.[33, 37] It is associated with symptoms that can negatively impact HRQoL, which are experienced before, during or after the headache itself.[47]

Migraine is a chronic disease manifesting as acute attacks. A migraine attack is characterised by the onset of a migraine headache and associated clinical signs. In addition to severe headache pain, migraine attacks are associated with a wide range of non-headache symptoms, which can include photophobia, lethargy, nausea and vomiting.[48] In adults, attacks typically last for four to 72 hours,[33] but evidence from a global study showed that just under one fifth of participants reported attacks lasting over three days.[7] The frequency of migraine attacks varies, with some

individuals experiencing them several times a week, while others may experience only one to two attacks per year.[49, 50]

Table 3: Non-headache symptoms associated with migraine

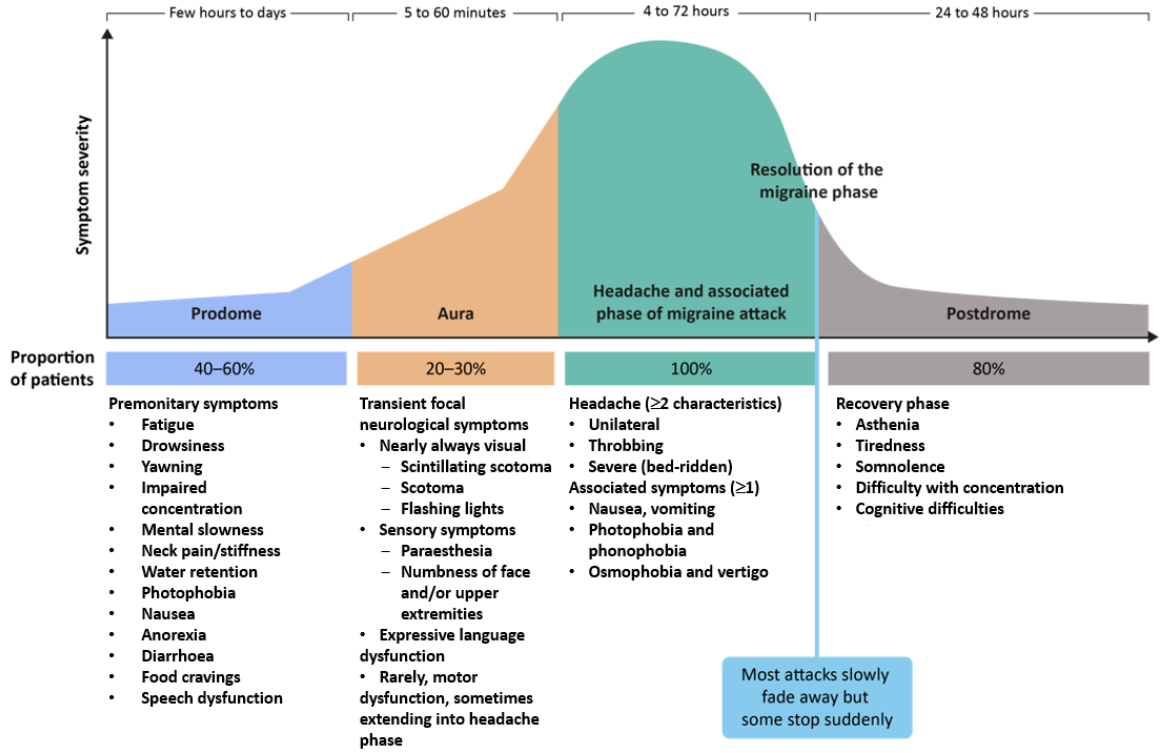
Sensory	Cognitive	Autonomic	Affective
• Photophobia • Phonophobia • Osmophobia (hypersensitivity to odours) • Allodynia (sensitivity to touch)	• Transient amnesia • Attention-deficit disorder • Difficulty finding words • Decreased ability to navigate familiar environments	• Yawning • Increased urination • Nausea • Vomiting • Diarrhoea • Congestion (nasal/sinus) • Runny nose • Flow of tears	• Irritability • Depression • Anxiety • Stress

Source: American Journal of Managed Care.[51]

Clinically, migraine attacks comprise a multiphasic process which includes a prodrome, or premonitory, phase, an aura phase, the migraine pain phase, and the postdrome phase (Figure 1).[48] Each phase is associated with different signs and symptoms, highlighting the complexity of migraine and the involvement of numerous neural networks and brain regions throughout an attack.[48] Migraine attacks can therefore fluctuate in frequency and severity and are often unpredictable.[52, 53] Key characteristics of each phase include:[54]

- **Premonitory phase:** This phase includes a broad range of symptoms that appear hours or days before the onset of the headache.[55] The most common prodromal symptoms include fatigue (49%), neck stiffness (46%) and mood changes (37%).[56]
- **Aura:** Roughly one third of the patients with migraine, particularly women, suffer from auras, a short-term sensory disturbance, before or during some of their headaches. Visual aura is most common (90%), followed by sensory (30–54%) and language aura (31%).[57]
- **Headache:** The activation of the trigeminal sensory pathways generates the throbbing pain in this phase.[58] The intensity of the headache often increases progressively or is explosive at the onset and disrupts daily activities.
- **Postdrome:** As the pain intensity increases, symptoms associated with this phase are likely to become more severe and prolonged. This phase is colloquially known as the “migraine hangover”.[59]

Figure 1: Phases of migraine



Source: Adapted from Ferrari et al 2022;[60] Karsan and Goadsby 2018;[61, 62] Mayo Clinic: Migraine Aura.[63]

During a migraine attack, patients may also experience various neurological signs, including photophobia (91.1%), sensitivity to 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%).[35] Over 70% of patients also experience cutaneous allodynia, a condition characterised by the perception of pain in response to typically non-painful stimuli on the affected skin area.[64]

Classification of migraine

According to the International Headache Society migraine is defined as either episodic migraine (EM; <15 headache days per month) which is experienced by approximately 90% of patients with migraine, or chronic migraine (CM; ≥15 headache days per month of which ≥8 days qualify as migraine for ≥3 consecutive months) which is experienced by approximately 10% of patients with migraine.[47, 65, 66] 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.[39, 67] Patients with migraine (EM or CM) may receive either preventive or acute treatments, with treatment decisions based on individual symptom presentation and patient preference.[8] The UK clinical care pathway for patients with migraine is discussed further in Section 1.3.3.

Aetiology

Migraine is thought to be linked to abnormal brain activity that impacts nerve signals, chemicals, and blood vessels within the brain.[68] Although not fully understood, migraine is thought to result from a combination of genetic factors, environmental factors, some comorbid conditions and stress.[27, 51] The attacks themselves can be caused by a variety of triggers, and can start anywhere between six hours and two days after the trigger happens.[69] Environmental factors that can potentially evoke an attack include hormonal fluctuations, comorbid diseases, sensory stimuli, fatigue, food and changes in the environment or habits.[39] Comorbid conditions are more

common in patients with more severe disease and can include allergies, respiratory illnesses, cardiovascular (CV) disorders, psychiatric disorders, arthritis, obesity, non-cephalic pain and ulcers.[39]

Epidemiology

Migraine is one of the most common neurological disorders worldwide with global prevalence of roughly 1 in 7 people.[6] There are limited data on the incidence of migraine, but 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.[70-72] In the UK, it is estimated that approximately ten million people experience the disease with 190,000 migraine attacks experienced every day.[10]

Whilst migraine can occur at any age, it tends to be most common in those aged between 25 to 55 years old.[33] Furthermore, migraine disproportionately affects women, as it is roughly two to three times more common in women than men.[65, 73-76] Women often experience migraine attacks that are more prolonged, with an increased likelihood of the headache returning, more significant impairment and extended recovery times compared to men.[77] This disparity may be caused by differences in hormones, genetic factors and exposure to environmental stressors.[39] On the other hand, given the lower prevalence of migraine in men, the condition may be overlooked, under-reported and insufficiently managed in men.[39]

1.3.2 Disease burden

Clinical burden

Migraine is a major public health issue with symptoms that are severe and incapacitating.[75] The debilitating symptoms patients experience can have a severe negative impact on their mental wellbeing, physical function, daily activities, and ability to lead a normal life.[12, 36-40] Data from the Global Burden of Disease Study 2023 indicates that migraine was a leading cause of years lived with disability worldwide in both males and females for the age group 15–49 years.[9]

Migraine headaches have been shown to be significantly more painful than tension-type headaches;[78] more than 90% of migraine patients experience moderate to severe pain intensity, and the pain intensity is agnostic of the mean number of headache days reported.[18] In a study of 244 women diagnosed with migraine who had experienced childbirth, using a 0–10 pain rating scale, a typical migraine was rated as 7.1, childbirth as 7.3, and the worst migraine 8.6.[79] For patients who experience this severe pain, the intensity of the pain is reported as unbearable and debilitating, with HRQoL comparable or worse to late-stage oncology diseases.[3, 80] This severity is reflected by the very low utility value of −0.2 previously accepted by NICE in the rimegepant appraisal; a negative utility value refers to a state worse than death.[3]

Migraine is also associated with psychological burden and comorbidities.[81] Depression affects almost 80% of people with migraine at one time or another.[82] People with migraine are also reported to be three times more likely to experience anxiety, insomnia, or gastric ulcers than those without migraine.[81] These comorbidities increase the risk of disease progression.[81]

The high symptom severity may also result in patients with migraine overusing acute medication which can lead to disease progression.[83, 84] A condition known as medication overuse headache (MOH) can occur when patients either develop a new type of headache or a worsening of their pre-existing headache due to overuse of headache medications.[60, 83-85] MOH is thought to affect

up to 2% of the population and not only prolongs headache symptoms but can also increase the risk of developing CM.[86,47]

Moreover, suboptimal treatments may increase the risk of EM transitioning to CM, a term known as migraine chronification. Patients on acute treatment with poor efficacy are more than three times more likely to experience an increase in frequency of attacks than patients on treatments with maximum efficacy.[87] This highlights the need for novel treatments to prevent disease progression and reduce the patient, clinical and economic burden caused by a higher occurrence of migraine attacks.

The clinical burden is further heightened in people unsuitable for triptans due to contraindications, intolerance or inadequate response; this group represents a substantial proportion of the migraine population and is consistently identified across real-world and epidemiological studies.[88, 89] In the absence of effective, migraine specific acute treatment options, these patients often achieve lower rates of pain freedom and functional recovery, rely more on nonspecific analgesics and antiemetics, face greater risk of MOH, and have higher use of urgent or unscheduled care.[88, 90, 91] This subgroup of patients therefore experiences a disproportionate clinical and HRQoL burden and represents a key unmet need for effective acute therapies.[89, 91]

Humanistic burden

Migraine has a considerable negative impact on the lives of affected individuals. The substantial pain and other symptoms experienced during migraine attacks can significantly impact individuals' daily lives. Evidence suggests that over 75% of people with migraine report a reduction in their ability to function normally during an attack and more than 50% have experienced severe impairment or require bed rest during this period.[73, 87] A global study of people with migraine found that 49% reported feeling limited in daily activities throughout all migraine phases.[7] This may also spill over into people's family lives as individuals report a reduced participation in family activities, a perception that their partners/spouses underestimate the severity of their disease and 44% of people with migraine report feeling guilty about the impact of migraine on their family.[7, 92, 93]

Working life for people with migraine can also be negatively impacted. A survey conducted in 2021 showed that migraine had direct impacts on the professional lives of 82% of respondents, due to factors including reduced confidence, elevated stress, and difficulty with time management and clarity of thought.[94] Another study found that 57% of people of migraine were absent for at least 5 days of work over 3 months and around one-third reported concern over their finances, including managing household expenses and long-term financial security.[92, 93] Each year in the UK, 5.7 workdays are lost per person with migraine, equating to 43 million workdays at a total cost of almost £4.4 billion. An further estimated £4.4 billion is lost each year due to reduced productivity associated with those with migraines continuing work.[14] Of particular note, migraine is more prevalent in women, occurring approximately two to three times more frequently than in men.[6] As a result, many working-age women with migraine are unable to work or look after their children due to the severity of their symptoms.

People with migraines experience a high symptom burden and a significantly impacted daily life. A number of large-scale survey studies have established significant and persistent impairments in HRQoL among people with migraine, including physical, social, functional and emotional domains.[95, 96] This highlights the considerable effect migraine can have on a patient's HRQoL and why adequate treatment is essential.

Economic burden

Approximately 10 million individuals in the UK suffer from migraine.[10] Therefore, the relatively high prevalence of this common condition imposes a significant economic burden. People with migraine are also frequent users of healthcare resources, which leads to a substantial economic burden compared to individuals without migraine.[11-13]

NHS expenditure on treating migraine is roughly £150 million per year.[97] Migraine is the most common neurological reason patients reach out to a GP, with 2.5 million appointments falling under this category annually.[98] Furthermore, in 2021–2022, there were 33,562 hospital admissions due to migraine.[99, 100] Increased A&E attendance for headache and migraine attacks have also been reported, with rises of 14% over the last five years.[98] Nationally, around 1 in 20 migraine patients are diagnosed in A&E.[98] A&E admissions may be required due to inadequate symptom control on some migraine treatments due to lack of efficacy and intolerable side effects.[101]

Furthermore, migraine negatively impacts work productivity and causes increased workplace absenteeism.[11] In the UK working population alone, based on the prevalence of migraine from the Global Burden of Disease Study (GBD) 2016 and an average of 11.4 equivalent workdays missed per person per year due to absenteeism and presenteeism, the Work Foundation estimated that employees with migraine in the UK lose 56 to 86 million days of work each year at an annual cost of £5.6 to £8.8 billion each year.[102] Data from the Office for National Statistics (ONS) indicate that 4.9% of sickness absence across the UK is caused by headaches and migraine.[103]

1.3.3 Clinical treatment pathway

Diagnosis

There is no specific diagnostic test or imaging tool used to diagnose the condition. Diagnosis depends on taking a clinical history and performing a clinical exam to rule out other potential causes for the attacks.[104] Patients may be referred to a specialist to further assess their disease and discuss treatment options, particularly if symptoms are not being controlled by current treatments.[105] Furthermore, evidence suggests that people with EM are less likely to seek medical consultation than those with CM.[106] Therefore, EM in particular is often underdiagnosed.[98]

Acute treatment of migraine

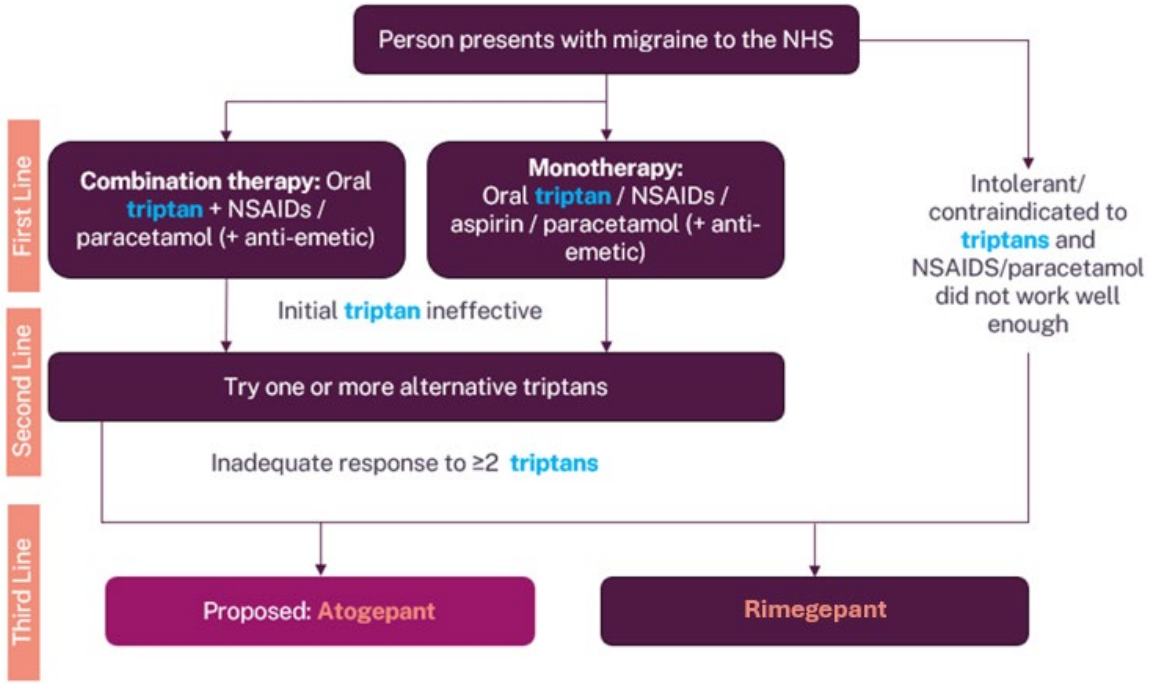
Acute management of migraine is currently informed by clinical guidelines published by NICE (CG150) and the British Association for the Study of Headache (2019).[15, 16] Acute treatment of migraine aims to stop the attack, or reduce the severity of the headache and other associated symptoms, whereas preventive treatment aims to reduce the frequency, severity, and duration of migraine attacks as well as the development of MOHs.[41]

The choice of acute treatment for migraine is guided by patient preference, response to previous treatments, severity and frequency of migraine attacks, additional related symptoms and any comorbidities.[41] Patients are advised to take acute medication early in the migraine attack, at the onset of symptoms. Other therapies may be introduced to provide further symptomatic relief during an attack, such as antiemetics.[107] Effective treatments are expected to induce a response

after two hours, after which either higher doses, alternative treatments or combinations should be considered, if there is no response.[8, 42]

The current acute treatment pathway for patients with migraine in the UK based on NICE guidance is summarised in Figure 2.

Figure 2: Current acute treatment pathway in the UK for migraine and proposed place for atogepant



Abbreviations: NSAID: non-steroidal anti-inflammatory drug.

Acute treatment: first and second lines

First-line therapy consists of treatments such as simple analgesics (i.e., ibuprofen, aspirin or paracetamol) or a triptan (with or without paracetamol or an NSAID). These can be taken either as a monotherapy or in combination. Antiemetics (e.g. metoclopramide or prochlorperazine) can also be considered as an add-on treatment even in the absence of vomiting and nausea.[15, 16]

Triptans are 5HT1-receptor agonists that act to reduce transmission of pain signals from these nerves and are used to treat attacks once symptoms have started.[44] Triptans can work well to treat symptoms for some people with migraine, however, between 55.2% and 81.5% of patients who use triptans discontinue treatment.[20] Reasons for discontinuation include inadequate efficacy, adverse events (AEs) and contraindications, with ≥20% of patients reporting CV conditions that specifically contraindicate treatment with triptans.[4, 19, 45, 46] In these instances, UK clinicians at an advisory board noted that patients may be prescribed higher doses or alternative triptans with different properties and side effect profiles to assess symptom improvement.[21]

Acute treatment: third line

If NSAIDs, paracetamol and at least two triptans have been tried and they did not work well enough, or triptans were contraindicated or not tolerated, the only NICE-recommended treatment

is rimegepant (TA919).[3] Rimegepant is an oral CGRP antagonist that is placed on or under the tongue to treat migraine attacks.

Unmet need

Up to half of people with migraine cannot control migraine-related symptoms with current acute treatment, reporting poor satisfaction with treatment.[17] Those who have an insufficient response to acute treatment experience worse migraine-related disability and MOH than those who respond to treatment.[108] This not only has a negative impact on patient and caregiver utility, but can also lead to increased healthcare resource use.[5] Therefore, suboptimal acute treatment may increase the risk of disease progression, with those with very poor acute treatment efficacy having more than a two-fold increased risk of disease progression.[87] Therefore, efficacious acute treatment can prevent recurrent attacks as well as provide immediate relief for patients.

First- to third-line oral generic treatments of migraine (simple analgesics, NSAIDs and anti-epileptics) often have limited efficacy,[43] likely reflecting that they were not specifically designed to treat migraine. Furthermore, in a cross-sectional survey conducted in Spain and Germany in 2020–2021, satisfaction with current acute treatments amongst patients was generally poor, regardless of migraine/headache severity, as measured by the Migraine Treatment Optimisation Questionaire.[18]

Limitations of current therapies

NSAIDs may be used for the acute treatment of migraine. However, they are associated with limited efficacy compared with migraine-specific agents, especially in moderate–severe attacks.[109] Additionally, NSAIDs are commonly associated with gastrointestinal, renal and hepatic side effects which limits their use, particularly in patients with comorbidities.[110] Furthermore, regular or over-use of NSAIDs can contribute to the development of MOH, providing a need for effective, well-tolerated acute treatments that minimise risk of MOH.[108]

Triptans are also commonly used for acute treatment of migraine, but 15–25% of patients are not adequately managed with them, with one publication reporting that total rates of poor and very poor treatment satisfaction were higher in people currently taking triptans compared with those using other acute treatments.[18] This is corroborated by the results of a cross-sectional survey of clinical experts across the EU4, UK and USA, which included 155 patients from the UK, 55% of whom were reported as triptan insufficient responders (those who did not report achieving pain freedom within two hours of taking acute medication in ≥3 of 5 attacks).[111] Triptan insufficient responders reported a higher level of migraine-related disability compared to the triptan responders based on the Migraine Disability Assessment questionnaire (MIDAS) score (MIDAS: 13.2 vs 7.7; $p<0.0001$).[111]

Furthermore, triptans are associated with high discontinuation rates, with 55–81.5% of participants taking oral triptans to manage migraine symptoms discontinuing treatment.[19, 20] Evidence suggests that this may be due to inadequate efficacy, intolerable adverse events and safety concerns associated with triptan usage.[4, 19, 45, 112] Additionally, triptans are specifically contraindicated in patients with CV comorbidities.[4, 19, 45, 46] HRQoL and work productivity have been found to be significantly impacted in patients who have an insufficient response to triptan therapy compared with those who have a good response.[111] International guidelines lack consensus on standard of care for people for whom triptans are ineffective or unsuitable.[113-116] Therefore, there are currently insufficient acute treatment options in individuals with migraine for whom triptans are ineffective or not well tolerated.

In this patient population, the only recently recommended treatment option by NICE is rimegepant (TA919). Although rimegepant has been found to treat migraine attacks acutely, demonstrating a well-tolerated safety profile, there remains an unmet need for clinicians and patients to have access to an alternative treatment option that is effective and well-tolerated. This need for additional options at this treatment line was established by clinical experts (n=5) consulted at an advisory board.[21]

Anticipated place of atogepant in UK clinical practice

In accordance with clinical expert feedback, atogepant is intended to be used within the NHS as an acute treatment option for patients with migraine in whom at least two triptans have been tried and they did not work well enough, or triptans were contraindicated or not tolerated. This is fully aligned with the population for which the oral CGRP antagonist rimegepant has received a positive recommendation from NICE.[3]

Atogepant is an oral CGRP antagonist which provides effective and sustained pain relief in addition to other clinically important benefits including improved ability to function normally, reduced use of rescue medication within 24 hours, absence of photophobia, phonophobia and nausea and improvements in HRQoL.[22] Consequently, the recommendation of atogepant would provide a much-needed, additional treatment option that provides effective relief for migraine patients with potential to improve productivity and enhance HRQoL.

1.4 *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.[117]

It is not expected that providing or not providing atogepant will exclude anyone protected by equality legislation, result in recommendations that impact these individuals differently from the wider population, or create adverse effects for people with particular disabilities. However, as noted above, migraine is a condition that is more prevalent in women than men, with women experiencing more significant impairment in their day to day lives. As such, the introduction of atogepant as a treatment option has the potential to reduce health inequality between men and women and may particularly benefit working-age women and contribute to greater equality of opportunity in the workplace. Additionally, women often play a larger role in caring for family including children or unwell parents, therefore reducing migraine in these patients could lead to wider social benefit.[118, 119]

2 Key drivers of the cost effectiveness of the comparator(s)

2.1 *Clinical outcomes and measures*

As discussed in Section 1.1, atogepant is intended for use in adults for the acute treatment of migraine who have either:

- Tried at least two triptans and they did not work well enough, or
- Have contraindications or intolerance to triptans, and have tried NSAIDs and paracetamol without adequate response.

This is in full alignment with the population for which rimegepant for the treatment of migraine as received a positive recommendation by NICE (TA919).[3]

The following section provides an overview of the key clinical outcomes and measures considered in the model for TA919 as well as discussion of the key conclusions raised during the evaluation.

Key discussion and conclusions of TA919 (rimegepant for treating migraine)

Time horizon

The submitting Company in TA919 used a 20-year time horizon in its original base case. The EAG disagreed with this assumption and instead used a two-year time horizon within their analysis. Given that a two-year time horizon was considered sufficient to capture all the cost and benefit differences of each migraine attack, it was the preferred choice by the Committee.

Population

The recommendation for rimegepant as an acute treatment of migraine in TA919 does not distinguish between patients with episodic and those with chronic migraine, whereas all the relevant clinical trials for rimegepant for the acute treatment of migraine that supported the appraisal only enrolled people with episodic migraine experiencing two to eight migraine attacks per month. In light of the clinical and patient expert feedback and considering the associated uncertainty, the Committee decided that the trial results were generalisable to both episodic and chronic migraine populations.

Rimegepant was recommended by NICE in TA919 for use in the subpopulation of interest based on clinical data from the overall mITT population (full trial population) rather than the population of interest within the appraisal. The EAG and Committee preferred using the mITT population for decision-making due to the larger sample size compared to the subpopulation of interest which accounted for only 9.3% of patients in the three pooled RCTs included within the submission, introducing uncertainty. It was considered that outcomes were similar between the subgroup and the mITT population. Given that the overall mITT population allowed use of all available trial data, the EAG and committee preferred the use of mITT for decision making.

Efficacy

In NICE TA919, the Company modelled the efficacy of rimegepant using a combined decision-tree and Markov framework.[3] In the initial decision-tree phase, people were classified as responders who continued treatment, or non-responders who stopped. The subsequent Markov phase captured the distribution of monthly migraine days (MMDs) across two health states: on

treatment and stopped treatment. Treatment response was defined using the endpoint pain relief at two hours. For each migraine attack, the model tracked the distribution of pain severity at key time points and quantified the average time spent in each pain state over the 48-hour cycle. These pain-hour distributions were used to derive HRQoL. The Committee considered the model structure and related efficacy outcomes appropriate for decision making.

Discontinuation and stopping rule

A 'Discontinue' health state was included in the Markov phase of the model in TA919. In the Markov phase, on-treatment responders were modelled to discontinue based on discontinuation patterns observed in long-term safety study BHV3000-201. Non-responders, in the decision-tree assessment period, also moved straight to the 'Discontinue' health state. It was assumed that response to a single dose of rimegepant would inform subsequent response to rimegepant. Therefore, in effect, this resulted in the application of a stopping rule if patients did not respond to the first dose. The Committee agreed on the appropriateness of the model structure for decision making though they concluded that a formal stopping recommendation was not needed.

Adverse events

Disutilities and costs associated with AEs were not included in the economic model given that when all AE severities were considered, all events occurred in <2% of the trial population, in both treatment arms of pooled single dose Phase 3 studies. The Committee did not indicate any preferences regarding the modelling of AEs that deviated from the Company's approach.

Health state utility values

Baseline utility values for patients not experiencing a migraine attack in every 48-hour cycle were derived by mapping Migraine-Specific quality of life questionnaire (MSQ)v2 values from the BHV3000-201 trial data to the EQ-5D. Mapping was carried out using the episodic migraine regression in Gillard *et al.* 2012.[120] Health state utility values (HSUV) according to pain severity were informed by Stafford *et al.* 2012[121] and were adjusted for this baseline using the multiplicative approach. No comments were made by the Committee on the approach to modelling HSUVs in TA919.

2.2 *Resource use assumptions*

Resource use considered in the relevant NICE technology appraisal for rimegepant (TA919) include:[3]

- Drug acquisition
    - Only drug acquisition costs for rimegepant were considered within the model.
    - No acquisition cost was included for BSC, given the proposed placement of rimegepant among triptan-failure patients where no other active comparators are available. This was considered a conservative assumption.
    - Non-responders who discontinued in the first model cycle incurred the cost of a whole pack of rimegepant.
- Resource use costs
    - Resource use costs, including those associated with GP visits, A&E visits and hospitalisations, were included.

- No adverse event costs were considered within the models given the low incidence observed in clinical trials.
- No monitoring costs were included in the economic analysis as treatment monitoring is not mandated in the summary of product characteristics (SmPC) for rimegepant. This was considered to be a conservative assumption by the EAG, however nothing further was raised by the Committee in the published documents.

No specific topics were flagged in the draft and final guidance consultation documents relating to the resource use assumptions made in TA919.[3] The resource use assumptions relevant to this appraisal are costs associated with drug acquisition, monitoring, drug wastage and healthcare resource use.

3 Clinical effectiveness

Summary of clinical effectiveness

- ECLIPSE is a Phase 3, randomised, double-blind, placebo-controlled, multiple-attack study with an open-label (OL) extension to evaluate the efficacy, safety, tolerability and the consistency of effect of atogepant for the acute treatment of migraine in patients with a history of migraine (with or without aura).

ECLIPSE trial results

- In ECLIPSE, patients treated with atogepant were statistically significantly more likely to achieve pain freedom at 2 hours than those who received placebo (OR: 2.36; 95% CI: 1.76, 3.15).[22] In addition, atogepant significantly increased the likelihood of MBS-free status at 2 hours and sustained pain relief from 2 to 24 hours, reflecting a durable response.[22]
- In addition, patients experienced meaningful enhancements in HRQoL and functioning at 24 hours when treated with atogepant rather than placebo, including greater gains in EQ-5D-5L and VAS scores, higher medication satisfaction, and improved MQoLQ domain scores for work, social functioning, energy, and migraine symptoms compared to placebo.[22]
- Furthermore, atogepant demonstrated an acceptable safety and tolerability profile for the acute treatment of migraine over the 24-week treatment period with no new safety signals were identified.[22]

Indirect and mixed treatment comparisons

- In the absence of head-to-head evidence for the efficacy and safety of atogepant versus rimegepant as acute treatments for patients with migraine, NMAs were performed.
- The results of the NMAs demonstrate atogepant and rimegepant to be similar in terms of efficacy and safety for the acute treatment of migraine.

Conclusions of the clinical evidence

- The clinical data demonstrate that atogepant provides meaningful pain relief and HRQoL improvements with an acceptable safety profile. NMAs show atogepant is equivalent to rimegepant in efficacy and safety, a conclusion supported by five UK clinical experts at an advisory board.[21]

3.1 *Identification and selection of relevant studies*

An SLR was conducted in August 2025 to identify relevant clinical evidence on the efficacy and safety of atogepant for adult patients (≥18 years old) with a migraine diagnosis, with or without aura.

The SLR identified 4,074 records (excluding duplicates) as of 4th August 2025. After title/abstract screening and full-text screening, a total of 169 publications reporting on 160 unique studies were identified in the SLR. This includes ECLIPSE, a Phase 3 study with atogepant as the primary intervention, which was retrospectively included on the basis of available clinical study reports (CSR) and data recently published at the European Headache Congress (EHC) 2025.[22]

Full details of the SLR methodology used to identify the clinical evidence relevant to atogepant in this submission, including the search and PICO strategy, PRISMA flow diagram, list of included studies, and list of excluded studies at full-text review, is provided in Appendix B.

3.2 *List of relevant clinical effectiveness evidence*

Of the 160 unique studies identified, the ECLIPSE trial was the only interventional trial that provided evidence on the clinical efficacy and safety of atogepant in the indication of interest for this evaluation. The ECLIPSE study was a Phase 3, randomised, double-blind, placebo-controlled, multiple-attack study with an open-label extension to evaluate the efficacy, safety, tolerability, and the consistency of effect of atogepant for the acute treatment of migraine in patients with a history of migraine (with or without aura).

An overview of ECLIPSE is provided in Table 4 with the methodology and results of the trial presented in the sections that follow.

Table 4: Clinical effectiveness evidence

Study	ECLIPSE (NCT06241313)
Study design	Phase 3, randomised, double-blind, placebo-controlled, multiple-attack study with an open-label extension
Population	Subjects 18 to 75 years (inclusive) with a history of migraine (with or without aura) according to the ICHD-3 for ≥12 months, and with a history of 2 to 8 migraine attacks of moderate to severe headache pain in each of the three months prior to screening per investigator judgment.
Number of participants	A total of [redacted] participants were randomised to double-blind treatment, and [redacted] participants entered the open-label period.
Intervention(s)	Atogepant tablets taken for the acute treatment of four qualifying migraine attacks during the double-blind period. After completing the double-blind period, subjects will treat qualifying migraine attacks with atogepant during the open label treatment period until the end of the study at Week 24.
Comparator(s)	Placebo
Indicate if study supports application for marketing authorisation	Yes
Reported outcomes specified in the decision problem	Primary efficacy endpoint: • Pain freedom at two hours after the double-blind dose for the first attack Secondary efficacy endpoints (for the first attack): • Absence of MBS, phono- and photophobia, nausea • Pain relief and sustained pain freedom • Use of rescue medication • Ability to function normally Health-related quality of life endpoints: • EQ-5D-5L • Patient satisfaction with study medication • Migraine quality of life questionnaire • Cognitive function scale • Patient global impression of change Safety evaluations include: • AE monitoring

All other reported outcomes	N/A

Abbreviations: AE: adverse events; EQ-5D-5L: EuroQoL quality of life questionnaire – 5 dimensions, 5 levels; ICHD: International Classification of Headache Disorders; MBS: most bothersome symptom; NA: not applicable.
Source: AbbVie. Data on File. ECLIPSE CSR (2025).[22]

3.3 *Summary of methodology of the relevant clinical effectiveness evidence*

3.3.1 Trial design

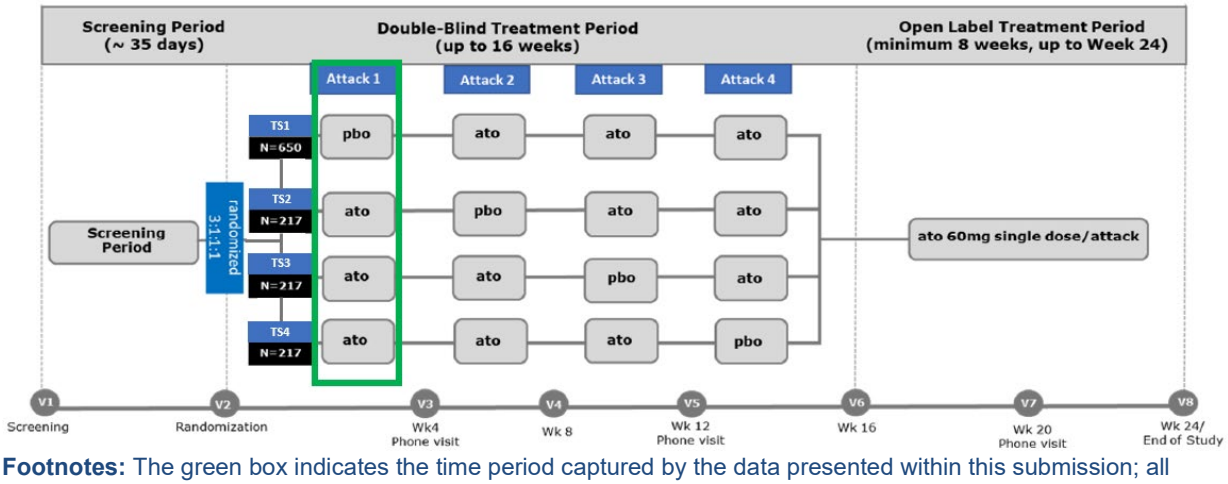
ECLIPSE is a Phase 3, multicentre, randomised, double-blind, placebo-controlled trial evaluating the efficacy, safety, tolerability and consistency of atogepant in patients with acute migraine (with or without aura). The ECLIPSE study design is presented in Figure 3.

The trial screened a total of [redacted] patients for eligibility. Among these, [redacted] were randomised (intention to treat [ITT] population) and [redacted] patients were treated (safety population). Randomisation in the main study was stratified by region, use of and response to triptans and current use of prophylactic concomitant medication for migraine.

The trial consisted of two phases for a total duration of 24 weeks: an up to 16-week double-blind phase and an OL phase up to 24 weeks. Eligible patients were randomised in a 3:1:1:1 ratio to one of four treatment sequence groups, in which each subject received a placebo to treat one qualifying migraine attack and atogepant to treat three qualifying migraine attacks during the double-blind treatment period (phase one) within 16 weeks after randomisation. After treating four qualifying migraine attacks, subjects entered an OL treatment period that continued until the end of the study at Week 24, where they treated qualifying migraine attacks with OL atogepant.

The primary objective of the study was to evaluate the efficacy of a single dose of atogepant 60 mg compared to placebo for the acute treatment of a single migraine attack; hence primary and key secondary endpoints have been designated for first attack only. Results for Attack 1 are therefore the most relevant for decision making and are presented below. This also aligns with the available data for the comparator, rimegepant, where the available clinical trials are single-attack only.

Figure 3: Study design of ECLIPSE trial



Footnotes: The green box indicates the time period captured by the data presented within this submission; all key primary and secondary endpoints refer to data collected in Attack 1.

Abbreviations: ato: atogepant; pbo: placebo; TS: treatment sequence; wk: week.
Source: AbbVie Data on File. ECLIPSE Protocol.[122]

3.3.2 Trial methodology

The ECLIPSE trial methodology is summarised in Table 5.

Table 5: Summary of ECLIPSE methodology

Trial Name	**ECLIPSE (NCT06241313)**
Location	147 sites including Belgium, Czechia, Germany, Hungary, Italy, Poland, Portugal, Slovakia, Spain, Sweden, **United Kingdom (11 sites)**, Japan, China, Korea, and Taiwan
Trial design	Phase 3, multicentre, randomised, double-blind, placebo-controlled trial
Eligibility criteria for participants	Full eligibility criteria for the ECLIPSE trial are presented in Section 5.1 of the protocol included in the reference pack.[122] Key criteria are listed below. **Key inclusion criteria:** • Aged 18 to 75 years (inclusive) with migraine onset before the age of 50 • History of migraine (with or without aura) according to the ICHD-3 for ≥12 months prior to Visit one/Screening • History of migraines lasting between 4 to 72 hours when untreated or treated unsuccessfully and migraine episodes separated by at least 48 hours of headache pain freedom • History of two to eight migraine attacks per month with moderate to severe headache pain in each of the three months prior to Visit one/Screening per investigator judgment • Has used prescription or nonprescription medication for the acute treatment of migraine in the past **Key exclusion criteria:** • Difficulty in distinguishing migraine headache from tension-type or other headaches • History of an average of 15 or more headache days per month in the six months prior to Visit one/Screening/a current diagnosis of chronic migraine as defined by ICHD-3 • Current diagnosis of new persistent daily headache, trigeminal autonomic cephalalgia (e.g., cluster headache), and painful cranial neuropathy as defined by ICHD-3 • Hospital/emergency room treatment required for migraine attacks on three or more occasions within six months prior to Visit one/Screening • ECG with clinically significant abnormalities • QTcF > 450 msec for males or QTcF > 470 msec for females • Hypertension (sitting systolic blood pressure > 160 mm Hg or sitting diastolic blood pressure > 100 mm Hg at Visit one/Screening or Visit two/Randomisation) • Clinically significant abnormalities or laboratory values meeting any of the following criteria: - ALT or AST > 1 × ULN; - Total bilirubin > 1 × ULN (except for subjects with a diagnosis of Gilbert's disease); - Serum albumin < 2.8 g/dL [4.06 µmol/L] • Presence of chronic, non-headache pain condition requiring daily pain medication • History of hypersensitivity or clinically significant adverse reaction to a

	CGRP receptor antagonist • Taken medication for acute treatment of headache (including acetaminophen, NSAIDs, triptans, ditans, ergotamine, opioids, gepants, or combination analgesics) 10 or more days per month in any of the 3 months prior to Visit 2/Randomisation • Exposure to any gepant within 30 days prior to Visit 2/Randomisation • Exposure to injectable monoclonal antibodies blocking the CGRP pathway within 6 months prior to Visit 2/Randomisation
Intervention	Atogepant 60 mg tablets taken for the acute treatment of four qualifying migraine attacks during the double-blind treatment period (up to 16 weeks) after which subjects treated qualifying migraine attacks with atogepant 60 mg during the open-label treatment period until the end of the study at Week 24.
Methods of study drug administration	Oral administration
Permitted and disallowed concomitant medication	**Permitted concomitant medications:** • Aspirin up to 325 mg/day is allowed for cardiac and cerebrovascular prophylaxis • Any oral medications used for migraine prophylaxis, irrespective of whether on-label or off-label (e.g., topiramate, amitriptyline, beta blockers, flunarizine, venlafaxine, etc) and injectable onabotulinum toxin A are permitted provided that the treatment is stable for at least three months prior to Visit two/Randomisation and continues without change in dose throughout the study • The following rescue medications are allowed for the acute treatment of migraines as needed during the study: any triptan, any ditan, any ergot derivative, any opioid, any NSAID, any other form of analgesic [including acetaminophen], any antiemetic agent **Disallowed concomitant medication:** • Initiation of new prophylactic medications are not permitted during the study • Use of rescue medication/therapy is not permitted within 48 hours prior to taking study drug to treat a qualifying migraine • Strong CYP3A4 inhibitors • Strong and moderate CYP3A4 inducers • Strong OATP1B1/OATP1B3 inhibitors • Drugs with narrow therapeutic margins with theoretical potential for CYP drug interactions • CBD oil and medical cannabis • Injectable medications blocking the CGRP pathway (e.g., eptinezumab, erenumab, galcanezumab, fremanezumab) within six months prior to Visit one/Screening and throughout the study period • Any gepants (other than the study drug, atogepant) including ubrogepant, rimegepant, zavegepant • Oral herbal medicine including, but not limited to, traditional Chinese medicine • Any investigational drug outside of this study
Primary endpoint	The primary efficacy endpoint is pain freedom at two hours after the double-blind dose for the first attack.
Key secondary endpoints[a]	• Absence of the MBS at two hours after the double-blind dose for the first attack • Pain relief at two hours after the double-blind dose for the first attack

	• Sustained pain relief from two to 24 hours and two to 48 hours after the double-blind dose for the first attack • Use of rescue medication within 24 hours after the double-blind dose for the first attack • Ability to function normally at one hour, two hours or eight hours after the double-blind dose for the first attack • Sustained pain freedom from two to 24 hours and two to 48 hours after the double-blind dose for the first attack • Absence of photophobia and phonophobia at two hours after the double-blind dose for the first attack • Pain freedom at eight hours after the double-blind dose for the first attack • Pain relief at 30 minutes or one hour after the double-blind dose for the first attack[b] • Absence of nausea at two hours after the double-blind dose for the first attack[b]
Safety endpoints	• AE monitoring • Clinical laboratory testing (haematology, chemistry, and urinalysis), vital sign measurements, ECG variables, and C-SSRS responses as measures of safety and tolerability for the entire study duration
Pre-planned subgroup analyses	Subgroup analyses were conducted for the following factors for the primary endpoint: • Region (Europe, China, Japan, or other) • Current use of prophylactic concomitant medication for migraine (yes or no) • Previous response to and use of triptans (triptan unsuitable, triptan experienced, or triptan naïve)
Duration of study and follow-up	The total study duration consists of a 35-day screening period, followed by up to 16 weeks of double-blind treatment, and then an open-label treatment phase lasting a minimum of 8 weeks and up to 24 weeks.

Footnotes: [a] In addition to the primary and key secondary endpoints presented above, the full list of secondary endpoints and exploratory endpoints assessed in ECLIPSE are available in the study protocol included within the reference pack. [b] These endpoints were not powered to detect statistically significant differences in effect between atogepant and placebo.
Abbreviations: AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CBD: cannabidiol; CGRP: calcitonin gene-related peptide; C-SSRS: Columbia Suicide Severity Rating Scale; CYP: cytochrome; ECG: electrocardiogram; ICHD: International Classification of Headache Disorders; MBS: most bothersome symptom; NSAID: non-steroidal anti-inflammatory drug; QTcF: corrected QT interval; ULN: upper limit of normal.
Source: AbbVie Data on File. ECLIPSE Protocol.[122]

3.3.3 Baseline characteristics

The baseline characteristics of patients included in the ECLIPSE trial for the mITT population for attack 1 are presented in Table 6. Baseline characteristics split out by atogepant and placebo are only available for the mITT for attack 1 due to the nature of the multi-attack trial design. Baseline characteristics for all randomised patients in ECLIPSE (ITT population) is presented in Appendix H.1 for completeness. Clinical experts (n=5) consulted during an advisory board noted that the baseline characteristics were generalisable to the patients they would expect to treat with atogepant in UK clinical practice and that they were similar to those seen in other similar clinical trials, including the rimegepant trials.[21]

Table 6: Baseline characteristics of patients included in the ECLIPSE trial for the attack 1 mITT population

Baseline characteristic	ECLIPSE (attack 1 mITT population)		
	Atogepant (N=[redacted])	Placebo (N=[redacted])	Total (N=[redacted])
Age (years); mean (SD)	[redacted]	[redacted]	[redacted]
Sex (female); n (%)	[redacted]	[redacted]	[redacted]
Weight (kg); mean (SD)	[redacted]	[redacted]	[redacted]
BMI (kg/m2); mean (SD)	[redacted]	[redacted]	[redacted]
Race			
White; n (%)	[redacted]	[redacted]	[redacted]
Asian; n (%)	[redacted]	[redacted]	[redacted]
Other;[a] n (%)	[redacted]	[redacted]	[redacted]
Region			
Europe	[redacted]	[redacted]	[redacted]
China	[redacted]	[redacted]	[redacted]
Japan	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Taiwan	[redacted]	[redacted]	[redacted]
South Korea	[redacted]	[redacted]	[redacted]
Triptan use response (actual); n (%)			
Triptan unsuitable[b]	[redacted]	[redacted]	[redacted]
Triptan experienced[c]	[redacted]	[redacted]	[redacted]
Current use of prophylactic concomitant medication (actual); n (%)			
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Baseline efficacy parameters	**Atogepant (N=[redacted])**	**Placebo (N=[redacted])**	**Total (N=[redacted])**
Migraine headache severity; n (%)			
Moderate Pain	[redacted]	[redacted]	976 (80.4)
Severe Pain	[redacted]	[redacted]	238 (19.6)
Migraine associated symptoms			
Photophobia			
No	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]
Phonophobia			
No	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]
Nausea			

No	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]
Vomiting			
No	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]
Most bothersome migraine-associated symptom			
Photophobia	[redacted]	[redacted]	535 (44.1)
Phonophobia	[redacted]	[redacted]	298 (24.5)
Nausea	[redacted]	[redacted]	381 (31.4)

[a] Other race includes Black or African American, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or Multiple races.[b] Defined as a subject who meets one of the two following criteria: Has a contraindication to triptans based upon local label and investigator judgment, irrespective of prior triptan use OR meets the following triptan failure definition for ≥2 different triptans: Currently uses a triptan or has used a triptan in the past and has not achieved pain relief at two hours post-dose in ≥2 out of 4 attacks based upon subject interview and investigator judgment OR used a triptan in the past but no longer uses a triptan due to AEs based upon subject interview and investigator judgment. [c] Defined as a subject who currently uses a triptan or has used ≥1 triptan in the past and does not meet the criterion for the 'Triptan Unsuitable' subgroup. The total mITT population includes 1223 patients; the mITT efficacy attack 1 population includes [redacted] patients.
Abbreviations: AEs: adverse events; mITT: modified intention to treat; SD: standard deviation.
Source: AbbVie. Data on File. ECLIPSE CSR (2025);[22] Van Dycke *et al.* (2025).[23]

3.3.4 Participant flow

A total of [redacted] patients were screened for eligibility at 147 sites, of whom 1,328 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 1,223 patients met the criteria for the mITT population (i.e., they recorded a baseline migraine headache severity measurement, and had at least one post-dose migraine headache severity or migraine-associated symptom measurement at or before the 48-hour timepoint based on headache eDiary for any attack during the double-blind period; Table 7; Section 3.4). The majority of the patients (n=[redacted] [redacted]) in the ITT population completed the double-blind treatment period, and the main reasons for study discontinuation ([redacted] participants) was 'participant did not treat four qualifying migraine attacks during the double-blind period' ([redacted] participants [redacted]%] total, with similar percentages across treatment sequences).

Further details on the patient disposition are presented in Appendix B.2.

3.4 *Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

The definitions used for the study populations in the trial are presented in Table 7. A summary of the statistical analysis methods used in the trials are presented in Table 8.

Table 7: Trial populations used for the analysis of outcomes in ECLIPSE

Analysis Set	Definition
ITT population	Includes all randomised participants.
mITT population	Consisted of all randomised subjects who received at least 1 dose of study drug during the double-blind treatment period, recorded a baseline migraine headache severity measurement, and had at least 1 postdose migraine headache severity or migraine-associated symptom measurement

	at or before the 48-hour timepoint based on headache eDiary for any attack during the double-blind period.
Safety population	Consisted of all subjects who received at least 1 dose of study drug during the double-blind treatment period.

Abbreviations: ITT: intention to treat; mITT: modified intention to treat.
Source: AbbVie Data on File. ECLIPSE Protocol [Section 7.2].[122]

Table 8: Statistical methods for the primary analysis

Trial	ECLIPSE
Hypothetical objective	The primary efficacy endpoint is pain freedom at two hours after the double-blind dose for the first attack: • **Null**: Atogepant 60 mg is equally effective to placebo in inducing pain freedom at two hours after the double-blind dose for the first attack • **Alternative**: Atogepant 60 mg is superior to placebo in inducing pain freedom at two hours after the double-blind dose for the first attack
Statistical analysis	Analysis of the primary endpoint was conducted on the mITT population based on treatment as randomised. A GLMM was used to analyse the pain freedom at two hours as repeated measures across four attacks. The model assumed a binary distribution for the response and uses a logit link. The analysis model included treatment group, attack, treatment group-by-attack interaction, region, historical triptan-response stratum, use of medication for migraine prevention, and baseline headache severity for the attack. Subjects were included as random effects with unstructured covariance matrix in the model to account for the correlation among repeated measurements. The treatment comparison in terms of odds ratio between atogepant and placebo for pain freedom at two hours after double-blind dose for the first attack was estimated from this model. Odds ratio, associated 95% confidence interval, and 2-sided p-values were reported. For each key secondary efficacy endpoint, the observed response proportions were analysed using the same methods as for the primary efficacy endpoint. The respective comparisons of the atogepant versus placebo for the first attack during the double-blind period were reported according to odds ratios from the GLMM together with 95% confidence intervals and p-values from the GLMM. For key secondary efficacy endpoints on migraine-associated symptoms, baseline presence/absence of the symptom was included as an additional covariate in the GLMM. For key secondary endpoints related to functional disability scale, baseline FDS value was added as a covariate.
Sample size, power calculation	A planned enrolment of approximately 650 randomised subjects per treatment group provided at least 90% power to detect the treatment difference between atogepant (60 mg) and placebo for the primary efficacy endpoint, pain freedom at two hours (7.5%). A fixed-sequence procedure was used for multiple comparisons to control Type I error rate at a 2-sided 0.05 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 were imputed as a non-responder for the endpoints of pain freedom, pain relief, absence of one symptom, or ability to function normally at a specific time point for any attacks during the double-blind treatment period. For other efficacy endpoints, including those evaluated during the OL treatment period, as well as ePRO endpoints evaluated during the double-

	blind treatment period, observed data were utilised in the analyses without missing values imputation. Missing data was handled using the following methods for the efficacy analyses of additional efficacy endpoints utilising repeated measurement models. • Descriptive statistics for efficacy endpoints was based on observed cases only. • A MMRM was applied for continuous endpoints, using observed data without imputation of missing values. • For GLMM on repeated binary endpoints, observed data from the double-blind treatment period was utilised, without imputing missing values.

Abbreviations: ePRO: electronic patient reported outcome; FDS: Functional Disability Scale; GLMM: generalised linear mixed effects model; mITT: modified intention to treat; MMRM: mixed model for repeated measures; NRI: non-responder imputation.
Sources: AbbVie Data on File. ECLIPSE Protocol [Sections 7.7, 7.8];[122] AbbVie Data on File. ECLIPSE Statistical Analysis Plan [Sections 8.0, 9.2, 9.3.3].[123]

Definition of outcome measures

The definitions of the efficacy outcomes used in ECLIPSE are presented in Table 9.

Table 9: Outcome definitions used in ECLIPSE

Outcome measure	Definition
Pain freedom	Reduction in headache severity from moderate/severe at baseline (pre-dose) to no pain
Pain relief	Reduction of a moderate/severe migraine headache at baseline (pre-dose) to a mild headache or to no headache
Sustained pain relief	Pain relief at two hours after the double-blind dose with no administration of rescue medication and no occurrence of a moderate/severe headache for a set period of time
Sustained pain freedom	Pain freedom at two hours after the double-blind dose with no administration of rescue medication and no occurrence of a mild/moderate/severe headache for a set period of time
Absence of MBS	Absence of the MBS at two hours after the double-blind dose; the MBS was identified at baseline for each patient enrolled in the trial
EQ-5D-5L	A generic instrument for use as a measure of health status. The EQ-5D-5L consists of two pages – the EQ-5D-5L descriptive system and the EQ VAS. During the double-blind treatment period, the EQ-5D-5L was completed by the subject in the eDiary at pre-dose and 24 hours after taking the double-blind dose of study drug to treat a qualifying migraine attack. During the OL treatment period, the EQ-5D-5L was completed each time a qualifying migraine attack occurred and was treated with study drug, at pre-dose and at 24 hours after taking the OL dose of study drug.
PSSM	Overall satisfaction with study medication for migraine was assessed using a single item with a 7-point rating scale ranging from extremely satisfied (0) to extremely dissatisfied (6). During the double-blind treatment period, the satisfaction with study medication question was answered by the patient in the

	eDiary at 2 and 24 hours after taking the double-blind dose of study drug to treat a qualifying migraine attack. During the OL treatment period, the satisfaction with study medication question was assessed each time a migraine attack occurred and was treated with study drug, at 2 and 24 hours after taking the OL dose of study drug.
MQoLQ	A questionnaire consisting of 15 questions in five domains. The five domains are (1) work functioning, (2) social functioning, (3) energy/vitality, (4) migraine symptoms, and (5) feelings/concerns. Each domain includes three questions, and each question was answered on a 7-point scale, with a value of 1 indicating maximum impairment of quality-of-life and a value of 7 indicating no impairment. During the double-blind treatment period, the MQoLQ was completed by the subject in the eDiary 24 hours after taking the double-blind dose of study drug to treat a qualifying migraine attack. During the OL treatment period, the MQoLQ was completed each time a migraine attack occurs and was treated with study drug, at 24 hours after taking the OL dose of study drug.
FDS	The FDS is a single item used to measure the subject's level of functional disability. Subjects are asked to rate the performance of daily activities using 4 response options ranging from 0 (no disability, able to function normally) to 3 (severely impaired, cannot do all or most things, bed rest may be necessary). During the double-blind treatment period, the FDS was assessed at pre-dose and one, two, four, and eight hours after taking the double-blind dose of study drug to treat a qualifying migraine attack. During the OL treatment period, the FDS was assessed each time a migraine attack occurs and was treated with study drug, at pre-dose and two hours after taking the OL dose of study drug.
CFS	The CFS is a single item used to measure the subject's difficulty in thinking clearly. Subjects are asked to rate their difficulty in thinking clearly using four response options ranging from 0 (not difficult at all) to 3 (very difficult). During the double-blind treatment period, the CFS was assessed at pre-dose and two, four, and eight hours after taking the double-blind dose of study drug to treat a qualifying migraine attack. During the OL treatment period, the CFS was assessed each time a migraine attack occurs and is treated with study drug, at pre-dose and two hours after taking the OL dose of study drug.
PGIC	The PGIC is a single item used to measure the subject's impression of overall change in migraine since the first dose of study medication. The measure uses a 7-point rating scale with responses ranging from "very much better" to "very much worse." During the double-blind treatment period, the PGIC was captured in the eDiary at two hours after taking the double-blind dose of study drug to treat a qualifying migraine attack.

	During the OL treatment period, the PGIC was assessed each time a migraine attack occurred and was treated with study drug, at two hours after taking the OL dose of study drug.

Abbreviations: CFS: Cognitive Function Scale; eDiary: Electronic Diary; EQ-5D-5L: EuroQol 5-Dimension 5-Level; EQ VAS: EuroQol Visual Analog Scale; FDS: Functional Disability Scale; MBS: Most Bothersome Symptom; MQoLQ: Migraine-Specific Quality of Life Questionnaire; OL: open-label; PGIC: Patient Global Impression of Change; PSSM: Patient Satisfaction with Study Medication.
Source: AbbVie Data on File. ECLIPSE Protocol.[122]

3.5 *Critical appraisal of the relevant clinical effectiveness evidence*

A summary of the quality assessments conducted based on the Cochrane Collaboration's tool for assessing the risk of bias (RoB) for RCTs for ECLIPSE trials are presented in Table 10.

Table 10: Assessment of quality and risk of bias in the ECLIPSE trial

	ECLIPSE
Selection bias	Low
Performance bias	Low
Attrition bias	Low
Detection bias	Low
Reporting bias	Low

Source: AbbVie Data on File. Update and Extension Clinical Systematic Literature Review Report.

3.6 *Clinical effectiveness results of the relevant studies*

As described in Section 1.1, the population of relevance to this submission is in line with the population in which NICE recommended rimegepant (TA919): patients with migraine who have had ≥2 triptans and they did not work well enough, or triptans were contraindicated or not tolerated.[3] To make use of all the available trial data from ECLIPSE, clinical effectiveness data is presented from the mITT population which includes patients for whom triptans were not effective or contraindicated.

When consulted at an advisory board, clinical experts (n=5) noted that results from the mITT population would be generally representative of patients who would receive atogepant in clinical practice and should be used to inform decision making.[21] This conclusion is in line with the EAG and Committee preferences from the rimegepant appraisal (TA919; discussed further in Section 2), which based their recommendation on the data from the overall population.[3] Therefore, data presented below are from the full mITT population.[21]

3.6.1 Primary outcome

As migraine attacks are associated with severe pain, which is highly disabling, achieving pain freedom is a crucial outcome in the treatment of migraine.[33] Pain freedom at 2 hours is therefore considered a gold standard endpoint in the acute treatment of migraine, with BASH recommending this as a relevant endpoint to establish an effective treatment.[16]

In the ECLIPSE trial, patients treated with atogepant were statistically significantly more likely to achieve pain freedom at two hours compared to those treated with placebo. The OR of 2.36

(95% CI: 1.76, 3.15) translates to an 136% increase in the odds of achieving pain freedom at two hours when treated with atogepant compared with placebo (Table 11).[23]

Table 11: Pain freedom at two hours after the double-blind dose for the first attack (mITT population)

	Atogepant (N=605)[a] n/N1 (%)[b]	Placebo (N=618)[a] n/N1 (%)[b]	OR (95%CI) vs Placebo[c]	P-value
Pain freedom at 2 hours	146/602 (24.3)	80/612 (13.1)	2.36 (1.76, 3.15)	<0.0001

Footnote: [a]N= number of subjects in the mITT population; [b]n=Number of responders/N1=number of patients who received the treatment for the specified attack and had baseline headache severity for that attack. Missing data were imputed as non-responder; [c]The odds ratios between group treatment differences for the primary endpoint are derived from the GLMM methods. The total mITT population includes 1223 patients; the mITT efficacy attack 1 population includes [redacted] patients.
Abbreviations: CI: confidence interval; GLMM: generalised linear mixed effects model; mITT: modified intent to treat.
Source: Van Dycke et al. (2025).[23]

3.6.2 Key secondary outcomes

Patients treated with atogepant showed significantly better response rates than patients treated with placebo for key secondary outcomes (adjusted p≤0.0001) (Table 12).

Clinical experts (n=5) consulted at an advisory board confirmed that the key endpoints presented below are most important and clinically meaningful, emphasising that effective symptom relief and the ability to function normally are central to patients' daily lives.[21] Consistent with this, ECLIPSE data demonstrates that atogepant provides significant improvements versus placebo in MBS-free at 2 hours, pain relief at 2 hours, and the ability to function normally at 2 hours, underscoring how quickly patients can return to their usual activities. Moreover, the significant improvement in sustained pain relief from 2 to 24 hours demonstrates the durability of the response, helping patients stay engaged in work, family, and other daily tasks throughout the day. Importantly, the reduction in rescue medication use within 24 hours indicates that atogepant can lessen the need for additional therapies, thereby reducing overall drug exposure and the risks associated with medication overuse headaches or AEs from supplementary treatments.

Table 12: Analysis results for the key secondary efficacy outcomes (mITT population)

	Atogepant (N=605)[a] n/N1 (%)[b,c]	Placebo (N=618)[a] n/N1 (%)[b,c]	OR (95%CI) vs Placebo[d]	P-value[e]
MBS free at 2 hours	263/602 (43.7)	200/612 (32.7)	1.77 (1.41, 2.24)	≤0.0001
Pain relief at 2 hours	434/602 (72.1)	333/612 (54.4)	2.35 (1.85, 2.98)	≤0.0001
Sustained pain relief 2 to 24 hours	348/602 (57.8)	164/612 (26.8)	4.04 (3.18, 5.15)	≤0.0001
Rescue medication use within 24 hours	91/602 (15.1)	327/613 (53.3)	0.14 (0.11, 0.19)	≤0.0001
Ability to function normally at 2 hours	288/602 (47.8)	245/613 (40.0)	1.68 (1.29, 2.18)	≤0.0001

Footnote: [a] N= number of subjects in the mITT population; [b] n=Number of responders/N=number of participants in that group; [c] The point estimate for all key secondary endpoints is responder rate; [d] The odds ratios between group treatment differences for the primary and all key secondary endpoints are derived from the GLMM methods; [e] Adjusted p-value use fixed-sequence procedure to control the overall type I error rate for multiple comparisons. The total mITT population includes 1223 patients; the mITT efficacy attack 1 population includes [redacted] patients.
Abbreviations: CI: confidence interval; GLMM: generalised linear mixed effects model; mITT: modified intent to treat.
Source: Van Dycke et al. (2025).[23]

3.6.3 Other secondary outcomes

Patients treated with atogepant showed significantly better response rates than those treated with placebo for 7 of the 11 other endpoints (adjusted p≤0.0001; Table 13). While a significant difference was not observed for the remaining four endpoints, it is important to note that the study was not powered to detect a treatment difference between the treatments for these endpoints.

Table 13: Analysis results for other efficacy outcomes (mITT population)

	Atogepant (N=605) n/N1 (%)[a]	Placebo (N=618) n/N1 (%)[a]	OR (95%CI) vs Placebo[b]	Nominal p-value
Sustained pain relief 2 to 48 hours	311/602 (51.7)	142/612 (23.2)	3.77 (2.95, 4.82)	≤0.0001
Sustained pain freedom 2 to 24 hours	107/602 (17.8)	39/612 (6.4)	3.58 (2.44, 5.25)	≤0.0001
Sustained pain freedom 2 to 48 hours	100/602 (16.6)	35/612 (5.7)	3.62 (2.43, 5.39)	≤0.0001
Absence of photophobia at 2 hours	309/602 (51.3)	256/612 (41.8)	1.74 (1.37, 2.19)	≤0.0001
Absence of phonophobia at 2 hours	364/602 (60.5)	300/612 (49.0)	1.96 (1.55, 2.48)	≤0.0001
Pain freedom at 8 hours	359/602 (59.6)	163/612 (26.6)	4.28 (3.36, 5.45)	≤0.0001
Ability to function normally at 8 hours	393/602 (65.3)	214/613 (34.9)	3.93 (3.08, 5.01)	≤0.0001
Pain relief at 1 hour	242/602 (40.2)	255/612 (41.7)	1.04 (0.83, 1.30)	[redacted]
Absence of nausea at 2 hours	435/602 (72.3)	410/612 (67.0)	1.24 (0.97, 1.60)	[redacted]
Pain relief at 30 minutes	116/602 (19.3)	152/612 (24.8)	0.82 (0.63, 1.06)	[redacted]
Ability to function normally at 1 hour	194/602 (32.2)	194/613 (31.6)	1.06 (0.75, 1.48)	[redacted]

Footnote: [a]The point estimate for all key secondary endpoints is responder rate; [b]The odds ratios between group treatment differences for the primary and all key secondary endpoints are derived from the GLMM methods; [c]Adjusted p-value use fixed-sequence procedure to control the overall type I error rate for multiple comparisons. The total mITT population includes 1223 patients; the mITT efficacy attack 1 population includes [redacted] patients.
Abbreviations: CI: confidence interval; GLMM: generalised linear mixed effects model; mITT: modified intent to treat.
Source: AbbVie. Data on File. ECLIPSE CSR (2025);[22] Van Dycke et al. (2025).[23]

3.6.4 HRQoL

European Quality of Life-5 Dimension – 5 level

The EQ-5D-5L descriptive system comprises five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). The EQ VAS records the respondent's self-rated health on a VAS where the endpoints are labelled as "best imaginable health state" and "worst imaginable health state". Nominally significantly greater improvements from baseline (mixed model for repeated measures [MMRM]) in EQ-5D-5L descriptive system index and VAS scores at 24 hours after the double-blind dose were demonstrated for participants treated with atogepant compared to placebo during the double-blind period (Table 14).

Table 14: Change from baseline in EQ-5D-5L scores at 24 hours after the double-blind dose (mITT population)

					Model-based results (N=[redacted])[a,b]				
					Within group change from baseline		Between groups difference (compared with placebo)		
Treatment	N_OBS[c]	Baseline mean (SD)	Postbaseline mean (SD)	Unadjusted mean CfB (SD)	LS mean (SE)	95% CI	LS Mean (SE)	95% CI	Nominal p-value
EQ-5D-5L descriptive system index score									
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Atogepant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ VAS score									
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Atogepant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnote: [a] MMRM analysis includes treatment group, attack, treatment group-by-attack interaction, region (Europe, China, Japan, and other), historical triptan-response stratum (Triptan Unsuitable, Triptan Experienced, or Triptan Naïve), use of medication for migraine prevention (yes/no) and baseline headache severity (moderate or severe) for the attack. The EQ-5D-5L baseline score and baseline-by-attack interaction will also be included in the model. Unstructured covariance structure is used. The model includes only observed data. No imputation used; [b]Number of unique subjects contributing to the model estimates; [c] Number of subjects with observed measurements at both baseline and post-baseline.
Abbreviations: CI: confidence interval; CfB: change from baseline; EQ-5D-5L: European Quality of Life-5 Dimensional-5 Level; LS, least square; mITT: modified intention to treat; MMRM: mixed model for repeated measures; OBS: observed; SD: standard deviation; SE: standard error; VAS: visual analogue scale.
Source: AbbVie. Data on File. ECLIPSE CSR (2025).[22]

Patient satisfaction with study medication

The PSSM assesses the subject's overall satisfaction with study medication for migraine. A significantly higher proportion of subjects treated with atogepant reported a rating of "satisfied" or "extremely satisfied" with study medication at 2 and 24 hours after the DB dose as assessed by the PSSM compared with placebo (Table 15).[22]

Table 15: PSSM at 2 and 24 hours after the double-blind dose for the first attack (mITT population)

Post-baseline Timepoint / Treatment	N_OBS[a]	Responder n (%)	Model-based results			
			Response rate		OR compared to placebo	
			Point estimate (%)[b]	95% CI	OR [95% CI]	Nominal p-value
2 hours after the double-blind dose						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]		
Atogepant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 hours after the double-blind dose						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]		
Atogepant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a]Number of subjects who received the treatment for the specific attack. Missing data were imputed as non-responders; [b]The point estimate is responder rate.
Abbreviations: CI: confidence interval; mITT: modified intention to treat; OBS: observed; OR: odds ratio; PSSM, patient satisfaction with study medication.
Source: AbbVie. Data on File. ECLIPSE CSR (2025).[22]

Migraine Quality of Life Questionnaire

The MQoLQ assesses impairment of quality-of-life in five domains, with higher scores in indicating less impairment (i.e., improvement). At 24 hours after taking double-blind study drug, participants treated with atogepant had nominally significantly higher LS mean scores than subjects treated with placebo for each of the 5 MQoLQ domains: work functioning, social functioning, energy/vitality, feelings/concern, and migraine symptoms (Table 16).[22]

Table 16: MMRM domain scores assessed at 24 hours after the double-blind dose (mITT population)

Treatment	N_OBS[c]	Postbaseline mean (SD)	Model-based results [N=[redacted]][a,b]				
			Postbaseline		Between group differences compared to placebo		
			LS mean (SE)	95% CI	LS Mean (SE)	95% CI	Nominal p-value
Work Functioning Score at 24 Hours after the double-blind dose							
Placebo	[redacted]	[redacted]	[redacted]	[redacted]			
Atogepant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Social Functioning Score at 24 Hours after the double-blind dose							
Placebo	[redacted]	[redacted]	[redacted]	[redacted]			
Atogepant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Energy/Vitality Score at 24 Hours after the double-blind dose							
Placebo	[redacted]	[redacted]	[redacted]	[redacted]			
Atogepant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Feeling/Concerns Score at 24 Hours after the double-blind dose							
Placebo	[redacted]	[redacted]	[redacted]	[redacted]			
Atogepant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Migraine Symptoms Score at 24 Hours after the double-blind dose							
Placebo	[redacted]	[redacted]	[redacted]	[redacted]			
Atogepant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnote: [a] MMRM analysis. Unstructured covariance structure is used. The model includes only observed data. No imputation used; [b]Number of unique subjects contributing to the model estimates; [c]Number of subjects with observed measurements at post-baseline.
Abbreviations: CI: confidence interval; LS, least square; mITT: modified intention to treat; MMRM: Migraine Quality of Life Questionnaire; OBS: observed; SD: standard deviation; SE: standard error.
Source: AbbVie. Data on File. ECLIPSE CSR (2025).[22]

Cognitive function scale

The CFS is a single item used to measure the participant's difficulty in thinking clearly. Participants are asked to rate their difficulty in thinking clearly using 4 response options ranging from 0 (not difficult at all) to 3 (very difficult). Achievement of ability to think clearly was defined as a rating of "not difficult at all" assessed via the CFS.

Treatment with atogepant led to nominally significantly higher responder rates compared with placebo for the achievement of ability to think clearly. Higher responder rates were observed at two hours and the difference between atogepant and placebo increased at four hours and at eight hours (Table 17).[22]

Table 17: Achievement of ability to think clearly after the double-bind dose assessed by CFS (mITT population)

Post-baseline Timepoint / Treatment	N_OBS[a]	Responder n (%)	Model-based results			
			Response rate		Odds ratio compared to placebo	
			Point estimate (%)[b]	95% CI	Odds ratio [95% CI]	Nominal p-value
2 hours after the double-blind dose						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]		
Atogepant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4 hours after the double-blind dose						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]		
Atogepant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8 hours after the double-blind dose						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]		
Atogepant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a]Number of subjects who received the treatment for the specific attack. Missing data were imputed as non-responders; [b]The point estimate is responder rate.
Abbreviations: CFS: cognitive function scale; CI: confidence interval; mITT: modified intention to treat; OBS: observed.
Source: AbbVie. Data on File. ECLIPSE CSR (2025).[22]

Patient global impression of change

The PGIC scale measures the participant's impression of overall change in migraine at two hours after taking double-blind study drug to treat a qualifying migraine attack using a 7-point rating scale with responses ranging from "very much better" to "very much worse."

Participants treated with atogepant had nominally significantly higher responder rates compared with placebo for the achievement of "much better" or "very much better" on the PGIC (Table 18). At two hours after the double-blind dose, the percentage of participants who rated their overall change in migraine as "much better" or "very much better" on the PGIC was [redacted] with atogepant and [redacted] with placebo (OR [redacted], nominal p[redacted]).[22]

Table 18: Achievement of a rating of "much better" or "very much better" at two hours after the double-blind dose assess by the PGIC (mITT population)

Post-baseline Timepoint / Treatment	N_OBS[a]	Responder n (%)	Model-based results			
			Response rate		Odds ratio compared to placebo	
			Point estimate (%)[b]	95% CI	Odds ratio [95% CI]	Nominal p-value
2 hours after the double-blind dose						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]		
Atogepant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a]Number of subjects who received the treatment for the specific attack. Missing data were imputed as non-responders; [b]The point estimate is responder rate.
Abbreviations: CI: confidence interval; mITT: modified intention to treat; OBS: observed; PGIC: patient global impression of change.
Source: AbbVie. Data on File. ECLIPSE CSR (2025).[22]

3.6.5 Conclusions of the clinical effectiveness results

The clinical results of ECLIPSE demonstrate that atogepant delivers statistically significant, clinically meaningful benefits across pain, function and patient experience compared to placebo. Patients treated with atogepant were statistically significantly more likely to achieve pain freedom at 2 hours than those on placebo (OR: 2.36; 95% CI: 1.76, 3.15), a 136% increase in the odds of pain freedom.[23] In addition, atogepant significantly increased the likelihood of MBS-free status at 2 hours and sustained pain relief from 2 to 24 hours, reflecting a durable response.[22] Beyond pain, patients experienced meaningful enhancements in HRQoL and functioning at 24 hours compared to placebo, including greater gains in EQ-5D-5L and VAS scores, higher medication satisfaction (PSSM at 2 and 24 hours), and improved MQoLQ domain scores for work functioning, social functioning, energy/vitality, feelings/concerns, and migraine symptoms.[22]

3.7 *Subgroup analysis*

To identify any variation in the efficacy of atogepant, the primary endpoint of pain freedom at 2 hours was analysed by several demographic and disease characteristics (Table 5; Section 3.3.2). Across the majority of demographic and disease characteristic subgroups, treatment with atogepant was associated with higher response rates compared with placebo across subgroups. In the subgroup of patients with migraine who have had ≥2 triptans and they did not work well enough, or triptans were contraindicated or not tolerated, atogepant demonstrated similarly positive results to the mITT population, with a primary endpoint OR versus placebo of [redacted] (95% CI: [redacted]). Full results of the subgroup analyses are provided in the CSR.[22]

3.8 *Meta-analysis*

As the ECLIPSE trial is the only relevant pivotal trial investigating the efficacy and safety of atogepant as an acute treatment for migraine, no meta-analysis has been conducted.

3.9 *Indirect and mixed treatment comparisons*

As outlined in Section 1.1, rimegepant represents the only relevant comparator for the cost-comparison analysis presented in this appraisal. In the absence of direct head-to-head data for the comparative efficacy and safety of atogepant versus rimegepant, NMAs were conducted to assess the relative efficacy and safety of atogepant versus rimegepant in the target indication. The methodology of these analyses is discussed in Section 3.9.3.5 below, and full details are presented in Appendix C.

These NMAs were designed to investigate the comparative efficacy and safety of atogepant versus rimegepant. In line with the Committee and EAG conclusion in TA919 and clinical expert feedback regarding the most appropriate population for decision making, the results for these NMAs are based on the mITT population.[3, 21]

3.9.1 Identification and selection of relevant studies

As reported in Section 3.1 and in line with the NICE methods guide, an SLR was conducted in August 2025 to identify relevant efficacy, safety, and tolerability data for existing and upcoming acute treatments of migraine. Overall, the SLR identified 159 (totalling 160, with the inclusion of ECLIPSE) RCTs meeting the inclusion criteria. Full details on the methodology and the results of the SLR, including a full list of search dates and PRISMA flow diagrams, are presented in Appendix B.

3.9.2 Eligibility for the NMA

The clinical SLR captured data from all potentially relevant studies from a global perspective. Therefore, a number of studies were not eligible for inclusion in the NMA, such as those not reporting relevant outcomes, or those investigating treatments that are not licenced for the acute treatment of migraine or investigated licenced treatments that did not represent relevant comparators for atogepant. A summary of the inclusion criteria for studies in the NMA is provided in Table 19.

Table 19: Inclusion criteria for studies in the NMA

Category	Inclusion Criteria
Population	Adults (18 years and older) with a migraine diagnosis (with or without aura)
Treatment(s) of interest	• Atogepant 60 mg • Rimegepant 75 mg • Placebo
Outcomes of interest	**Efficacy outcomes** • Pain freedom at 2 hours • Absence of the most bothersome symptom at 2 hours • Pain relief at 2 hours • Sustained pain relief at 2-24 hours • Sustained pain relief at 2-48 hours • Rescue medication use within 24 hours • Ability to function normally at 2 hours • Sustained pain freedom at 2-24 hours • Sustained pain freedom at 2-48 hours **Safety outcomes:** • Any AEs

Abbreviations: AE: adverse event; NMA: network meta-analysis.

Included studies

Of the 160 RCTs identified in the SLR, eight were identified as relevant for inclusion in the NMAs for the overall population based upon inclusion of at least one treatment of interest (atogepant or rimegepant). As outlined above, in line with TA919, data for the full mITT population is used in this submission as proxy for subpopulation data.[3]

A summary of the studies included in the NMAs are presented in Table 20 below..

Table 20: Overview of studies included in the NMAs

Study	Author and Year	Treatments	Phase	Study setting	Blinding	Number of attacks
ECLIPSE	AbbVie (data on file) 2025[22]	• Atogepant 60 mg QD • Placebo	Phase 3	Multi-centre international	Double-blind	Multiple attacks[a]
BHV3000-302	Lipton 2019[124]	• Rimegepant 75 mg QD • Placebo	Phase 3	Multi-centre US	Double-blind	Single attack
Marcus 2014	Marcus 2014[125]	• Rimegepant 75 mg QD • Placebo	Phase 2	Multi-centre US	Double-blind	Single attack
BHV3000-301	Lipton 2024[126]	• Rimegepant 75 mg QD • Placebo	Phase 3	Multi-centre US	Double-blind	Single attack
BHV3000-310	Yu 2023[127]	• Rimegepant 75 mg QD • Placebo	Phase 3	Multi-centre China/South Korea	Double-blind	Single attack
BHV3000-303	Croop 2019[128]	• Rimegepant 75 mg QD • Placebo	Phase 3	Multi-centre US	Double-blind	Single attack
BHV3000-313	Ikeda 2025[129]	• Rimegepant 75 mg QD • Placebo	Phase 3	Multi-centre Japan	Double-blind	Single attack
BHV3000-406	Ashina 2025[130]	• Rimegepant 75 mg QD • Placebo	Phase 4	Multi-centre international	Double-blind	Single attack

Footnotes: [a] Primary efficacy analyses in ECLIPSE were conducted using data for the first attack only.
Abbreviations: mITT: modified intention to treat; N/A: not applicable; NMA: network meta-analysis; QD: once daily.

3.9.3 Feasibility assessment

The comparability of the evidence identified in the SLR was investigated extensively through a NMA feasibility assessment. Heterogeneity with respect to patient characteristics, study design, interventions, and outcomes were assessed and the potential implications of identified differences are summarised in the sections below. In summary, the studies included in the NMA were found to be broadly comparable, with limited heterogeneity between trials identified. In support of this, when consulted at an advisory board, UK clinical experts specialising in headache and neurology (n=5) did not consider there to be any meaningful differences between the studies included in this NMA.[21] Further details on the feasibility assessment are provided in Appendix C.1.

3.9.3.1 Population

As the patient population criteria of the SLR stipulated that patients must be adults and have a migraine diagnosis, with or without aura, all studies included in the SLR have a patient population relevant for inclusion in the NMA.

Details of baseline characteristics of patients (such as age, sex, race, body mass index [BMI] and MMD) across the studies included in the NMA are available in Appendix C.1. Most trials had highly comparable inclusion criteria and populations with respect to the baseline characteristics.

However, BHV3000-313[129] and BHV3000-310[127] were conducted in exclusively east Asian populations, while other rimegepant trials were conducted in US or multinational populations and the ECLIPSE trial was conducted in a non-US, multinational population.[22] To assess whether any differences in baseline characteristics, such as in ethnicity, could be considered as potential treatment effect modifiers (TEMs) in the acute treatment of migraine, a targeted review of the literature was conducted and no conclusive evidence of TEMs were identified. Clinical experts (n=5) were also consulted in individual consultations and at an advisory board conducted for this submission and considered that the baseline characteristics of the included studies were broadly similar and did not consider that there would be any relevant TEMs.[21] Therefore, the populations of the studies included in the NMAs are considered comparable, with limited heterogeneity between the patient populations in the different trials.

This conclusion of comparability is further supported by the results of sensitivity analyses conducted in ECLIPSE.[22] Sensitivity analyses were conducted using generalised linear mixed models (GLMM) and included region (Europe, China, Japan, and other) as a stratification factor.[22] Results from the sensitivity analyses supported the robustness of the primary approach and demonstrated that the treatment effect of atogepant was not influenced by region.[22] Full details of the sensitivity analyses are available in the CSR.[22]

3.9.3.2 Outcomes

The outcomes of interest in the conducted NMAs are presented in Table 19. Detailed definitions of the outcomes from each trial included in the NMA are presented in Appendix C.1. In summary, the outcomes were considered to be well defined across the more recent trials which investigated the acute treatment of migraine, though exact definitions differed slightly across the studies.

Data on all outcomes of interest were available for all but two studies in the NMAs (Marcus 2014 and BHV3000-310), but based on the outcomes assessment that was conducted, no trials were

excluded from the NMAs for not reporting data for any of the endpoints of interest and neither were any trials excluded due to the definitions of their endpoints.

3.9.3.3 Time points

All primary NMA analyses were based on the efficacy assessed at the primary endpoint of each trial. For all trials included in these NMAs, the primary endpoint was defined with respect to the first migraine attack for which the trial's acute medication was given. All included trials consider equivalent 'time points' in the sense that they measured the response following the first migraine attack.

3.9.3.4 Study design

Of the eight trials included in the NMA, all were exclusively double-blind, placebo-controlled, multi-centre trials. None were OL and no crossover was reported across any of the studies. Three of the included studies were international multi-centre trials, four were conducted in the US and one was conducted solely in Japan. The phase of the study was also reported in all eight trials; six were Phase 3 and one each were Phase 2 and Phase 4.

Other than ECLIPSE, all trials were single attack trials; however, the primary and key secondary efficacy endpoints of ECLIPSE only considered the first attack, in line with the other trials included in the NMA. As discussed previously, this study design in ECLIPSE did not preclude its use as a suitable data source in this NMA and therefore the primary efficacy endpoints from ECLIPSE were also included in these analyses. Further details of the feasibility assessment of study design are presented in Appendix C.1.

3.9.3.5 Summary of feasibility assessment

As discussed in the previous sections, none of the eight studies assessed within the NMA feasibility assessment were excluded, based on a robust assessment of the outcomes, treatments, dosage, patient characteristics, study characteristics and design, or outcomes measures reported within the studies.

3.9.4 Methodology

All NMAs were conducted using a Bayesian hierarchal generalised linear model approach, with model estimates generated using Monte Carlo Markov chains (MCMC) in accordance with guidance provided within NICE Decision Support Unit (DSU) technical support document (TSD) 2 and 3.[131, 132] Fixed effects (FE) and random effects (RE) models were fitted for each endpoint. Both FE and RE WinBUGS models were extracted directly from NICE TSD DSU 3, and vague priors were placed on all parameters of interest, other than the between-trial standard deviation in RE models, which were informative due to the sparsity of the networks investigated.[131] In primary outcomes of interest in which sufficient data was available for any theoretical estimation of between-trial heterogeneity, vague priors were also considered on the between-trial standard deviation parameter. The vague priors and relevant parameters were $\mu_i \sim N(0, 10000)$, $\sigma \sim U(0.0001, 5)$, $d_j \sim N(0, 10000)$ (mu is trial mean, sigma is standard deviation, and d is treatment effect). The informative prior chosen was a half normal distribution with mean of 0 and a standard deviation of 0.32.

Statistical assessments of heterogeneity were based on model fit comparisons of FE and RE models using deviance information criteria (DIC) and total residual deviance. DIC was defined as

the sum of the posterior mean of the total residual deviance and the total leverage. Differences in DIC of <4 indicated that the models were appropriate for use.

The endpoints that were included in the NMA were in line with those discussed in the feasibility assessment in Section 3.9.3. NMA results for relative treatment effects were summarised as odds ratios (ORs) and 95% credible intervals (CrI) for all endpoints. Statistical significance was defined in the Bayesian context as any result in which the 95% CrI did not include the null value (i.e., OR = 1 for dichotomous models using the logit link). Absolute effects of treatment (e.g., the absolute probability of pain freedom at 2 hours) were also estimated; placebo meta-analyses were conducted to allow for the estimation of the absolute effect for placebo for each outcome; these were then combined with the estimated relative treatment effects (for each treatment versus placebo) to estimate the absolute effect for each treatment.

Full descriptions of the statistical methods employed in the NMA, are presented in Appendix C.2.

3.9.5 Results

3.9.5.1 Model fit statistics

To ensure a comprehensive methodological approach, both FE and RE NMAs were conducted, and statistical assessments of heterogeneity were based on model fit comparisons of FE and RE models using DIC and total residual deviance, as presented in Table 21.[133]

Model fit was similar across the FE and RE models for all endpoints in the mITT NMAs. In all outcomes assessed in the NMAs except for sustained pain relief from 2 to 24 hours, there were no meaningful (< 3 points) to borderline meaningful (between 3 and 5 points) deviances between the models. As residual deviance was notably improved using a RE model indicating better statistical fit, the RE model was selected for use in all base case analyses.[131] To account for the heterogeneity in sparse networks without inflating credible intervals (CrI) to unrealistically wide margins, the RE model with an informative prior was selected over a vague prior as the primary models for all networks.

Table 21: Model fit statistics

Outcome	Model	DIC	Residual Deviance	SD
Pain freedom at two hours	FE	[redacted]	[redacted]	[redacted]
	RE (IP)	[redacted]	[redacted]	[redacted]
	RE (VP)	[redacted]	[redacted]	[redacted]
Absence of MBS at two hours	FE	[redacted]	[redacted]	[redacted]
	RE (IP)	[redacted]	[redacted]	[redacted]
	RE (VP)	[redacted]	[redacted]	[redacted]
Pain relief at two hours	FE	[redacted]	[redacted]	[redacted]
	RE (IP)	[redacted]	[redacted]	[redacted]
	RE (VP)	[redacted]	[redacted]	[redacted]
Sustained pain relief from 2 to 24 hours	FE	[redacted]	[redacted]	[redacted]
	RE (IP)	[redacted]	[redacted]	[redacted]
	RE (VP)	[redacted]	[redacted]	[redacted]
	FE	[redacted]	[redacted]	[redacted]

Sustained pain relief from 2 to 48 hours	RE (IP)	[redacted]	[redacted]	[redacted]
Use of rescue medication within 24 hours	FE	[redacted]	[redacted]	[redacted]
	RE (IP)	[redacted]	[redacted]	[redacted]
Ability to function normally at two hours	FE	[redacted]	[redacted]	[redacted]
	RE (IP)	[redacted]	[redacted]	[redacted]
Sustained pain freedom from 2 to 24 hours	FE	[redacted]	[redacted]	[redacted]
	RE (IP)	[redacted]	[redacted]	[redacted]
	RE (VP)	[redacted]	[redacted]	[redacted]
Sustained pain freedom from 2 to 48 hours	FE	[redacted]	[redacted]	[redacted]
	RE (IP)	[redacted]	[redacted]	[redacted]
Any AE	FE	[redacted]	[redacted]	[redacted]
	RE (IP)	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse events; DIC: deviance information criterion; FE: fixed effects; IP: informative prior; mITT: modified intent to treat; NMA: network meta-analysis; RE: random effects; SD: standard deviation; VP: vague prior.

3.9.5.2 Summary of results

A summary of the efficacy and safety outcomes for atogepant versus rimegepant is presented in Table 22. The results of the NMAs are presented by efficacy and safety outcome, with pairwise ORs and 95% CrIs presented. As described in Section 3.9.5.1 above, all results are based on RE models with informative priors as the most appropriately fitting models. A more detailed description of the results from the NMAs is presented in Appendix C.4, alongside network diagrams and absolute effects of the endpoints analysed. Also presented in Appendix C.4 are results for the NMA versus placebo, and results from other models (RE models with vague priors, where available, and FE models).

As shown in Table 22, results across the majority of the key endpoints demonstrate equivalence in outcomes between atogepant and rimegepant, with no statistically significant differences. This is reflected by the [redacted]. The only exception to this was the use of rescue medication, where treatment with atogepant was associated with a statistically significant reduction in the risk of needing rescue medication during a migraine attack, compared with rimegepant.

Table 22: Summary of efficacy and safety outcomes from the NMA

	Atogepant vs. rimegepant OR (95% CrI)
Pain freedom at two hours (primary endpoint)	[redacted]
Absence of MBS at two hours	[redacted]
Pain relief at two hours	[redacted]
Sustained pain relief from 2 to 24 hours	[redacted]
Sustained pain relief from 2 to 48 hours	[redacted]
Use of rescue medication within 24 hours	[redacted]
Ability to function normally at two hours	[redacted]
Sustained pain freedom from 2 to 24 hours	[redacted]
Sustained pain freedom from 2 to 48 hours	[redacted]

Any AE	[redacted]

Footnotes: Bold denotes a statistically significantly lower OR of the assessed outcome for treatment with atogepant compared with treatment with rimegepant. ORs are based on the RE model with informative prior.
Abbreviations: AE: adverse event; CrI: credible interval; MBS: most bothersome symptom of migraine; NMA: network meta-analysis; OR: odds ratio.

3.9.6 Uncertainties in the indirect and mixed treatment comparisons

As previously noted, the NMAs performed were informed by a comprehensive and methodologically robust SLR. The studies included in the NMA were comparable in terms of outcomes reported and the definitions for those outcomes, and all outcomes were reported after patients had experienced one migraine attack. Furthermore, the inclusion criteria across the studies were also highly comparable. Details of the included studies, including baseline demographic and disease characteristics, were presented to clinical experts (n=5) at an advisory board, who confirmed that the included studies were similar.[21] Therefore, these analyses provide a methodologically robust estimation of the comparative efficacy and safety of atogepant versus rimegepant in the absence of direct head-to-head data.

However, in spite of these strengths of the analyses, performing any indirect comparison is associated with some uncertainties. Some heterogeneity in baseline characteristics, trial design and extent of endpoint availability was identified, as discussed below.

The variability in baseline characteristics across studies was investigated in the feasibility assessment (for age, sex, race, BMI, baseline MMD), as discussed in Section 3.9.3. While most trials had highly comparable inclusion criteria and populations with respect to these baseline characteristics, Ikeda 2025[129] and Yu 2023[127] were conducted on exclusively east Asian populations, other rimegepant trials were conducted on US or multinational populations, and the ECLIPSE trial was conducted on a non-US multinational population. However, as discussed in Section 3.9.3, there are no TEMs given that none were identified from a targeted review of the literature and from discussions with UK clinical experts (n=5).[21] Therefore, it is assumed that observed differences in efficacy are not due to varying baseline characteristics. Sensitivity analyses conducted in the ECLIPSE trial further supported the robustness of the efficacy analyses and were not indicative of treatment effect modifications due to region or other variables.[22]

Additionally, data on all outcomes of interest were available for all but two studies in the NMAs (Marcus 2014 and BHV3000-310).[125 127] These two studies were excluded from the networks for outcomes for which they did not report any data. However, ultimately, none of the studies assessed for inclusion in the NMA were excluded following a robust assessment of the outcomes, treatments, dosages, patient and study characteristics and study design reported within the studies.

To assess the impact of these potential areas of heterogeneity on the results of the NMAs, statistical assessments of heterogeneity were conducted and evaluated using comparisons of FE and RE model fit statistics, specifically DIC and residual deviance. As mentioned in Section 3.9.5, there were minimal differences in the measures of model appropriateness between the FE and RE models, suggesting that heterogeneity between the outcomes in the included studies was not meaningful and the FE model may be appropriate. However, as a conservative assumption, the RE model with an informative prior was selected for the primary analyses as it

demonstrated better statistical fit to the data compared to the FE model, and its use is aligned with guidance published by the NICE DSU TSD 3.[131]

Overall, despite the inherent uncertainty associated with indirect comparisons, these results provide robust and methodologically sound indirect estimations of efficacy and safety for atogepant versus rimegepant, with UK health economic experts (n=2) at an advisory board validating the appropriateness of the methodology of the indirect comparisons conducted. The clinical experts (n=5) further confirmed that the conclusion of equivalent efficacy between these treatments aligns with their clinical expectation.[21]

3.9.7 Conclusions

Overall, the results of the NMA demonstrate that the efficacy of atogepant and rimegepant for the acute treatment of migraine are similar, and this interpretation was established by UK clinical (n=5) and health economic (n=2) experts consulted for this appraisal. In the absence of head-to-head studies for these treatments, these results provide supportive evidence to inform the relative efficacy of atogepant versus rimegepant and support the assumption that atogepant offers a clinical benefit that is equivalent to that of the only currently available comparator, rimegepant, in the population of interest.

3.10 *Adverse reactions*

All TEAEs were summarised using Medical Dictionary for Regulatory Activities (MedDRA®, version 28.0). The number and proportion of patients with reported TEAEs were summarised by MedDRA® primary system organ class (SOC) and preferred term (PT). As ECLIPSE is a multi-attack study, TEAEs were linked to a specific study drug based on their timing within the study. The linked study drug for a TEAE was the latest study drug taken prior to the occurrence of the TEAE. A TEAE was assigned to a study drug if it occurred on or after the date/time of that study drug administration and before the date/time of the next study drug administration. A TEAE was assigned to the last study drug of the treatment sequence if it occurred on or after the date/time of the last study drug administration. All AEs and SAEs presented in this section were treatment-emergent, unless otherwise noted.

The overall incidence of AEs reported during ECLIPSE was low, particularly within 48 hours after treating a migraine attack.[22, 23] Most AEs were mild or moderate in severity. There were no deaths, and few subjects experienced SAEs or AEs leading to treatment discontinuation.

3.10.1 Summary of adverse events during the double-blind period

Within 48 hours of treating the first migraine attack, the incidences of AEs were similar between atogepant and placebo (Table 23).[22, 23] No SAEs, severe AEs, or AEs leading to treatment discontinuation were reported by patients in the 48 hours after taking atogepant to treat the first migraine attack. No specific AEs were reported in ≥2% of subjects after treating the first migraine (both within the 48-hour post-dose window and for all AEs assigned to a double-blind dose of study drug after treating the first migraine attack).[22, 23]

Over the entire double-blind period, the incidence of AEs was higher with atogepant than with placebo. However, it is important to note that during this period, participants were treated with atogepant for three migraine attacks, whereas they received placebo for only one attack. Despite

this, the incidence of SAEs, severe AEs and AEs leading to discontinuation remained low for patients treated with atogepant during the full double-blind period, and these events were only marginally more common than in those treated with placebo. During the entire double-blind period, the AEs reported in ≥2% of all subjects were nasopharyngitis (4.6%) and upper respiratory tract infection (2.3%). Data on the AEs experienced by patients for all migraine attacks during the double-blind period in ECLIPSE are presented in the CSR.[22, 23]

Table 23: Overview of adverse events for the first migraine attack during the double-blind period (Safety Population)

Event, n (%)	Placebo (N=624)	Atogepant (N=607)
TEAE	84 (13.5)	76 (12.5)
TEAE related to study treatment	20 (3.2)	25 (4.1)
Severe TEAE	1 (0.2)	0
Serious TEAE	1 (0.2)	0
TEAE leading to discontinuation of study treatment	1 (0.2)	1 (0.2)
TEAE leading to death	0	0
All death	0	0
Reported within 48 hours following administration of study drug		
48-hour TEAE	34 (5.4)	34 (5.6)
48-hour TEAE related to study treatment	16 (2.6)	24 (4.0)
Severe 48-hour TEAE	1 (0.2)	0
Serious 48-hour TEAE	0	0
48-hour TEAE leading to discontinuation of study treatment	1 (0.2)	0
48-hour TEAE leading to death	0	0

Abbreviations: TEAE: treatment emergent adverse event.
Source: Van Dycke *et al.* (2025).[23]

3.10.2 Summary of adverse events during the Open Label period

The incidence of AEs reported during the OL period was generally low. Most events were nonserious and mild or moderate in severity (Table 24). During the OL period, the AEs reported in ≥2% of subjects were [redacted], [redacted], and [redacted] (Table 25).

Table 24: Overview of adverse events during the OL period

Event, n (%)	Atogepant (N=982)
TEAE	341 (34.7)
TEAE related to study treatment	41 (4.2)
Severe TEAE	1 (0.1)
Serious TEAE	3 (0.3)
TEAE leading to discontinuation of study treatment	1 (0.1)
AE leading to discontinuation of study treatment during the OL period	1 (0.1)
TEAE leading to death	0
All death	0

Reported within 48 hours following administration of study drug	
48-hour TEAE	120 (12.2)
48-hour TEAE related to study treatment	23 (2.3)
Severe 48-hour TEAE	0
Serious 48-hour TEAE	2 (0.2)
48-hour TEAE leading to discontinuation of study treatment	0
48-hour TEAE leading to death	0

Abbreviations: OL: open-label; TEAE: treatment emergent adverse event.
Source: Van Dycke *et al.* (2025).[23]

Table 25: Common (≥2%) TEAE during the OL period by preferred term (Safety Population)

MedDRA 28.0 preferred term, n (%)	Atogepant (N=982)
Nasopharyngitis	[redacted]
Upper respiratory tract infection	[redacted]
Influenza	[redacted]

Abbreviations: MedDRA: Medical Dictionary for Regulatory Activities; OL: open-label; TEAE: treatment emergent adverse event.
Source: AbbVie. Data on File. ECLIPSE CSR (2025).[22]

3.11 *Conclusions about comparable health benefits and safety*

As described in Section 1.1, in accordance with clinical expert feedback (n=5), atogepant as an acute treatment option for migraine is intended for use within the NHS as an alternative to rimegepant: for patients with migraine who have had at least two prior triptans and they did not work well enough or triptans were contraindicated or not tolerated. This is in line with the population in which rimegepant, the only relevant comparator, received a positive recommendation from NICE for the acute treatment of migraine in adults in TA919. Similar to rimegepant, atogepant is an oral CGRP antagonist which provides effective and sustained pain relief in addition to other clinically important benefits, including ability to function normally, reduced use of rescue medication within 24 hours, absence of photophobia, phonophobia and nausea and improvements in HRQoL.[22] Consequently, the recommendation of atogepant by NICE would provide a much-needed additional acute treatment option for patients in the UK with migraine.

In ECLIPSE, atogepant demonstrated statistically significant, clinically meaningful benefits across pain, function and patient experience compared to placebo (Section 3.6).[22] The primary endpoint demonstrated that patients treated with atogepant were significantly more likely to achieve pain freedom at 2 hours than those on placebo (OR 2.36, 95% CI 1.76 – 3.15). Pre-specified subgroup analyses confirmed similar efficacy across all assessed subgroups (including region, current use of prophylactic concomitant medication and previous response to and use of triptans). Significant improvements in HRQoL outcomes, patient satisfaction and functional endpoints were also observed. Additionally, atogepant demonstrated an acceptable safety and tolerability profile for the acute treatment of migraine over the 24-week treatment period with no new safety signals identified.[22]

In the absence of direct head-to-head data for the comparative efficacy and safety of atogepant versus rimegepant, NMAs were conducted to assess the relative efficacy and safety of atogepant and rimegepant in the target indication (Section 3.9). The NMA found no statistically significant differences in treatment with atogepant compared to treatment with rimegepant in the majority of outcomes assessed, [redacted], supporting equivalence between the

two treatments. In individual consultations and during an advisory board five clinical experts agreed that this similarity in outcomes between atogepant and rimegepant was expected and that they considered the two treatments to be equivalent in terms of both efficacy and safety.[21]

Based on these NMA results, and given the same mechanism of action and similar mode of administration between atogepant and rimegepant, a cost-comparison between the two treatments is appropriate to inform decision making, as presented in Section 4.

3.12 *Ongoing studies*

The ECLIPSE trial is ongoing. However, no new data are expected to become available within the time frame of this submission.

4 Cost-comparison analysis

Summary of cost-comparison analysis

- As described in Section 1.1, atogepant is anticipated to be used as an alternative treatment option to rimegepant; as confirmed by UK clinical experts (n=5) at an advisory board meeting, rimegepant represents established standard of care in this population and the two treatments have a similar mechanism of action and mode of administration.[21, 134]
- Therefore, an analysis was conducted to estimate the economic value of atogepant versus rimegepant in patients with migraine as proxy for the subset of patients who have had at least two triptans and they did not work well enough, or triptans were contraindicated or not tolerated, in line with the NICE Committee and EAG preferences in TA919.[3]
- Results from the NMAs (see Section 3.9.5.2) showed comparable efficacy between atogepant and rimegepant. Therefore, a cost-comparison approach between the two treatments was deemed appropriate for this submission.
- For completeness, and to ensure robustness, a cost-comparison model was developed in Microsoft Excel in line with the NICE reference case and TA919.[3] The model adopted a two-year time horizon and incorporated drug acquisition, monitoring, drug wastage and healthcare resource use costs for atogepant and rimegepant.
- With the exception of the drug acquisition costs which differed between treatments (atogepant 60 mg being cheaper than rimegepant 75 mg), all other parameters were set to equal in the cost-comparison analysis, in line with the assumptions of clinical equivalence discussed above.

Cost-comparison results

- Over the model time horizon, atogepant was associated with cost savings versus rimegepant of £[redacted] per patient in the base case analysis.
- Scenario analyses were conducted to consider alternative time horizons, use of different healthcare resource use assumptions including related to varying the pack sizes of atogepant, and the inclusion of general population mortality and cost discounting. Alongside the results of a one-way sensitivity analysis, the results from these scenario analyses had no impact on the conclusions of the base case analysis and demonstrated that the model is robust to uncertainty in model parameters and alternative assumptions.
- Overall, the cost-comparison analysis demonstrates that the use of atogepant over rimegepant will provide cost-savings to the NHS, as well as providing an equally efficacious treatment option in patients with migraine who have had at least two triptans and they did not work well enough, or triptans were contraindicated or not tolerated.[3]

4.1 *Changes in service provision and management*

As atogepant has the same mode of administration as rimegepant (oral), it is not anticipated that the introduction of atogepant to clinical practice would require any changes to current service provision or management.

4.2 *Cost-comparison analysis inputs and assumptions*

As described in Section 1.1 and in line with the population in which rimegepant is recommended, atogepant is intended for use in adults for the acute treatment of migraine who have either tried

at least two triptans and they did not work well enough, or have contraindications or intolerance to triptans and have tried NSAIDs and paracetamol without adequate response.

In this population, rimegepant represents the only relevant comparator within this cost-comparison analysis for the following reasons:

- In the population of interest, patients will have used triptans and NSAIDs in earlier lines of treatment with these therapies considered not effective, or are otherwise not suitable. Therefore, patients would not be given triptans and NSAIDs at this line of therapy, so they are not relevant comparators.
- Rimegepant represents established UK clinical practice in the proposed target population, as established by five UK clinical experts at an advisory board, who further confirmed that no other treatments are licensed or used in practice in this population.[21]
- Atogepant and rimegepant have a similar mechanism of action and mode of administration, and are expected to be licensed in the same population for this indication. As such, clinical experts would consider atogepant as an alternative to rimegepant in this patient population.[21]
- The results of NMAs (Section 3.9) comparing atogepant and rimegepant produced [redacted], demonstrating equivalence in efficacy and safety outcomes between the two treatments.
    - A total of five clinical experts and two economic experts consulted during individual consultations and an advisory board confirmed that atogepant and rimegepant have similar efficacy and safety profiles, based on the NMA results.[21]

Therefore, a cost-comparison approach between the two treatments was deemed appropriate for this submission. Although only the drug acquisition costs are expected to differ between atogepant and rimegepant, a cost-comparison model aligned to the model in TA919 has been provided to ensure robustness.[3] The NICE cost-comparison template suggested format tables for acquisition costs and resource costs are also included in Appendix G for completeness. The methodology and results of the cost-comparison analysis are presented below.

4.2.1 Features of the cost-comparison analysis

Population

The target population for atogepant in this appraisal is for patients with migraine who have had at least two prior triptans and they did not work well enough or triptans were contraindicated or not tolerated. This aligns with the population in which NICE recommended rimegepant (TA919), the only relevant comparator.[3] As outlined above, the full mITT population data is used as proxy for the subpopulation in alignment with TA919.[3] The baseline characteristics used within the model, sourced from the mITT population of the ECLIPSE trial, are presented in Table 26.

Table 26: Model baseline characteristics

Characteristic	Mean
Baseline patient age	[redacted]
Baseline % female	[redacted]
Baseline MMDs	[redacted]

Abbreviations: CI: confidence interval; MMD: monthly migraine day.
Source: AbbVie Data on File. ECLIPSE CSR.[22]

Intervention and comparators

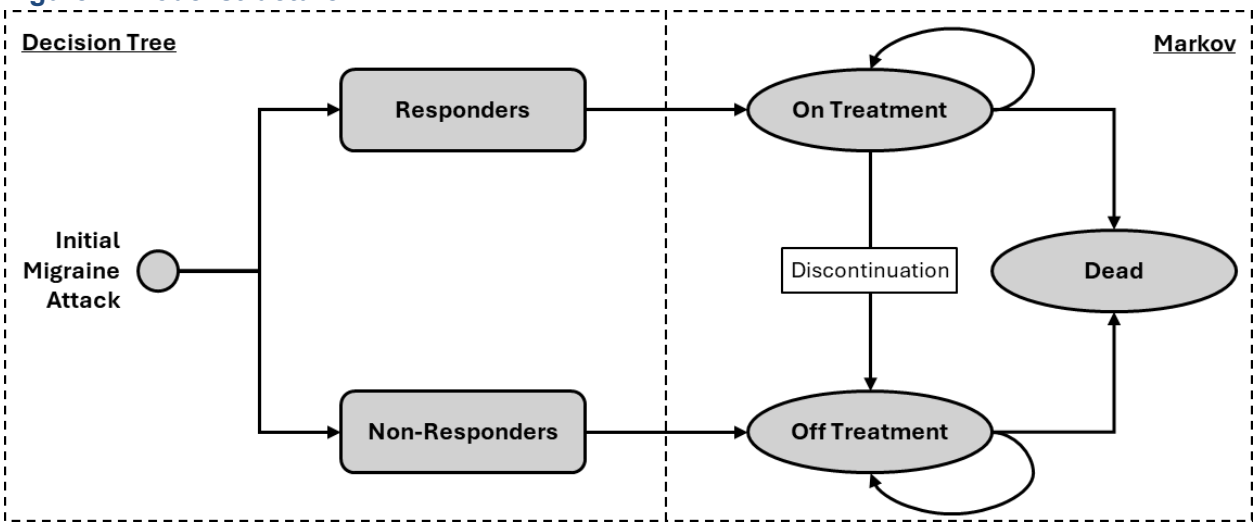
Within the model, the intervention is atogepant (60 mg) and the comparator is rimegepant (75 mg). Both are administered orally as needed, once daily.[2, 134]

Model structure

A cost-comparison model has been developed in Microsoft Excel to evaluate the incremental cost to the NHS of using atogepant versus rimegepant for the treatment of migraine. The model adopts the perspective of the NHS and Personal Social Services (PSS). A time horizon of two years is used within the base case, as this was considered appropriate to capture all relevant differences in costs between atogepant and rimegepant, based on UK clinical expert opinion (n=5) and alignment with Committee preferences in the appraisal of rimegepant in the same indication (TA919; see Section 2 for further details).[3, 21]

In further alignment with TA919, the model uses a two-phase structure (decision tree phase and Markov phase).[3] In the decision tree phase, all patients experience a single migraine attack, and are subsequently classified as responders or non-responders to treatment with atogepant or rimegepant. The second phase is a 3-state Markov model that tracks patients who are on treatment, off treatment or dead (Figure 4).

Figure 4: Model structure



Footnote: Patients who are categorised as being "On treatment" in the Markov phase of the model are modelled to receive treatment in any given cycle only if they experience an attack in that cycle of the model. The proportion of patients experiencing a migraine attack in each cycle is derived from the baseline frequency of migraine days per month, assuming that each migraine attack lasted 2 days (frequency of migraine days per month/2 migraine days per attack = migraine attacks per month).

Following the initial migraine attack within the decision tree phase of the model, patients are classified by response to treatment. Response is defined by pain relief at 2 hours and the proportion of patients who respond is informed by ECLIPSE trial data (Table 27). It is assumed that patients who responded in the initial migraine attack would respond in all subsequent attacks.

Consistent with TA919, patients who respond to treatment during the initial migraine attack continue treatment and enter the Markov phase in the 'on treatment' health state. Patients can remain in this health state or transition to the 'off treatment' health state through natural discontinuation (Table 27). Patients who are categorised as being "On treatment" in the Markov phase of the model are modelled to receive treatment in any given cycle only if they experience

an attack in that cycle of the model. Patients who do not respond to treatment during the initial migraine attack enter the Markov phase in the 'off treatment' health state and remain here until death.

In the Markov phase of the model, each cycle length is 48 hours long. This reflects the typical length of a migraine attack and is consistent with the cycle length used in the cost-effectiveness model in TA919, as well as with the period of efficacy assessments in the ECLIPSE trial.[3, 22] During each cycle, a proportion of all living patients experience a migraine attack. The proportion of patients experiencing a migraine attack in each cycle is derived from the baseline frequency of migraine days per month (Table 27), assuming that each migraine attack lasted 2 days (frequency of migraine days per month/2 migraine days per attack = migraine attacks per month). The proportion of patients experiencing a migraine attack in any given cycle is not dependent on whether patients are on treatment nor which treatment patients are receiving. In line with the Committee's preferred assumption in TA919 (see Section 2 for further details), treatment with atogepant or rimegepant as an acute treatment is not modelled to impact the frequency of monthly migraine days.[3]

Within the model, patients can also transition to the absorbing 'Dead' state at any time. In line with previous migraine submissions, the model assumes that migraine is not associated with an increased mortality risk.[1, 135, 136] The England general population mortality rates (2021–2023) are therefore used for the transitions between all model states and the 'Dead' state.[137]

Efficacy inputs

As evidence from the NMAs demonstrated that atogepant and rimegepant have similar efficacy (see Section 3) and in line with guidance on the cost-comparison process, all efficacy inputs within the model are set as equal between atogepant and rimegepant. The response rate and proportion of patients in moderate/severe pain at 24 hours are sourced from the mITT population of the ECLIPSE trial.[23, 138]

Long-term discontinuation data for atogepant are not available from the ECLIPSE trial. Therefore, the model uses discontinuation data from the rimegepant appraisal (TA919), which were sourced from the long-term safety study of rimegepant (BHV3000-201).[3, 139] Based on the NMA findings which indicated no significant difference in efficacy or safety between atogepant and rimegepant, no differences in discontinuation rate between the two treatments is expected, which is aligned with clinical expert feedback (n=5).[21] To align with other efficacy inputs and the Committee's preferred approach in the rimegepant appraisal (TA919), the model uses discontinuation data from the mITT population of BHV3000-201.[3, 139] Clinical inputs used within the base case analysis are summarised in Table 27.

Table 27: Clinical inputs for the cost-minimisation model

Clinical input	Value	Source
Response rate (pain relief at 2 hours)	72.1%	mITT population of the ECLIPSE trial
Proportion in moderate/severe pain at 24 hours	[redacted]	mITT population of the ECLIPSE trial
Annual discontinuation	13.5%	mITT population of BHV3000-201 trial

Abbreviations: mITT: modified intention-to-treat.
Source: Van Dycke *et al.* (2025);[23] AbbVie Data on File. MAAP Priority 1 Analysis;[138] Johnston *et al*, 2024.[140]

4.2.2 Intervention and comparator's acquisition costs

The only costs expected to differ in this cost-comparison analysis are drug acquisition costs, given the similarity in outcomes between atogepant and rimegepant and therefore all other costs described in subsequent sections are included for completeness.

All patients incur treatment costs of acute medication for the initial migraine attack. Within the Markov phase of the model, patients who are on-treatment are assumed to treat every migraine attack with acute treatment and incur the associated acquisition costs.

A summary of the acquisition costs included for atogepant and rimegepant is presented in Table 28. No confidential discounts are included within the analysis, as neither atogepant nor rimegepant are associated with a patient access scheme (PAS).

Table 28: Acquisition costs of the intervention and comparator technologies

	Atogepant	Rimegepant
Pharmaceutical formulation	60 mg tablet	75 mg tablet
(Anticipated) care setting	Primary and secondary care	
Acquisition cost per pack (excluding VAT)	2-pack: £25.78 7-pack: £90.23 28-pack: £182.16[a]	2-pack: £25.80 8-pack: £103.20
Assumed proportions of each pack[b]	2-pack: 100% 7-pack: 0% 28-pack: 0%	2-pack: 100% 8-pack: 0%
Method of administration	Oral	
Doses	60 mg	75 mg
Dosing frequency	Up to once daily, as needed	
Dose adjustments	No dose adjustments are made in the model	
Average length of a course of treatment	N/A – both treatments are taken as required.	
Average cost of a course of treatment (acquisition costs only)	N/A – both treatments are taken as required.	
(Anticipated) average interval between courses of treatment	N/A – both treatments are taken as required.	
(Anticipated) number of repeat courses of treatment	N/A – both treatments are taken as required.	

[a] Usage of the 28-pack is explored in a scenario analysis only. [b] The proportions of each pack are varied in a scenario analysis presented in Section 4.4.2
Abbreviations: N/A: not applicable; VAT: value added tax.

Drug wastage costs

The model assumes that all patients incur the cost of one full package at the start of the model. Patients who do not respond, and are therefore deemed as non-responders, to the initial migraine attack (initial decision-tree part of model) discontinue treatment and are assumed to waste the remainder of that initial package as they will not take any further treatment. In the base

case, the 2-pack sizes are used for both atogepant and rimegepant, hence wastage is assumed the same for both treatments. This is a conservative assumption chosen to model the most comparable pack sizes; a scenario is included in Table 35 to explore possible pack usage in practice. Patients who discontinue treatment for any reason after the initial migraine attack (Markov part of model) do not incur wastage, as it is assumed that patients will use the rest of the pack of medication that they have and then not request any more prescriptions, as opposed to switching to being a non-responder and therefore wasting the pack. The impact of this assumption on the economic results is explored in a scenario analysis (Section 4.4.2).

4.2.3 Intervention and comparators' healthcare resource use and associated costs

An SLR was conducted in August 2025 to identify studies reporting cost and healthcare resource use data in migraine. Full details of the methodology and results of the SLR are presented in Appendix E. In total, 23 publications reporting resource use data and 13 publications reporting cost data were included in the SLR.

The costs considered in the base case cost-comparison analysis include drug acquisition costs, healthcare resource costs, and one-off monitoring costs. As outlined above, the only costs expected to differ between the treatments are drug acquisition costs; any other costs are included for completeness. It is assumed that atogepant and rimegepant incur no administration cost as they are oral treatments self-administered by patients. Drug acquisition costs are detailed above (Section 4.2.2); further details on the healthcare resource use and monitoring costs included in the model are provided below. The resource use and costs for atogepant and rimegepant are also summarised in Appendix G, in line with the NICE cost comparison user guide, for completeness.

Healthcare resource use costs

Healthcare resource use costs considered in the model include costs for hospitalisations, A&E visits and GP visits. While the clinical input of the proportion of patients in moderate/severe pain at 24 hours does not influence patient movement through the model, healthcare resource use costs are impacted: for each migraine attack, rates of healthcare resource utilisation costs are applied to those experiencing moderate to severe pain at 24 hours post dose. However, given that atogepant and rimegepant are assumed to have equal efficacy in the model, total healthcare resource costs are identical for atogepant and rimegepant. As such, these costs are included in the model for completeness and to provide face validity for the total costs within each treatment arm.

The base case inputs for healthcare resource unit costs are summarised in Table 29. These were based on the healthcare resource use costs included in TA919,[3] updated to the most recent data available from the NHS England 2024/25 National Schedule of NHS Costs and the Personal Social Services Research Unit (2024).[141, 142]

The base case inputs for the rate of healthcare resource utilisation are presented in Table 30. These rates are in line with the healthcare resource utilisation rates used and accepted in TA919, which were originally based on a study of European respondents in the National Health and Wellness Survey (Vo *et al*, 2018).[3, 11]

Table 29: Base case inputs for healthcare resource unit costs

Resource	Unit cost	Description	Source
Hospitalisation	£882.35	Weighted average of AA31C, AA31D, and AA31E across all departments	NHS England
A&E visit	£182.12	Weighted average of VB09Z across all departments	NHS England
GP visit	£45.00	Cost per minute (£4.50) of a GP consultation, multiplied by average length (10 minutes), including direct care staff costs with qualification costs	PSSRU

Abbreviations: A&E: accident and emergency; GP: general practitioner; NHS: National Health Service; PSSRU: Personal Social Services Research Unit.
Source: NHS England, 2024/25 National Schedule of NHS Costs;[141] PSSRU, Unit Costs of Health and Social Care 2024 Manual.[142]

Table 30: Base case inputs for healthcare resource utilisation rates

Healthcare resource	Utilisation[a]	Standard error	Source
Hospitalisation	0.003	0.001	Johnston *et al,* 2024,[140] derived from Vo *et al*, 2018[11]
A&E visit	0.01	0.003	
GP visit	0.066	0.009	

[a] Data represent the number of resources utilised per patient with moderate or severe migraine pain at 24 hours after onset of a migraine attack.
Abbreviations: A&E: accident and emergency; GP: general practitioner.
Source: Johnston *et al*, 2024;[140] Vo *et al*, 2018.[11]

Monitoring costs: one-off specialist visit cost

In TA919, clinical experts indicated that they would expect rimegepant to be prescribed by hospital specialists initially. The EAG subsequently included the cost of the initial visit with a specialist in its preferred base case.[3] Given this feedback in TA919, costs for an initial visit with a specialist are included in the cost-comparison model for this submission, reflecting the fact that clinicians would similarly prescribe atogepant in a specialist setting at least initially. This cost was sourced from the NHS England 2024/25 National Schedule of NHS Costs (Table 31) and is applied as a one-off cost for all patients.

However, since the publication of TA919, there has been local variation in the prescribing setting of rimegepant with some NHS organisations allowing initiation and/or follow up in a primary care setting. Similarly, atogepant for use as a preventive treatment for migraine is also currently initiated in the primary care setting in several parts of the UK. Therefore, the assumption that atogepant would be initiated in a specialist setting is a conservative assumption with clinical experts consulted at an advisory board agreeing that atogepant would be prescribed in a primary care setting in some areas, similar to rimegepant.[21] The impact of this assumption on the economic results is explored in a scenario analysis (Section 4.4.2). It is important to note that the costs for the initial specialist visit are expected to be the same for atogepant and rimegepant.

Table 31: Base case inputs for cost of initial visit with a specialist

Input	Cost	Source
Initial visit with a specialist	£211.64	National Schedule of NHS Costs 2024/25, Consultant led neurology visit (service code 400) unit cost, WF01D code

Source: NHS England, 2024/25 National Schedule of NHS Costs.[141]

4.2.4 Adverse reaction unit costs and resource use

As reported in Section 3.9.5.2, results of the NMA analyses for AEs indicated that the incidence of AEs associated with the use of atogepant and rimegepant are similar. Therefore, in line with prior cost-comparison appraisals (TA596, TA521 and TA803), it is assumed that the costs associated with treating AEs would be similar and any difference would be negligible, so AE costs were omitted from the analysis.[143-145] In addition, no AEs with an incidence of ≥2% were included within the model for the rimegepant appraisal (TA919), and no AEs with an incidence of ≥2% were reported in ECLIPSE, further supporting that it is appropriate to exclude costs associated with treatment within the model.[3]

4.2.5 Miscellaneous unit costs and resource use

No further unit costs or resource use were included in the model.

4.2.6 Model validation

The model method was designed to align with NICE's preferred methods, and key model assumptions applied in the cost-comparison model were validated by clinical experts (n=5) experienced in the treatment of migraine as well as by external health economic experts (n=2).[21] Quality control procedures were undertaken to ensure the programming and physical implementation of the conceptual model was completed correctly. Once the model was finalised, it was validated by internal modellers, and a programmer (different to the programmer who built the model) reviewed all formulae and labelling in the model, to ensure accuracy. In addition, an independent health economic expert also validated the model.

4.2.7 Uncertainties in the inputs and assumptions

A summary of the inputs used in the cost-comparison analysis are summarised in Table 32 with uncertainty in the inputs assessed within the sensitivity and scenario analyses presented in Section 4.4. The key assumptions are presented in Table 33 with uncertainty assessed within the scenario analysis presented in Section 4.4.

Table 32: Summary of base case model inputs

Input	Parameter value	Source
Time horizon (years)	2	Assumption; aligned with UK clinical expert opinion (n=5) and Committee preferences in NICE TA919[3]
Discount rate	0%	NICE cost-comparison guidelines[146]
Perspective	NHS/PSS	NICE reference case
Baseline characteristics		
Age (years)	[redacted]	AbbVie Data on File. ECLIPSE CSR (mITT population)[22]
Sex (% female)	[redacted]	
Baseline MMDs	[redacted]	
Clinical inputs		
Response rate (pain relief at 2 hours)	72.1%	Van Dycke *et al.* ECLIPSE Trial (mITT population)[23]

Proportion in moderate/severe pain at 24 hours	[redacted]	AbbVie Data on File. ECLIPSE MAAP Priority 1 Analysis (mITT population)[138]
Annual discontinuation	13.5%	Johnston *et al.* BHV3000-201 trial (mITT population)[140]
Acquisition costs		
Atogepant: cost per pack	2-pack: £25.78	British National Formulary[147]
	7-pack: £90.23	
	28-pack: £182.16	
Rimegepant: cost per pack	2-pack: £25.80	
	8-pack: £103.20	
Healthcare resource use		
Hospitalisation: unit cost	£882.35	NHS England[141]
A&E visit: unit cost	£182.12	
GP visit: unit cost	£45.00	PSSRU[142]
Hospitalisation: rate of utilisation	0.003	Johnston *et al,* 2024,[140] derived from Vo *et al,* 2018[11]
A&E visit: rate of utilisation	0.01	
GP visit: rate of utilisation	0.066	
Initial visit with a specialist	£211.64	National Schedule of NHS Costs 2024/25[141]

Abbreviations: A&E: accident and emergency; CSR: Clinical Study Report; GP: general practitioner; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; MAAP: Market Access Analysis Plan; MMD: monthly migraine day; PSS: Personal Social Services; PSSRU: Personal Social Services Research Unit.

Table 33: Key assumptions of the analysis

Assumption	Rationale for assumption	Relevant scenario analysis
2-year time horizon	This time horizon is considered appropriate to capture all relevant differences in costs between atogepant and rimegepant based on UK clinical expert opinion (n=5) and in alignment with Committee preferences in the appraisal of rimegepant in the same indication (TA919).[3]	Alternative time horizons of 10-years and 20-years are explored within scenario analyses.
Model perspective	In line with the NICE reference case, the model adopted the perspective of the NHS and PSS.	N/A
Discount rate	No discount rate was included as recommended by NICE in the user guide applicable to cost-comparison analyses.	A discount rate of 3.5% was explored within scenario analyses.
All modelled treatments have the same efficacy	Inherent with the cost-comparison approach, all modelled treatments are assumed to have the same efficacy. This is based on evidence from the NMAs (Section 3.9), which demonstrate equivalence in both efficacy and safety between atogepant and rimegepant.	N/A
Patients who respond to treatment during the initial	This is a simplifying assumption in line with the assumption used within the	N/A

migraine attack will always respond to treatment.	rimegepant appraisal.[3] Given the assumption of equal efficacy between atogepant and rimegepant, while altering this assumption would impact the total costs within the model, there would be no impact on the incremental costs.	
Patients who do not respond to treatment during the initial migraine attack discontinue treatment.	This is a simplifying assumption in line with the assumption used within the rimegepant appraisal.[3]	N/A
Migraine-related healthcare resource utilisation is limited to patients with moderate or severe migraine pain at 24 hours after onset.	This is a simplifying assumption in line with the assumption used within the rimegepant appraisal.[3] It is assumed that this subset of patients serves as a reasonable proxy for patients who would be expected to seek medical care for a migraine attack.	N/A
Patients who initially respond to treatment but who then discontinue treatment over the long term do not incur wastage.	It is assumed that patients will use the medication that they have and then not request any more prescriptions.	A scenario analysis was explored in which patients who discontinued treatment in the Markov phase of the model incur 50% pack wastage.

Abbreviations: AE: adverse event; NICE: National Institute for Health and Care Excellence; MUD: medication use day; N/A: not applicable; NMA: network meta-analysis; SC: subcutaneous; SmPC: Summary of Product Characteristics; TA: technology appraisal.

4.3 *Base case results*

Base case results for the cost-comparison analysis of atogepant versus rimegepant are presented in Table 34. Over the model time horizon of 2 years, atogepant is associated with cost savings versus rimegepant of £[redacted] per patient, driven by the lower drug acquisition costs of atogepant. These findings demonstrate that atogepant is associated with lower total costs than rimegepant over the modelled period, while providing comparable efficacy, thereby representing a lower cost treatment option for the NHS.

Overall, the cost-comparison analysis demonstrates that the use of atogepant as an alternative to rimegepant would provide cost-savings to the NHS in patients with migraine who have had ≥2 triptans and they did not work well enough, or triptans were contraindicated or not tolerated, using the mITT population as proxy for this subgroup, in line with TA919.[3]

Table 34: Base case results

Technology	Drug acquisition costs	Healthcare resource use costs	Total costs
Atogepant	[redacted]	[redacted]	[redacted]
Rimegepant	[redacted]	[redacted]	[redacted]
Incremental costs per patient (for atogepant)	[redacted]	[redacted]	[redacted]

4.4 *Sensitivity and scenario analyses*

4.4.1 One-way sensitivity analysis

A series of one-way sensitivity analyses were performed to evaluate the sensitivity of the model results (i.e., the incremental costs of atogepant versus rimegepant) to individual inputs, holding all else constant. The lower and upper bounds of each parameter in the deterministic sensitivity analysis are based on the 95% confidence interval; in the absence of any reported confidence intervals, the input value was varied by 20%.

The tornado diagram with parameters shown in descending order of cost difference sensitivity is presented in Figure 5. The model was most sensitive to all-cause discontinuation rate followed by response rate, although varying these inputs had no impact on the overall conclusion of the analysis that use of atogepant over rimegepant would represent a cost-saving option for the NHS.

Figure 5: Results of the one-way sensitivity analysis

Abbreviations: A&E: accident and emergency; GP: general practitioner; MMD: monthly migraine days.

4.4.2 Scenario analyses

Scenario analyses were conducted to explore the impact of varying the model inputs and assumptions implemented in the base case cost-comparison analysis. These scenario analyses and the associated results are described in Table 35 and demonstrate that atogepant is cost-saving across all scenario analyses conducted.

Table 35: Scenario analyses

Model Assumption	Base Case	Scenario	Difference in cost versus rimegepant
Base Case			[redacted]
Atogepant and rimegepant pack size usage	100% of patients receive 2-pack prescription of atogepant and rimegepant.	Atogepant pack usage: 2-pack: 65% 7-pack: 25% 28-pack:10% Rimegepant pack usage: 2-pack: 70% 8-pack: 30%	[redacted]
One-time specialist visit at treatment initiation	Cost of visit included	Cost of visit excluded	[redacted]
Long-term pack wastage	No wastage assumed for patients who are responders discontinuing treatment after the first model cycle	50% of all packs are wasted for patients who are responders discontinuing after the first model cycle	[redacted]
Time horizon	2-year time horizon	10-year time horizon	[redacted]
		20-year time horizon	[redacted]
General population mortality	Included within the model	Excluded within the model	[redacted]
Discounting	No discounting of costs included	3.5% discounting of costs included	[redacted]

Abbreviations: mITT: modified intention-to-treat.

4.5 *Subgroup analysis*

No subgroup analyses were performed.

4.6 *Interpretation and conclusions of economic evidence*

Atogepant is a once daily, oral treatment which provides effective and sustained pain relief, in addition to other clinically important benefits for patients with migraine. The efficacy of atogepant is supported by results from the ECLIPSE trial, a Phase 3 placebo-controlled RCT, which showed atogepant to be associated with clinically meaningful, significant improvements compared to placebo in pain freedom at 2 hours, MBS freedom at 2 hours, pain relief at 2 hours, sustained pain relief between 2 to 24 hours, rescue medication use within 24 hours and ability to function normally at 2 hours as well as most of the remaining secondary endpoints (see Section 3.6).[22]

Furthermore, atogepant is well-tolerated with comparable rates of TEAEs leading to treatment discontinuation to placebo, demonstrating an acceptable safety and tolerability profile with no specific AEs occurring at an incidence of ≥2% of patients (see Section 3.10).

Within this appraisal, atogepant is compared with rimegepant, a technology recommended in published NICE technology appraisal guidance for the same indication and patient population, with a similar mechanism of action and mode of administration for the acute treatment of migraine in adults who have had ≥2 triptans and they did not work well enough, or triptans were contraindicated or not tolerated, which represents the only relevant comparator (Section 1.1). As shown by the NMAs presented in Section 3.9, atogepant has comparable health benefits in terms of efficacy to rimegepant for the treatment of migraine. This conclusion of equivalent efficacy and safety between atogepant and rimegepant was supported by clinical experts (n=5) consulted in individual consultations and an advisory board.[21]

Results of the cost-comparison analysis demonstrate that atogepant is cost-saving when compared to rimegepant, with these cost savings realised due to the lower drug acquisition costs associated with atogepant. In addition, a series of sensitivity and scenario analyses demonstrates the robustness of the base case analysis to variation in a range of input variables, confirming atogepant as a cost-saving option.

In addition, as noted in the rimegepant NICE appraisal (TA919), there is a potential long-term preventative treatment effect in which acute treatment with rimegepant could lead to a reduction in MMDs with continued use.[3] During the TA919 appraisal, the Committee acknowledged this potential reduction as a small uncaptured benefit of using rimegepant. Given the equivalent efficacy and similar mode of action of atogepant and rimegepant, it is likely that this potential preventative treatment effect would also be realised with use of atogepant. While not explicitly captured within the model, this should be considered an uncaptured benefit of treatment with atogepant.

Overall, atogepant is an oral treatment option which provides effective and sustained pain relief, in addition to other clinically important benefits and is well tolerated by patients.[22] The results of the cost-comparison analysis demonstrates the cost-saving potential of atogepant versus rimegepant. Consequently, the recommendation of atogepant would provide a much-needed, additional treatment option in an underserved patient population that would provide effective acute relief for migraine patients in the UK with potential to enhance HRQoL and improve work productivity.

References

1. National Institute for Health and Care Excellence (NICE). Atogepant for preventing migraine (TA973). Available at: https://www.nice.org.uk/guidance/TA973. [Last accessed: 24 October 2025].
2. AbbVie Data on File [CONFIDENTIAL]. Atogepant Summary of Product Characteristics. .
3. National Institute for Health and Care Excellence (NICE). Rimegepant for treating migraine (TA919). Available at: https://www.nice.org.uk/guidance/ta919 [Last accessed: October 2025].
4. Wells RE, Markowitz SY, Baron EP, et al. Identifying the factors underlying discontinuation of triptans. Headache 2014;54:278-89.
5. Linde M, Gustavsson A, Stovner LJ, et al. The cost of headache disorders in Europe: the Eurolight project. European journal of neurology 2012;19:703-711.
6. National Institute for Health and Care Excellence (NICE). Migraine: How common is it? Available at: https://cks.nice.org.uk/topics/migraine/background-information/prevalence/. [Last accessed: August 2025]. .
7. Martelletti P, Schwedt TJ, Lanteri-Minet M, et al. My Migraine Voice survey: a global study of disease burden among individuals with migraine for whom preventive treatments have failed. The journal of headache and pain 2018;19:1-10.
8. National Institute for Health and Care Excellence (NICE). Scenario: Migraine in adults. Available at: https://cks.nice.org.uk/topics/migraine/management/adults/. [Last accessed: August 2025].
9. Steiner TJ, Husøy A, Stovner LJ. GBD2021: headache disorders and global lost health - a focus on children, and a view forward. J Headache Pain 2024;25:91.
10. The Migraine Trust. The State of the Migraine Nation. Who is living with migraine in the UK? Rapid research review. Available at: https://migrainetrust.org/wp-content/uploads/2021/08/State-of-the-Migraine-Nation-population-rapid-review.pdf. [Last accessed: December 2025].
11. Vo P, Fang J, Bilitou A, et al. Patients' perspective on the burden of migraine in Europe: a cross-sectional analysis of survey data in France, Germany, Italy, Spain, and the United Kingdom. J Headache Pain 2018;19:82.
12. Buse DC, Yugrakh MS, Lee LK, et al. Burden of Illness Among People with Migraine and ≥ 4 Monthly Headache Days While Using Acute and/or Preventive Prescription Medications for Migraine. J Manag Care Spec Pharm 2020;26:1334-1343.
13. Müller B, Dresler T, Gaul C, et al. Use of outpatient medical care by headache patients in Germany: a population-based cross-sectional study. J Headache Pain 2020;21:49.
14. National Migraine Centre. Migraine and work. Available at: https://www.nationalmigrainecentre.org.uk/corporate-wellbeing/migraine-and-work/. [Last accessed: 05 January 2026].
15. National Institute for Health and Care Excellence (NICE). Headaches in over 12s: diagnosis and management. Available at: https://www.nice.org.uk/guidance/cg150/chapter/Recommendations. [Last accessed: August 2025].
16. British Association for the Study of Headache. National headache management system for Adults. Available at: https://bash.org.uk/wp-content/uploads/brizy/custom_files/01_BASHNationalHeadache_Management_SystemforAdults_2019_guideline_versi.pdf [Last accessed: August 2025]

17. Lipton RB, Munjal S, Buse DC, et al. Predicting inadequate response to Acute Migraine Medication: results from the American migraine prevalence and Prevention (AMPP) Study. Headache: The Journal of Head and Face Pain 2016;56:1635-1648.
18. Evers S, Dell'Agnello G, Novick D, et al. Acute Treatment Patterns, Migraine Burden, and Healthcare Resource Use in People With Migraine: Results From the OVERCOME (EU) Observational Study. Pain Ther 2024;13:589-607.
19. Alam A, Munjal S, Reed M, Bostic R, Buse D, Schwedt T, et al. Triptan Use and Discontinuation in a Representative Sample of Persons With Migraine: Results From Migraine in America Symptoms and Treatment (MAST) Study (P4.10-019). Neurology. 2019;92(15 Supplement):P4.10-019.
20. Yarnitsky D, Dodick DW, Grosberg BM, Burstein R, Ironi A, Harris D, et al. Remote Electrical Neuromodulation (REN) Relieves Acute Migraine: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial. Headache: The Journal of Head and Face Pain. 2019;59(8):1240-52.
21. AbbVie Data on File [CONFIDENTIAL]. Atogepant in Migraine UK Advisory Board Meeting Report, 2025.
22. AbbVie Data on File [CONFIDENTIAL]. ECLIPSE Clinical Study Report, 2025.
23. Dycke AV, Brand-Schieber E, Ornello R, et al. Efficacy, Safety, and Tolerability of Atogepant for the Acute Treatment of Migraine: Results from the ECLIPSE Trial, In 19th European Headache Congress (EHC), Lisbon, Portugal, 2025.
24. National Insitute for Health and Care Excellence (NICE). Rimegepant for preventing migraine (TA906). Available at: https://www.nice.org.uk/guidance/ta906. [Last accessed: 9 January 2026].
25. Russell FA, King R, Smillie SJ, et al. Calcitonin gene-related peptide: physiology and pathophysiology. Physiol Rev 2014;94:1099-142.
26. Ailani J, Lipton RB, Goadsby PJ, et al. Atogepant for the Preventive Treatment of Migraine. N Engl J Med 2021;385:695-706.
27. Goadsby PJ, Holland PR, Martins-Oliveira M, et al. Pathophysiology of Migraine: A Disorder of Sensory Processing. Physiol Rev 2017;97:553-622.
28. Schuster NM, Rapoport AM. New strategies for the treatment and prevention of primary headache disorders. Nat Rev Neurol 2016;12:635-650.
29. Edvinsson L, Haanes KA, Warfvinge K, et al. CGRP as the target of new migraine therapies - successful translation from bench to clinic. Nat Rev Neurol 2018;14:338-350.
30. Goadsby PJ, Dodick DW, Ailani J, et al. Safety, tolerability, and efficacy of orally administered atogepant for the prevention of episodic migraine in adults: a double-blind, randomised phase 2b/3 trial. Lancet Neurol 2020;19:727-737.
31. Bell I. Discovery of AGN-241689: A potent, orally-acting CGRP receptor antagonist for migraine prophylaxis. Available at: https://www.morressier.com/o/event/5fc63c8003137aa5256f9993/article/5fc63d629e0a135cbed006aa. [Last accessed: 05 January 2026].
32. Medicines and Healthcare products Regulatory Agency. Atogepant- Summary of product Characteristics. Available at: https://products.mhra.gov.uk/search/?search=atogepant&page=1 [Last accessed: August 2025].
33. National Institute for Health and Care Excellence (NICE). Migraine: What is it? Available at: https://cks.nice.org.uk/topics/migraine/background-information/definition/. Last accessed: August 2025.
34. Institute for Health Metrics and Evaluation (IHME). GBD Compare Data Visualization. Seattle, WA: IHME, University of Washington, 2025. Available at: https://vizhub.healthdata.org/gbd-compare. [Last accessed: November 2025].

35. Health Union. Migraine in America. Available at: https://www.bing.com/search?q=health+union+migraine+in+america&cvid=e5354fe6cab04d80b8c98d2c57d54463&gs_lcrp=EgRlZGdlKgYIABBFGDkyBggAEEUYOTIGCAEQABhAMgYIAhAAGEAyBggDEAAYQDIGCAQQABhAMgYIBRAAGEAyBggGEAAYQDIGCAcQABhAMgYICBAAGEAyCAgJEOkHGPxV0gEIMzE1NGowajSoAgiwAgE&FORM=ANAB01&PC=DCTS [Last accessed: 18 October 2022].
36. Steel N, Ford JA, Newton JN, et al. Changes in health in the countries of the UK and 150 English Local Authority areas 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2018;392:1647-1661.
37. Steiner TJ, Stovner LJ, Jensen R, et al. Migraine remains second among the world's causes of disability, and first among young women: findings from GBD2019. The Journal of Headache and Pain 2020;21:137.
38. Steiner TJ, Stovner LJ, Birbeck GL. Migraine: the seventh disabler. 2013;33:289-290.
39. Agosti R. Migraine burden of disease: From the patient's experience to a socio-economic view. Headache: The Journal of Head and Face Pain 2018;58:17-32.
40. WHO. Headache disorders. Available at: https://www.who.int/news-room/fact-sheets/detail/headache-disorders [Last accessed: 10/10/2022]. 2016.
41. National Institute for Health and Care Excellence. BNF Treatment Summaries Migraine. Available at: https://bnf.nice.org.uk/treatment-summaries/migraine/ [Last accessed: 24 October 2022].
42. Edmeads J. Defining response in migraine: which endpoints are important? Eur Neurol. 2005;53 Suppl 1:22-28.
43. Gartlehner G, Dobrescu A, Wagner G, et al. Pharmacologic treatment of acute attacks of episodic migraine: a systematic review and network meta-analysis for the American College of Physicians. Annals of Internal Medicine 2025;178:507-524.
44. The migraine trust. Triptans. Available at: https://migrainetrust.org/live-with-migraine/healthcare/treatments/triptans/#:~:text=These%20formulations%20can%20work%20faster,make%20a%20difference%20for%20you. [Last accessed: August 2025].
45. Cooper W, Doty EG, Hochstetler H, Hake A, Martin V. The current state of acute treatment for migraine in adults in the United States. Postgraduate medicine. 2020;132(7):581-9. .
46. Dodick DW, Shewale AS, Lipton RB, et al. Migraine Patients With Cardiovascular Disease and Contraindications: An Analysis of Real-World Claims Data. J Prim Care Community Health 2020;11:2150132720963680.
47. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1-211.
48. The Migraine Trust. Stages of a migraine attack. Available at: https://migrainetrust.org/understand-migraine/stages-of-a-migraine-attack/. [Last accessed: August 2025].
49. MedicineNet. How Many Migraines a Month Is Normal? Available at: https://www.medicinenet.com/how_many_migraines_a_month_is_normal/article.htm. [Last accessed: 12 January 2026].
50. NHS. Migraines. Available at: https://www.nhs.uk/conditions/migraine/. [Last accessed: August 2025].
51. American Journal of Managed Care (2017). Emerging Therapies and Preventive Treatments for Migraine. Available at: https://www.ajmc.com/view/emerging-therapies-and-preventive-treatments-for-migraine-article. [Last accessed: October 2025]

52. Serrano D, Lipton RB, Scher AI, et al. Fluctuations in episodic and chronic migraine status over the course of 1 year: implications for diagnosis, treatment and clinical trial design. The journal of headache and pain 2017;18:1-12.
53. Martins IP, Westerfield M, Lopes M, et al. Brain state monitoring for the future prediction of migraine attacks. Cephalalgia 2020;40:255-265.
54. Aguilar-Shea AL, Membrilla Md JA, Diaz-de-Teran J. Migraine review for general practice. Aten Primaria 2022;54:102208.
55. Maniyar F.H., Sprenger T., Monteith T., Schankin C.J., Goadsby P.J. The premonitory phase of migraine – what can we learn from it? Headache. 2015;55:609–620. doi: 10.1111/head.12572.
56. Eigenbrodt AK, Christensen RH, Ashina H, et al. Premonitory symptoms in migraine: a systematic review and meta-analysis of observational studies reporting prevalence or relative frequency. J Headache Pain 2022;23:140.
57. Kissoon N.R., Cutrer F.M. Aura and other neurologic dysfunction in or with migraine. Headache. 2017;57:1179–1194. doi: 10.1111/head.13101
58. Dodick D.W. Migraine. Lancet. 2018;391:1315–1330. doi: 10.1016/S0140-6736(18)30478-1. .
59. Bose P., Karsan N., Goadsby P.J. The migraine postdrome. Contin Lifelong Learn Neurol. 2018;24(4-Headache):1023–1031. doi: 10.1212/CON.0000000000000626. .
60. Ferrari MD, Goadsby PJ, Burstein R, et al. Migraine. Nat Rev Dis Primers 2022;8:2.
61. Karsan N, Goadsby PJ. Biological insights from the premonitory symptoms of migraine. Nat Rev Neurol 2018;14:699-710.
62. Migraine Buddy. The Stages of a Migraine – Migraine Attack. Available at: https://migrainebuddy.com/the-stages-of-a-migraine-migraine-attack/ [Last Accessed: December 2022]. 2018.
63. Mayo Clinic. Migraine aura. Available at: https://www.mayoclinic.org/diseases-conditions/migraine-with-aura/multimedia/migraine-aura/vid-20084707 [Last accessed: 17th December 2022].
64. Lambru G, Andreou AP, Guglielmetti M, et al. Emerging drugs for migraine treatment: an update. Expert Opin Emerg Drugs 2018;23:301-318.
65. National Migraine Centre. What is migraine? Available at: http://www.nationalmigrainecentre.org.uk/migraine-and-headaches/migraine-and-headache-factsheets/what-is-migraine/ [Last accessed: October 2025]. .
66. Katsarava Z, Manack A, Yoon M, et al. Chronic migraine: classification and comparisons. Cephalalgia 2011;31:520-529.
67. Bigal ME, Serrano D, Buse D, et al. Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. Headache 2008;48:1157-68.
68. Marco A. Pescador Ruschel; Orlando De Jesus. Migraine Headache. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025.
69. The Migraine Trust. Migraine attack triggers. Available at: https://migrainetrust.org/live-with-migraine/self-management/common-triggers/?gad_source=1&gad_campaignid=644020078&gclid=EAIaIQobChMIodLcqaeFjwMVSJFQBh2G5w7qEAAYASAAEgJtj_D_BwE. [Last accessed: August 2025].
70. Baykan B, Ertas M, Karli N, et al. Migraine incidence in 5 years: a population-based prospective longitudinal study in Turkey. J Headache Pain 2015;16:103.
71. Lipton RB, Reed ML, Munjal S, et al. One-Year incidence of migraine in the U.S. population: Results from the Migraine in America Symptoms and Treatment (MAST) study. Presented at the American Headache Society Annual Scientific Meeting; Philadelphia, PA; 11-14 July. 2019.

72. Lyngberg AC, Rasmussen BK, Jorgensen T, et al. Incidence of primary headache: a Danish epidemiologic follow-up study. Am J Epidemiol 2005;161:1066-73.
73. Lipton RB, Bigal ME, Diamond M, et al. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology 2007;68:343-349.
74. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet 2012;380:2163-2196.
75. Scher AI, Wang S-J, Katsarava Z, et al. Epidemiology of migraine in men: results from the chronic migraine epidemiology and outcomes (CaMEO) study. Cephalalgia 2019;39:296-305.
76. Stovner LJ, Nichols E, T.J. S, et al. Global, regional, and national burden of migraine and tension-type headache, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2018;17:954-76.
77. Vetvik KG, MacGregor EA. Sex differences in the epidemiology, clinical features, and pathophysiology of migraine. Lancet Neurol 2017;16:76-87.
78. Mongini F, Deregibus A, Raviola F, et al. Confirmation of the distinction between chronic migraine and chronic tension-type headache by the McGill Pain Questionnaire. Headache 2003;43:867-77.
79. Neilsen. Migraine Impact Report. Available at: https://www.multivu.com/players/English/8259051-lilly-migraine-impact-report/docs/ExecutiveSummary_1516320372594-121193785.pdf [Last accessed: 05 January 2026].
80. Pourrahmat M-M, Kim A, Kansal AR, et al. Health state utility values by cancer stage: a systematic literature review. The European Journal of Health Economics 2021;22:1275-1288.
81. Buse DC, Reed ML, Fanning KM, et al. Comorbid and co-occurring conditions in migraine and associated risk of increasing headache pain intensity and headache frequency: results of the migraine in America symptoms and treatment (MAST) study. The journal of headache and pain 2020;21:1-16.
82. Jahangir S, Adjepong D, Al-Shami HA, et al. Is There an Association Between Migraine and Major Depressive Disorder? A Narrative Review. Cureus 2020;12:e8551.
83. Bigal ME, Lipton RB. Excessive acute migraine medication use and migraine progression. Neurology 2008;71:1821-8.
84. Ferrari A, Baraldi C, Sternieri E. Medication overuse and chronic migraine: a critical review according to clinical pharmacology. Expert Opin Drug Metab Toxicol 2015;11:1127-44.
85. Schwedt TJ, Alam A, Reed ML, et al. Factors associated with acute medication overuse in people with migraine: results from the 2017 migraine in America symptoms and treatment (MAST) study. J Headache Pain 2018;19:38.
86. Ghiotto N, Sances G, Galli F, Tassorelli C, Guaschino E, Sandrini G, et al. Medication overuse headache and applicability of the ICHD-II diagnostic criteria: 1-year follow-up study (CARE I protocol). Cephalalgia. 2009;29(2):233-43.
87. Lipton RB, Fanning KM, Serrano D, et al. Ineffective acute treatment of episodic migraine is associated with new-onset chronic migraine. Neurology 2015;84:688-95.
88. Leroux E, Buchanan A, Lombard L, et al. Evaluation of Patients with Insufficient Efficacy and/or Tolerability to Triptans for the Acute Treatment of Migraine: A Systematic Literature Review. Advances in Therapy 2020;37:4765-4796.
89. Lipton RB, Gendolla A, Abraham L, et al. Relative frequency, characteristics, and disease burden of patients with migraine unsuitable for triptan treatment: A systematic literature review. Headache: The Journal of Head and Face Pain 2025;65:164-179.

90. Sacco S, Di Ciaccio S, Di Virgilio R, et al. Acute treatment of migraine: quantifying the unmet need through real-world data in Italy. Neurological Sciences 2024;45:4427-4435.
91. Hirata K, Ueda K, Komori M, et al. Unmet Needs in Japanese Patients Who Report Insufficient Efficacy with Triptans for Acute Treatment of Migraine: Retrospective Analysis of Real-World Data. Pain and Therapy 2021;10:415-432.
92. Buse DC, Fanning KM, Reed ML, et al. Life With Migraine: Effects on Relationships, Career, and Finances From the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study. Headache 2019;59:1286-1299.
93. Buse DC, Scher AI, Dodick DW, et al. Impact of Migraine on the Family: Perspectives of People With Migraine and Their Spouse/Domestic Partner in the CaMEO Study. Mayo Clin Proc 2016;91:596-611.
94. Begasse de Dhaem O, Sakai F. Migraine in the workplace. eNeurologicalSci 2022;27:100408.
95. Terwindt G, Ferrari M, Tijhuis M, et al. The impact of migraine on quality of life in the general population: the GEM study. Neurology 2000;55:624-629.
96. Gajria K, Lee LK, Flores NM, et al. Humanistic and economic burden of nausea and vomiting among migraine sufferers. Journal of Pain Research 2017:689-698.
97. NHS England. Improved NHS migraine care to save thousands of hospital stays. Available at: https://www.england.nhs.uk/2020/01/improved-nhs-migraine-care/ [Last Accessed: October 2025]
98. The Migraine Trust. State of the Migraine Nation Dismissed for too long: Recommendations to improve migraine care in the UK. Available at: https://migrainetrust.org/wp-content/uploads/2021/09/Dismissed-for-too-long_Recommendations-to-improve-migraine-care-in-the-UK.pdf [Last Accessed: 16 December 2022].
99. NHS. Hospital Admitted Patient Care Activity, 2021-22. Available at: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2021-22 [Last accessed: December 2022].
100. The Migraine Trust. Heading in the wrong direction: Challenges in migraine care and why people with migraine deserve better. Available at: https://migrainetrust.org/wp-content/uploads/2023/09/TMT-Heading-In-The-Wrong-Direction-2023-FINAL.pdf. [Last accessed: August 2025].
101. Harris L, L'Italien G, O'Connell T, Hasan Z, Hutchinson S, Lucas S. A Framework for Estimating the Eligible Patient Population for New Migraine Acute Therapies in the United States. Adv Ther. 2021;38(10):5087-97.
102. The Work Foundation. Society's headache. The socioeconomic impact of migraine. April 2018. Available at: https://www.lancaster.ac.uk/media/lancaster-university/content-assets/documents/lums/work-foundation/SocietysHeadacheTheSocioeconomicimpactofmigraine.pdf. Last accessed: [November 2025].
103. Office for National Statistics (2020). Sickness absence in the UK labour market: 2020. Available at: https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/labourproductivity/articles/sicknessabsenceinthelabourmarket/2020. [Last accessed: August 2025].
104. The Migraine Trust. Diagnosis. Available at: https://migrainetrust.org/live-with-migraine/healthcare/diagnosis/#page-section-1. [Last accessed: August 2025].
105. NHS Inform. Migraine. Available at: https://www.nhsinform.scot/illnesses-and-conditions/brain-nerves-and-spinal-cord/migraine/ [Last accessed: October 2025].

106. Buse DC, Armand CE, Charleston IV L, et al. Barriers to care in episodic and chronic migraine: results from the chronic migraine epidemiology and outcomes study. Headache: The Journal of Head and Face Pain 2021;61:628-641.
107. Ross-Lee LM, Eadie MJ, Heazlewood V, Bochner F, Tyrer JH. Aspirin pharmacokinetics in migraine. The effect of metoclopramide. European Journal of Clinical Pharmacology. 1983;24(6):777-785.
108. Fischer MA JA. Medication-Overuse Headache. Available at: https://www.ncbi.nlm.nih.gov/books/NBK538150/. [Last accessed: September 2025].
109. Karlsson WK, Ostinelli EG, Zhuang ZA, et al. Comparative effects of drug interventions for the acute management of migraine episodes in adults: systematic review and network meta-analysis. BMJ 2024;386:e080107.
110. Migraine.com. NSAIDs (Non-Steroidal Anti-Inflammatory Drugs). Available at: https://migraine.com/migraine-treatment/nsaids-for-migraine-headaches. [Last accessed: 05 January 2026].
111. Lombard L, Farrar M, Ye W, et al. A global real-world assessment of the impact on health-related quality of life and work productivity of migraine in patients with insufficient versus good response to triptan medication. The journal of headache and pain 2020;21:41.
112. De Felice M, Ossipov MH, Porreca F. Update on medication-overuse headache. Current pain and headache reports 2011;15:79-83.
113. Puledda F, Sacco S, Diener HC, et al. International Headache Society global practice recommendations for the acute pharmacological treatment of migraine. Cephalalgia 2024;44.
114. Ailani J, Burch RC, Robbins MS, et al. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. Headache 2021;61:1021-1039.
115. Alsaadi T, Kayed DM, Al-Madani A, et al. Acute Treatment of Migraine: Expert Consensus Statements from the United Arab Emirates (UAE). Neurol Ther 2024;13:257-281.
116. Eigenbrodt AK, Ashina H, Khan S, et al. Diagnosis and management of migraine in ten steps. Nat Rev Neurol 2021;17:501-514.
117. The Migraine Trust. Migraine - Managing Migraine at Work. Available at: https://migrainetrust.org/live-with-migraine/migraineandwork/managing-migraine-at-work/ [Last Accessed: 05 September 2023].
118. National Bureau of Economic Research (NBER). Gender, Work, and Family: Progress and Ongoing Challenges. Available at: https://www.nber.org/reporter/2024number4/gender-work-and-family-progress-and-ongoing-challenges?page=1&perPage=50. [Last accessed: 05 January 2026].
119. Pacheco Barzallo D, Schnyder A, Zanini C, et al. Gender Differences in Family Caregiving. Do female caregivers do more or undertake different tasks? BMC Health Serv Res 2024;24:730.
120. Gillard PJ, Devine B, Varon SF, et al. Mapping from disease-specific measures to health-state utility values in individuals with migraine. Value Health 2012;15:485-94.
121. Stafford MR, Hareendran A, Ng-Mak DS, et al. EQ-5D™-derived utility values for different levels of migraine severity from a UK sample of migraineurs. Health Qual Life Outcomes 2012;10:65.
122. AbbVie Data on File [CONFIDENTIAL]. ECLIPSE Protocol, 2023.
123. AbbVie Data on File [CONFIDENTIAL]. ECLIPSE Statistical Analysis Plan, 2024.
124. Lipton RB, Croop R, Stock EG, et al. Rimegepant, an Oral Calcitonin Gene-Related Peptide Receptor Antagonist, for Migraine. N Engl J Med 2019;381:142-149.

125. Marcus R, Goadsby PJ, Dodick D, et al. BMS-927711 for the acute treatment of migraine: a double-blind, randomized, placebo controlled, dose-ranging trial. Cephalalgia 2014;34:114-25.
126. Lipton RB, Thiry A, Morris BA, et al. Efficacy and Safety of Rimegepant 75 mg Oral Tablet, a CGRP Receptor Antagonist, for the Acute Treatment of Migraine: A Randomized, Double-Blind, Placebo-Controlled Trial. J Pain Res 2024;17:2431-2441.
127. Yu S, Kim BK, Guo A, et al. Safety and efficacy of rimegepant orally disintegrating tablet for the acute treatment of migraine in China and South Korea: a phase 3, double-blind, randomised, placebo-controlled trial. Lancet Neurol 2023;22:476-484.
128. Croop R, Goadsby PJ, Stock DA, et al. Efficacy, safety, and tolerability of rimegepant orally disintegrating tablet for the acute treatment of migraine: a randomised, phase 3, double-blind, placebo-controlled trial. The Lancet 2019;394:737-745.
129. Ikeda K, Matsumori Y, Kudo M, et al. Efficacy and safety of rimegepant for the acute treatment of migraine in Japan: A dose-ranging, double-blind, randomized controlled trial. Headache 2025.
130. Messoud Ashina et al., “A Phase 4 Randomized Double-blind Placebo-Controlled Study of Rimegepant for Acute Treatment of Migraine in Adults Unsuitable for Triptan Use,” in Annual Metting of the American Headache Society, Minneapolis, 2025.
131. National Institute for Health and Clinical Excellence (NICE). NICE DSU Technical Support Document 3: Heterogeneity: Subgroups, Meta-Regression, Bias and Bias-Adjustment. Available at: https://www.ncbi.nlm.nih.gov/books/NBK395886/pdf/Bookshelf_NBK395886.pdf. [Last accessed: 18 December 2025].
132. Dias S, Welton NJ, Sutton AJ, et al. NICE Decision Support Unit Technical Support Documents. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. London: National Institute for Health and Care Excellence (NICE)

133. Linde DJSNGBBPCAvd. Bayesian Measures of Model Complexity and Fit. Available at: https://sites.stat.washington.edu/courses/stat527/s13/readings/Spiegelhalter_etal_RSSB_2002.pdf. [Last accessed: 05 January 2026].
134. Rimegepant (Vydura). Summary of product Characteristics. Available at: https://ec.europa.eu/health/documents/community-register/2022/20220425155292/anx_155292_en.pdf. [Last accessed: October 2025].
135. NICE. Fremanezumab for preventing migraine (TA764). Available at: https://www.nice.org.uk/guidance/TA764. [Last accessed: 24 October 2025].
136. NICE. Galcanezumab for preventing migraine (TA659). Available at: https://www.nice.org.uk/guidance/TA659. [Last accessed: 24 October 2025].
137. Office for National Statistics (ONS). National life tables. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables [Last Accessed: 24 October 2025]
138. AbbVie Data on File [CONFIDENTIAL]. MAAP Priority 1 Analysis, 2025.
139. Johnston K, Harris L, Powell L, et al. Monthly migraine days, tablet utilization, and quality of life associated with Rimegepant - post hoc results from an open label safety study (BHV3000-201). J Headache Pain 2022;23:10.
140. Johnston K, Powell LC, Popoff E, et al. Cost-effectiveness of rimegepant oral lyophilisate compared to best supportive care for the acute treatment of migraine in the UK. J Med Econ 2024;27:627-643.

141. NHS England. National Cost Collection for the NHS. Available at: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/ [Last accessed: 24 October 2025]
142. PSSRU. Unit Costs of Health and Social Care 2024 Manual. Available at: https://kar.kent.ac.uk/109563/ [Last accessed: 24 October 2025]
143. NICE. Risankizumab for treating moderate to severe plaque psoriasis (TA596). Available at: https://www.nice.org.uk/guidance/TA596. [Last accessed: 24 October 2025].
144. NICE. Guselkumab for treating moderate to severe plaque psoriasis (TA521). Available at: https://www.nice.org.uk/guidance/TA521. [Last accessed: 24 October 2025].
145. NICE. Risankizumab for treating active psoriatic arthritis after inadequate response to DMARDs (TA803). Available at: https://www.nice.org.uk/guidance/TA803. [Last accessed: 24 October 2025].
146. NICE. User guide for the cost comparison company evidence submission template (PMG32) Available at: https://www.nice.org.uk/process/pmg32/chapter/cost-comparison-analysis. [Last accessed: 24 October 2025].
147. National Institute for Health and Care Excellence. British National Formulary (BNF). Available at: https://bnf.nice.org.uk/ [Last accessed: November 2025].

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal: cost-comparison

Atogepant for treating migraine [ID6615]

Summary of Information for Patients (SIP)

January 2026

File name	Version	Contains confidential information	Date
ID6615_Atogepant in Migraine_SIP [noCON]	V1	No	**23rd January 2026**

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:

NICE are appraising this treatment for **acute** treatment of migraine with or without **aura** in adults, only if for previous migraines:

- At least 2 triptans were tried and they did not work well enough *or*
- Triptans were **contraindicated** or not tolerated, and **nonsteroidal anti-inflammatory drugs (NSAIDs)** such as ibuprofen, and paracetamol were tried but did not work well enough

Please note: Throughout this document, some words and phrases are highlighted in **black bold text**. Further explanations for these words and phrases are provided in the glossary (**Section 4b**). Cross-references to other sections of this document, or to other documents, are highlighted in **orange**.

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. It sets out the conditions for use of a drug based on evidence of its safety and clinical effectiveness.

Atogepant has been studied in a **phase 3 trial** (ECLIPSE) for the acute treatment of migraine. Marketing authorisation is pending. More information on this can be found in **Section 3.3** of the **Company Submission**.

Atogepant has previously received marketing authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA) for the prevention of migraine in adults who have at least 4 migraine days per month.[1]

More information on this can be found in **Section 1.2** of the **Company Submission**.

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.

The condition for which NICE is evaluating atogepant is the acute treatment of migraine

What is migraine?

Migraine is a complex, long-term health condition. If you have migraine you will have repeated **migraine attacks**, which can be a whole-body experience.[2]

What are the signs, symptoms and stages of migraine?

The experience of migraine is unique to each person. Different people experience different symptoms which can vary in severity.

Migraine attacks tend to happen in stages, and different symptoms can be experienced at each stage. There can be three or four stages of a migraine attack that lead on from each other. Not everyone will experience every stage, and the stages can overlap, with some symptoms continuing across all stages. Each stage, and the combination of stages experienced, can vary from attack to attack.[3]

In the prodrome/premonitory stage people often experience 'warning' symptoms of a migraine attack such as:

- Tiredness
- Difficulty concentrating
- Mood changes
- Being very sensitive to light or sound
- Neck pain

These symptoms can last for hours or days.[4, 5]

The next stage may be aura, which is experienced in up to 1 in 3 people who get migraine attacks. Aura includes symptoms such as:

- Visual problems, for example seeing flashing lights
- Numbness or tingling sensations
- Feeling dizzy
- Difficulty speaking
- Hearing loss or changes

Each symptom may last from 5 to 60 minutes.[3, 5]

The third stage is the headache/main attack. This is a moderate to severe headache, often felt as a throbbing pain on one side of the head which can be made worse by movement.[3] Other common symptoms at this stage include:[4, 5]

- Being very sensitive to light or sound
- Tiredness
- Feeling sick and being sick

These symptoms can last from four hours to three days.[6]

The final stage is postdrome/recovery where the headache resolves, but other symptoms such as fatigue, difficulty concentrating and mood changes can continue for hours or days.[3, 5, 7]

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.[8] Migraine attacks can be triggered by factors such as changes in hormones, other diseases, tiredness, diet, and stress.[9]

How many people get migraine?

Migraine is one of the most common **neurological** diseases worldwide, affecting around 10 million people in the UK.[5] Migraine can occur at any age but it is most common in those aged between 25 to 55 years old and is two to three times more common in women than men.[5, 10-14]

What is the impact of migraine (disease burden)?

Symptoms

Migraines can have a huge impact on people's lives. The severe symptoms patients experience can have a significant negative impact on their mental wellbeing, physical function, daily activities, and ability to lead a normal life.[9, 15-19] In addition to the pain experienced during an attack, people with migraine can experience additional neurological symptoms such as:[8]

- Sensitivity to light
- Sensitivity to sound
- Difficulty concentrating
- Feeling or being sick

In addition to the physical symptoms, migraine can also have considerable negative impacts on mental health. People with migraine are two to four times more likely to experience depression than patients who do not have migraine, with roughly 80% of people with migraine experiencing depression.[20-22] Furthermore, between migraine attacks, people with migraine are three times more likely to experience anxiety, potentially due to the anticipation of the next painful attack or whether this will impact future plans.[21, 23]

Impact on daily life

Mirgraine has a considerable negative impact on the lives of affected people and it affects their ability to carry out daily activities. As a result, migraine is the fourth highest cause of disability globally in people who are 15–49 years of age.[24] A large study found that nearly half of people with migraine reported feeling limited in daily activities throughout all migraine phases.[25] This may also spill over into people's family lives, as individuals report

reduced participation in family activities and feeling guilty about the impact of migraine on their family.[25-27]

Impact on quality of life

The high symptom burden for people with migraine coupled with the significant impact on their daily life can result in significant reductions in quality of life (QoL), with evidence from large-scale survey studies showing that QoL scores are generally lower in those with migraine compared with the general population.[28-30] This highlights the negative effect migraine has on people's quality of life and why effective treatment is essential.

Impact on working life and costs

Migraine also negatively impacts people's ability to work and causes increased workplace **absenteeism**.[31] In the UK, migraine causes approximately 86 million lost workdays a year due to absence, resulting in costs of over £8.8 billion due to absenteeism and **presenteeism**.[32]

In total, treating migraine costs the NHS roughly £150 million per year.[33] Migraine is the most common neurological reason for visiting a general practitioner (**GP**), resulting in 2.5 million appointments every year.[34] Migraine is also a leading reason for attending Accident and Emergency (A&E) in the UK and around 1 in 20 migraine patients are diagnosed in A&E. NHS England estimates that nearly 16,500 emergency admissions for headaches and migraine attacks could be prevented by optimising care pathways, and £11.5 million could be saved on non-elective admissions.[34]

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. Diagnosis of migraine will depend on a GP taking a detailed medical history and a thorough examination including a neurological assessment may be carried out.[35] People with migraine may be asked 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.[36] Patients may also be referred to a specialist to discuss potential treatment options that could be prescribed if current acute treatment is not working.[37]

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 the medicine is 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.

Current acute treatment options for migraine

While there is no cure for migraine, people with migraine may receive **acute treatment**, which aims to end an attack and minimise the pain of the headache.[38]

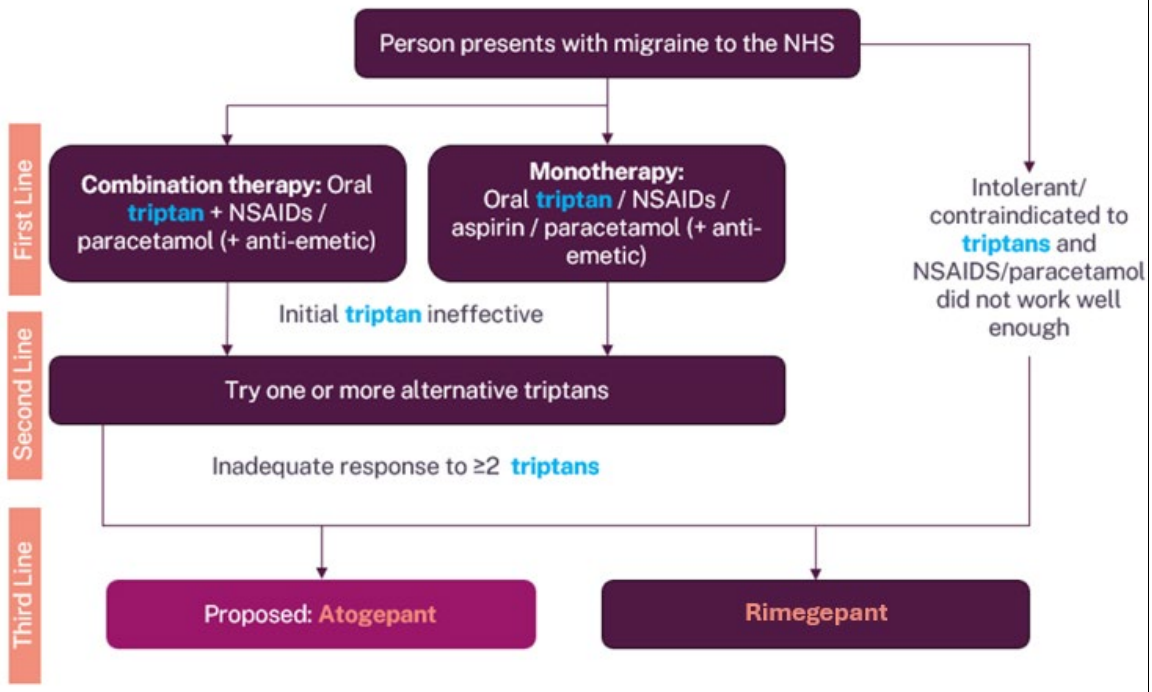
Figure 1 shows the acute treatments that are offered to people with migraine.

Typically, people with migraine are first prescribed painkillers, anti-sickness medications or triptans, which can all be taken orally.[39, 40] Triptans are treatments specifically for migraines and they work well for some people, but not in others, and they are not suitable (**contraindicated**) for some people.[41]

If a person with migraines has tried painkillers and at least two triptans and neither have helped control their symptoms during a migraine attack, or if triptans are contraindicated for them or were not tolerated, the only other option for acute treatment is rimegepant. Rimegepant is a **calcitonin gene-related peptide** (CGRP) **receptor antagonist**. It is taken when people with migraine experience a migraine attack and it is an **orally disintegrating tablet (ODT)** placed on or under the tongue.[42] Therefore, there is currently a lack of acute treatment options in individuals with migraine for whom triptans are ineffective or are not well tolerated.

In this appraisal, atogepant is proposed as a new acute treatment for migraine in people who have tried at least two triptans and they have not worked well enough, *or* in whom triptans were contraindicated or not tolerated. Atogepant is a tablet that is taken during a migraine attack and will be offered as an alternative to rimegepant, as it works in a similar way.

Figure 1: Current treatment pathway for acute treatment of migraine and proposed positioning of atogepant



Abbreviations: NSAID: non-steroidal anti-inflammatory drug; NHS: National Health Service.

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.[10, 43] Furthermore, a global study of people with migraine found that:[25]

- 83% had sleeping difficulties
- 74% spend time in darkness due to migraine
- 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.[25-27] As a result, many people with migraine report hiding their migraine from friends, family and even employers.[44] A survey of people with migraine found that two thirds of patients had not previously taken sick leave when experiencing a migraine attack because they worried about being disciplined or losing their job, or because they had previously been treated badly for doing so.[45]

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.

Atogepant is a medicine that works by blocking the action of a molecule called **CGRP**. CGRP is released by certain nerves in the body during a migraine attack. It is involved in transmitting pain signals in your nervous system, which contributes to the symptoms of a migraine attack.[46] By blocking CGRP from attaching to its receptor, atogepant can help reduce symptoms of a migraine, including pain.[1]

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 treatment.

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? Atogepant is a tablet that should be swallowed whole. This differs from rimegepant, which is supplied as an ODT that is placed on or under the tongue to dissolve and does not need to be swallowed whole. **How much medicine do patients take and when?** Atogepant tablets are 60 mg each. One 60 mg tablet should be taken orally as needed, with or without food. The maximum dose for acute treatment of migraine is 60 mg of atogepant per day. A once daily 10 mg dose is available to be used in patients who have severe **renal impairment** or **end-stage renal disease**, or those currently receiving other treatments in the form of strong cytochrome P450 3A4 (CYP3A4) and/or organic anion transporting polypeptide (OATP) inhibitors. CYP3A4 inhibitors and OATP inhibitors are classes of medicines that reduce the ability to clear certain medicines from the body. This reduced clearance means that any other medicines taken by the person at the same time as these inhibitors can stay in the body for longer than usual.[47, 48] For this reason, in patients taking these medicines, a lower dose of atogepant is recommended.

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 of atogepant for the acute treatment of migraine

One **clinical trial** (**ECLIPSE;** NCT06241313) has studied atogepant for the acute treatment of migraine.[49, 50]

ECLIPSE was a **Phase 3 trial**. The trial assessed how well atogepant 60 mg reduced the frequency and severity of migraine (i.e., its **efficacy**) and improved patient quality of life as compared with a **placebo** (the **comparator**).[49, 50] The trial also assessed the safety and tolerability of atogepant compared to placebo, including how frequently side effects occurred, how severe these side effects were, and whether patients had to stop treatment because of them.[49, 50] A summary of the key information about ECLIPSE is provided in **Table 1**.

The ECLIPSE trial included adult patients who have had migraines for at least a year, with the migraines starting before the age of 50.[49, 50] Migraines could have occurred with or without aura. Patients were also required to have had 2 to 8 migraine attacks with moderate to severe pain each month over the past 3 months.[49, 50] These attacks needed to have lasted 4 to 72 hours if not effectively treated, with at least 48 hours headache-free between attacks.[49, 50]

More information on this trial can be found in **Section 3.3** of the **Company Submission.**

Table 1: Trial investigating atogepant for the acute treatment of migraine

Trial name and number	Location	Trial design	Population	Treatment	Comparator
ECLIPSE (NCT06241313)	BE, CN, CZ, DE, HU, IT, JP, PL, PO, SL, SK, SP; SW, TW, UK.	Phase 3	Adult patients with migraine	Atogepant 60 mg	Placebo

Abbreviations: BE: Belgium; CN: China; CZ: Czechia; DE: Germany; HU: Hungary; IT: Italy; JP: Japan; PL: Poland; PO: Portugal; SL: Slovakia; SK: South Korea; SP: Spain; SW: Sweden; TW: Taiwan; UK: United Kingdom.

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

As outlined in Section 3d above, the efficacy of atogepant as an acute treatment of migraine was studied in the ECLIPSE trial. In ECLIPSE, the effectiveness of atogepant, in comparison to placebo, was primarily measured according to how many patients reported being free from pain (**pain freedom**) two hours after treatment. ECLIPSE also measured the effectiveness of atogepant in terms of how well it:[49, 50]

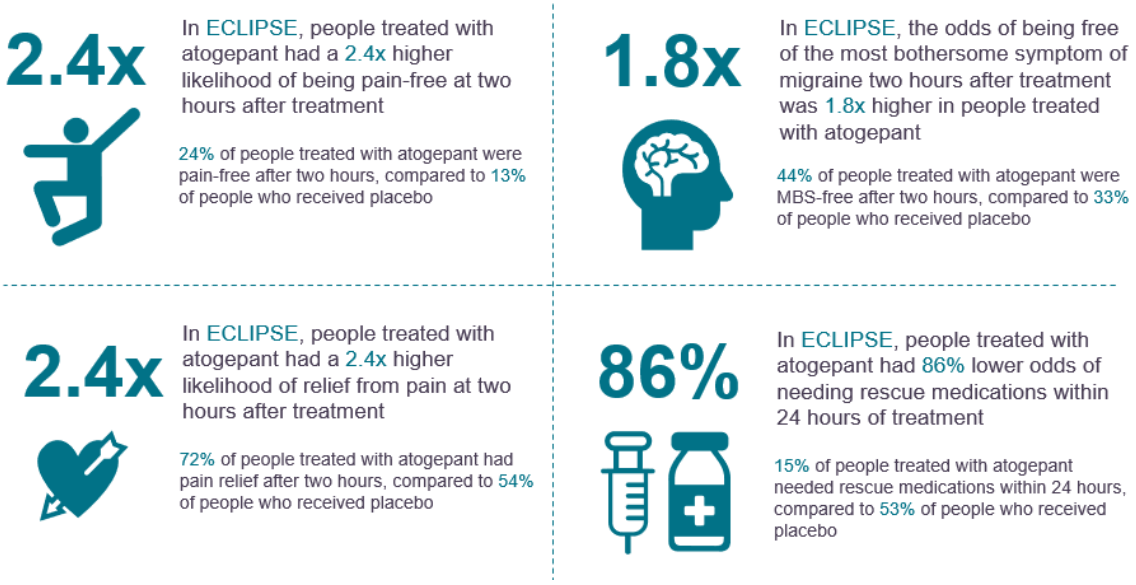
- Freed patients of their **most bothersome symptoms** of migraine (MBS)
- Provided and sustained **pain relief**
- Restored the ability for patients to function normally
- Reduced the need for patients to take **rescue medications**

Figure 2 shows the key efficacy results of ECLIPSE after treatment with atogepant, compared to placebo.

In summary, the ECLIPSE trial demonstrated that treatment with atogepant statistically significantly provided greater freedom from pain (at two hours) compared to treatment with placebo.[50] Patients treated with atogepant reported greater freedom from their MBS after two hours of taking atogepant, compared to those who had received placebo.[50] Pain relief was also sustained for up to 24 hours in over twice as many patients who were treated with atogepant than those treated with placebo.[50]

More efficacy results from ECLIPSE can be found in Section 3.6 of the Company Submission.

Figure 2: Key efficacy results for ECLIPSE.[50]



Indirect treatment comparison

As outlined in Section 2c above, atogepant is intended for use as an alternative to rimegepant. However, the ECLIPSE trial compared atogepant to placebo only. Therefore,

no direct data are available for atogepant versus rimegepant. As such, a statistical analysis called an **indirect treatment comparison** was performed, to produce an estimate of how effective atogepant is compared with rimegepant. This statistical analysis is explained in further detail in the **Company Submission, Section 3.9.**

Overall, compared to rimegepant, the indirect treatment comparison showed that atogepant is as effective as rimegepant in reducing migraine frequency and severity, and is a well-tolerated treatment option for the acute treatment 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 ECLIPSE trial, the QoL of patients was assessed through several measures, including:[49, 50]

- The **EQ-5D-5L** questionnaire was used to determine how the patient's self-reported **health-related quality of life** (HRQoL) had changed after treatment with atogepant or placebo, compared to the study baseline
- The **Migraine Quality of Life Questionnaire** (MQoLQ) is a disease-specific measure of HRQoL, and was used to understand the impact that treatment with atogepant or placebo had on patient impairment on the domains of work, social functioning, energy, general feeling/concerns and migraine symptoms
- The **Cognitive Function Scale** (CFS) was used to study the ability of patients to think clearly, before versus after treatment with atogepant or placebo

Overall, patients treated with atogepant had better quality of life results compared with patients treated with placebo.[51] Further details on HRQoL, as observed in ECLIPSE, are presented in **Section 3.6.4** of the **Company Submission.**

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 ECLIPSE, atogepant was generally well **tolerated** and was associated with infrequent, mild side effects. Across the full 24-week duration of the trial, only 2% of patients treated with atogepant reported a side effect that was considered to be related to the study treatment within 48 hours of receiving treatment.[50] Furthermore, very few patients (0.2%) who were treated with atogepant experienced a serious side effect within 48 hours of receiving treatment in ECLIPSE.[50] Similar trends were observed up to 30 days after treatment with atogepant.[50] Overall, no new side effects were observed for atogepant as compared with the known safety profile for other treatments in the same treatment class (called **gepants**).[50]

Information on other potential side effects for atogepant in acute treatment of migraine are available in the **Patient Information Leaflet**, and results from the ECLIPSE trial are reported in **Section 3.10** of the **Company Submission.**

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.

According to Phase 3 clinical trial evidence, as presented above, atogepant is an effective option for the acute treatment of migraine.[50]

Based on a robust indirect treatment comparison, the effectiveness of atogepant in providing freedom and relief from pain is comparable to that of rimegepant and no new safety concerns were identified.

Therefore, atogepant represents an additional acute treatment option for patients with migraine who have tried at least two triptans and these have not worked well enough or in whom triptans were contraindicated or not tolerated.

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, as is the case with any medicine, atogepant may not work for everyone and some patients might not experience any improvement in their migraines.

Additionally, as for any other active treatment, some patients may experience side effects while they are taking the treatment. The most common side effect related to treatment with atogepant was nausea. This safety profile is in line with what has previously been observed for rimegepant in acute treatment of migraine.

3i) 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 patients is likely to improve if they take it. The pharmaceutical company that develops the medicine 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 costs of the new treatment (atogepant) with the existing treatment or comparator (rimegepant).

What type of model was created?

Since atogepant demonstrated in the indirect treatment comparison (see Section 3e) above) that it can provide similar or greater benefits than an existing therapy available in this disease area (rimegepant), a cost comparison tool was created with the aim of comparing the costs associated with treatment when using atogepant as compared with when using rimegepant. Notably, under this approach, the model did not incorporate any clinical data. Instead, it is assumed that these treatments have the same clinical efficacy, and only differences in costs were considered.

How the model reflects migraine

The economic model was designed to reflect the key features of acute treatment of migraine and **clinical practice** in the UK. Key features of the model were aligned with the approach taken in the prior NICE appraisal of rimegepant (TA919).[52]

Modelling how the costs of treatment differ with the new treatment

A range of costs are included in the model for the different migraine treatments (atogepant or rimegepant). These costs include:

- The cost to purchase the medicine itself
- The costs of using the healthcare system such as those associated with going into hospital, visiting A&E, or having a GP appointment

Cost comparison results

When assuming identical efficacy for atogepant and rimegepant, results from the cost comparison model indicate that atogepant will reduce costs for the NHS compared with rimegepant as a treatment for migraine. Several assumptions were made in the model that were validated by clinicians. Information on these assumptions can be found in Section 4.2.7 of the Company Submission.

Variations of other inputs in the model were also tested. These results, which are presented and explained in full in Section 4.3 of the Company Submission, found atogepant is a cost-saving option for the NHS versus rimegepant.

Conclusion

The benefits outlined in Section 3h and the economic analysis results above suggest that atogepant represents good value for money and a good use of NHS resources as a new acute treatment for patients with migraine.

3j) 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 additional option in the acute treatment of migraine

Migraine is a condition that can have a significant impact on a patient's mental health, emotional wellbeing, and quality of life. Despite this, there is no cure for migraine and there is currently only one acute treatment option available for patients with migraine who have not found relief despite trying two or more triptan medications, or in whom triptans were contraindicated or not tolerated.

Atogepant works in the same way as rimegepant and has been shown to be similarly effective in relieving the severity of pain and symptoms associated with migraine. Moreover, atogepant has been demonstrated to have a similar side effect profile to rimegepant, with no new safety concerns observed. Given these considerations, the introduction of atogepant to NHS clinical practice would add to the available treatment options against acute treatment of migraine, representing a tolerable and efficacious alternative to rimegepant in this patient population.

3k) 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 expected that providing or not providing atogepant will exclude anyone protected by equality legislation, result in recommendations that impact these individuals differently from the wider population, or create adverse effects for people with particular disabilities.

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
- What is migraine? What is migraine? - National Migraine Centre
- Overview Migraine. Migraine - NHS (www.nhs.uk)
- Migraine hurts. Migraine Hurts – The Migraine Trust
- Acute medicines. Acute Medicines
- Gepants. Gepants – The Migraine Trust
- Heading in the wrong direction: Challenges in migraine care and why people with migraine deserve better Heading in the wrong direction – The Migraine Trust

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. Acute treatments are used to stop migraines, or reduce their impact, once symptoms have started.

Aura	Sensory symptoms that may happen as part of a migraine attack 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
Calcitonin gene-related peptide	A protein 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, with migraine symptoms on at least 8 days, for at least three months.
Clinical practice	The agreed-upon and customary means of delivering health care by doctors, nurses and other healthcare professionals.
Clinical trial	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.
Cognitive Function Scale	A measure to quantify subjective cognitive symptoms during migraine attacks
Comparator	Another treatment that can be used as a standard for comparison.
Contraindicated	A medicine or treatment that should not be used because it could be harmful given your health history or other medicines you take.
Cost comparison	A comparison of the costs of different treatment options to help determine value or which option is cheaper.
Efficacy	The ability of a drug to produce the desired beneficial effect on your disease or illness in a clinical trial.
Episodic migraine	A classification of migraine that includes people who experience headache less than 15 days per month.
EQ-5D-5L	A short questionnaire that asks about five areas of health (mobility, self-care, usual activities, pain/discomfort, and mood) to measure overall health-related quality of life.
Gepants	A class of migraine medicines that work by blocking CGRP activity in the brain, helping to prevent or treat migraine attacks.
GP	A general health practitioner, which is a doctor based in the community that treats people with minor or chorionic 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.
Health-related quality of life	A measure of a person's overall well-being and ability to carry out daily activities, influenced by health status, symptoms, and treatment effects. It includes physical, mental, and social aspects of life.
Indirect treatment comparison	An analysis that compares medicines that have not been compared directly in a head-to-head, randomised clinical trial.
Marketing authorisation	The legal approval by a regulatory body that allows a medicine to be given to patients in a particular country.
Medicines and Healthcare Product Regulatory Agency (MHRA)	The regulatory body that evaluates, approves and supervises medicines throughout the United Kingdom.
Migraine attacks	An episode usually involving moderate or severe headache in combination with other symptoms such as sensitivity to light, sounds and smells, and nausea or vomiting.
Migraine diary	A diary that can be kept to learn more about people's migraines and what triggers them.
Migraine Quality of Life Questionnaire	A short questionnaire you fill out to describe how migraines impact your daily activities, energy, and mood.
Most bothersome symptom	The symptom of a migraine that you find most troublesome (for example, nausea, sensitivity to light, or a pounding head). In research, participants identify which symptom bothers them the most.
Neurological	Relates to diseases of the nervous system, which is the part of the body that controls actions and senses.
NSAIDs (non steroidal anti-inflammatory drugs)	A group of medications such as ibuprofen or aspirin used to relieve pain, reduce inflammation, and lower fever
Orally disintegrating tablet	A tablet that dissolves quickly in the mouth without needing water to swallow.
Pain freedom	Complete absence of headache pain within a set time after taking treatment (often about 2 hours in trials).
Pain relief	A reduction in headache pain after taking treatment, which may not be complete disappearance.
Phase 3 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.
Presenteeism	The act of employees coming to work while feeling unwell, which may lead to reduced productivity and a higher risk of making mistakes.
Receptor antagonist	A drug that binds to a receptor in the body and blocks it to reduce an effect.
Rescue medications	Medicines taken during the course of a migraine to relieve migraine symptoms if other acute medications taken earlier in the course of the migraine have not worked sufficiently. Examples may include triptans, painkillers or NSAIDs.
Side effect (also called adverse event)	An unexpected medical problem that arises during treatment. Side effects may be mild, moderate or severe.
Tolerated	The ability of a patient to persist a treatment, despite the treatment's side effects.

4c) References

1. Medicines and Healthcare products Regulatory Agency. Atogepant- Summary of product Characteristics. Available at: https://products.mhra.gov.uk/search/?search=atogepant&page=1 [Last accessed: August 2025].
2. The Migraine Trust. Migraine attack triggers. Available at: https://migrainetrust.org/live-with-migraine/self-management/common-triggers/?gad_source=1&gad_campaignid=644020078&gclid=EAIaIQobChMIodLcqaeFjwMVSJFQBh2G5w7qEAAYASAAEgJtj_D_BwE. [Last accessed: August 2025].
3. The Migraine Trust. Stages of a migraine attack. Available at: https://migrainetrust.org/understand-migraine/stages-of-a-migraine-attack/. [Last accessed: August 2025].
4. Migraine Buddy. The Stages of a Migraine – Migraine Attack. Available at: https://migrainebuddy.com/the-stages-of-a-migraine-migraine-attack/ [Last Accessed: December 2022].
5. National Institute for Health and Care Excellence (NICE). Migraine: What is it? Available at: https://cks.nice.org.uk/topics/migraine/background-information/definition/. [Last accessed: August 2025].
6. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1-211.
7. Mayo Clinic. Migraine aura. Available at: https://www.mayoclinic.org/diseases-conditions/migraine-with-aura/multimedia/migraine-aura/vid-20084707 [Last accessed: 17th December 2022].
8. NHS Inform. Migraine. Available at: https://www.nhsinform.scot/illnesses-and-conditions/brain-nerves-and-spinal-cord/migraine/ [Last accessed: October 2025].
9. Agosti R. Migraine burden of disease: From the patient's experience to a socio-economic view. Headache: The Journal of Head and Face Pain 2018;58:17-32.
10. Lipton RB, Bigal ME, Diamond M, et al. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology 2007;68:343-349.
11. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet 2012;380:2163-2196.
12. National Migraine Centre. What is migraine? Available at: http://www.nationalmigrainecentre.org.uk/migraine-and-headaches/migraine-and-headache-factsheets/what-is-migraine/ [Last accessed: October 2025]. .
13. Scher AI, Wang S-J, Katsarava Z, et al. Epidemiology of migraine in men: results from the chronic migraine epidemiology and outcomes (CaMEO) study. Cephalalgia 2019;39:296-305.
14. Stovner LJ, Nichols E, T.J. S, et al. Global, regional, and national burden of migraine and tension-type headache, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2018;17:954-76.
15. Steel N, Ford JA, Newton JN, et al. Changes in health in the countries of the UK and 150 English Local Authority areas 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2018;392:1647-1661.

16. Steiner TJ, Stovner LJ, Jensen R, et al. Migraine remains second among the world's causes of disability, and first among young women: findings from GBD2019. J Headache Pain 2020;21:137.

17. Steiner TJ, Stovner LJ, Birbeck GL. Migraine: the seventh disabler. 2013;33:289-290.

18. Buse DC, Yugrakh MS, Lee LK, et al. Burden of Illness Among People with Migraine and ≥ 4 Monthly Headache Days While Using Acute and/or Preventive Prescription Medications for Migraine. J Manag Care Spec Pharm 2020;26:1334-1343.

19. WHO. Headache disorders. Available at: https://www.who.int/news-room/fact-sheets/detail/headache-disorders [Last accessed: 10/10/2022]. 2016.

20. Jahangir S, Adjepong D, Al-Shami HA, et al. Is There an Association Between Migraine and Major Depressive Disorder? A Narrative Review. Cureus 2020;12:e8551.

21. Buse DC, Reed ML, Fanning KM, et al. Comorbid and co-occurring conditions in migraine and associated risk of increasing headache pain intensity and headache frequency: results of the migraine in America symptoms and treatment (MAST) study. The journal of headache and pain 2020;21:1-16.

22. Antonaci F, Nappi G, Galli F, et al. Migraine and psychiatric comorbidity: a review of clinical findings. J Headache Pain 2011;12:115-25.

23. Brandes JL. The migraine cycle: patient burden of migraine during and between migraine attacks. Headache 2008;48:430-41.

24. Steiner TJ, Husøy A, Stovner LJ. GBD2021: headache disorders and global lost health - a focus on children, and a view forward. J Headache Pain 2024;25:91.

25. Martelletti P, Schwedt TJ, Lanteri-Minet M, et al. My Migraine Voice survey: a global study of disease burden among individuals with migraine for whom preventive treatments have failed. The journal of headache and pain 2018;19:1-10.

26. Buse DC, Fanning KM, Reed ML, et al. Life With Migraine: Effects on Relationships, Career, and Finances From the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study. Headache 2019;59:1286-1299.

27. Buse DC, Scher AI, Dodick DW, et al. Impact of Migraine on the Family: Perspectives of People With Migraine and Their Spouse/Domestic Partner in the CaMEO Study. Mayo Clin Proc 2016;91:596-611.

28. Domitrz I, Golicki D. Health-Related Quality of Life in Migraine: EQ-5D-5L-Based Study in Routine Clinical Practice. J Clin Med 2022;11.

29. Terwindt G, Ferrari M, Tijhuis M, et al. The impact of migraine on quality of life in the general population: the GEM study. Neurology 2000;55:624-629.

30. Gajria K, Lee LK, Flores NM, et al. Humanistic and economic burden of nausea and vomiting among migraine sufferers. Journal of Pain Research 2017:689-698.

31. Vo P, Fang J, Bilitou A, et al. Patients' perspective on the burden of migraine in Europe: a cross-sectional analysis of survey data in France, Germany, Italy, Spain, and the United Kingdom. The journal of headache and pain 2018;19:82.

32. The Work Foundation. Society's headache. The socioeconomic impact of migraine. April 2018. Available at: https://www.lancaster.ac.uk/media/lancaster-university/content-assets/documents/lums/work-

foundation/SocietysHeadacheTheSocioeconomicimpactofmigraine.pdf. Last accessed: [November 2025].

33. NHS England. Improved NHS migraine care to save thousands of hospital stays. Available at: https://www.england.nhs.uk/2020/01/improved-nhs-migraine-care/ [Last Accessed: October 2025]

34. The Migraine Trust. State of the Migraine Nation Dismissed for too long: Recommendations to improve migraine care in the UK. Available at: https://migrainetrust.org/wp-content/uploads/2021/09/Dismissed-for-too-long_Recommendations-to-improve-migraine-care-in-the-UK.pdf [Last Accessed: 16 December 2022].

35. The Migraine Trust. Diagnosis. Available at: https://migrainetrust.org/live-with-migraine/healthcare/diagnosis/#page-section-1. [Last accessed: August 2025].

36. The Migraine Trust. Keeping a Headache Diary. Available at: https://migrainetrust.org/live-with-migraine/self-management/keeping-a-migraine-diary/. [Last accessed: September 2025].

37. The Migraine Trust. Headache Clinics. Available at: https://migrainetrust.org/live-with-migraine/healthcare/migraine-clinics/. [Last accessed: September 2025].

38. National Institute for Health and Care Excellence. BNF Treatment Summaries Migraine. Available at: https://bnf.nice.org.uk/treatment-summaries/migraine/ [Last accessed: 24 October 2022].

39. National Institute for Health and Care Excellence. CG150: Headaches in over 12s: diagnosis and management. Available at: https://www.nice.org.uk/guidance/cg150/chapter/Recommendations#management-2 [Last accessed: 20/10/2022].

40. British Association for the Study of Headache. Available at: https://www.bash.org.uk/ [Last Accessed: 15 Dec 2022].

41. NICE (2025). Migraine: Drugs for acute migraine. Available at: https://cks.nice.org.uk/topics/migraine/prescribing-information/drugs-for-acute-migraine/ [Last accessed: October 2025].

42. Wells RE, Markowitz SY, Baron EP, Hentz JG, Kalidas K, Mathew PG, et al. Identifying the factors underlying discontinuation of triptans. Headache. 2014;54(2):278-89.

43. Lipton RB, Fanning KM, Serrano D, et al. Ineffective acute treatment of episodic migraine is associated with new-onset chronic migraine. Neurology 2015;84:688-95.

44. Mitsikostas DD, Daniel O, Cohen JM, et al. Patient perceptions of the impact and burden of migraine: An international survey of 12,545 patients across 16 countries. Abstract presented at the Migraine Trust Virtual Symposium 2020; 3-9 October. 2020.

45. The Migraine Trust. Challenging Stigma Workplace Briefing. Available at: https://migrainetrust.org/wp-content/uploads/2025/09/Challenging-stigma-Workplace-briefing-2025.pdf. [Last accessed: November 2025]. 2025.

46. The Migraine Trust. Treatments: Gepants. Available at: https://migrainetrust.org/live-with-migraine/healthcare/treatments/gepants/#page-section-2. [Last Accessed: November 2025]. 2024.

47. Biology Insights. What Are CYP3A4 Inhibitors and What Do They Do? Available at: https://biologyinsights.com/what-are-cyp3a4-inhibitors-and-what-do-they-do/. [Last accessed: 05 January 2026].

48. Synapse. What are OAT inhibitors and how do they work? Available at: https://synapse.patsnap.com/article/what-are-oat-inhibitors-and-how-do-they-work. [Last accessed: 05 January 2026].

49. ClinicalTrials.gov. Study of Oral Atogepant Tablets to Assess Safety and Efficacy in Adult Participants With Migraine (ATO ACUTE) (NCT06241313). Available at: https://www.clinicaltrials.gov/study/NCT06241313 [Last accessed: October 2025].

50. Dycke AV, Brand-Schieber E, Ornello R, et al. Efficacy, Safety, and Tolerability of Atogepant for the Acute Treatment of Migraine: Results from the ECLIPSE Trial, In 19th European Headache Congress (EHC), Lisbon, Portugal, 2025.

51. AbbVie Data on File [CONFIDENTIAL]. ECLIPSE Clinical Study Report, 2025.

52. National Institute for Health and Care Excellence (NICE). Rimegepant for treating migraine (TA919). Available at: https://www.nice.org.uk/guidance/ta919 [Last accessed: October 2025].

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Atogepant for treating migraine [ID6615]

Clarification questions

February 2026

File name	Version	Contains confidential information	Date
ID6615 atogepant clarification questions_Response_ Combined [CON]	V4	Yes	15.05.26

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.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Network meta-analyses

A1. Priority question. The EAG notes that the network meta-analyses (NMAs) were conducted using WinBUGS and R. Please provide the full set of analysis files used to generate the NMA results, including WinBUGS model code and associated data files, R scripts used for data preparation, model execution, post-processing and plotting, and any supporting documentation needed to run or interpret the analysis. Please also provide the summary data used from each of the individual trials in the NMAs and model convergence plots for each outcome.

> **a) We note that question A1 has been expanded from the original wording communicated via email to also request model convergence plots for each outcome. We would still like the company to provide these. In addition to the convergence plots already requested, please could the company also provide additional standard NMA diagnostic**

and results plots (e.g. Gelman–Rubin diagrams, Rankograms, SUCRA and/or cumulative SUCRA plots).

Gelman-Rubin plots, rank plots, surface under the cumulative ranking curve (SUCRA) plots, leverage plots, and trace plots have all been generated and provided in the reference pack in the zip file "**A1_diagnostics_and_results**".

b) We note that the company has provided NMA input files for the outcome "ability to function normally at 1 hour (ANF at 1 hour)". However, meta-analysis results for this outcome have not been reported in the company submission or appendices. Please could the company provide the NMA results for this outcome (using fixed-effect and random-effects models with both vague and informative priors), comment on the findings, and clarify why these results were omitted previously.

Outcomes for the ECLIPSE study were evaluated using a gatekeeping procedure. The "ability to function normally (AFN) at 1 hour" endpoint was ranked last in the hierarchical testing sequence. In accordance with clinical practice guidelines, which recognise 2 hours post-dose as the primary timepoint and gold standard for assessing therapeutic efficacy of intervention for the acute treatment of migraine, AFN at 1 hour was considered not clinically relevant for inclusion in the network meta-analysis (NMA).[1] However, for completeness, the data for this endpoint were presented in the clinical effectiveness section of the Company submission (Section 3.6.3), and the corresponding NMA results are included below. The NMA was conducted using a random effects (RE) model with informative prior distributions; this is the selected model as per the rationale in section 3.9.5.1 of the Company submission. Given the sparse network, a RE model with a vague prior distribution could not be fit for this endpoint. The results shown in Table 1 indicate a lack of statistical significance, supporting the conclusion of comparable efficacy between atogepant and rimegepant for this endpoint.

Table 1. NMA results for AFN at 1 hour post-dose (RE with an informative prior model)

	Atogepant vs. rimegepant OR (95% CrI)
AFN at 1 hour	[redacted]

Abbreviations: AFN: ability to function normally; CrI: credible interval; NMA: network meta-analysis; OR: odds ratio; RE: random effects.

A2. Priority question: Please could the company elaborate on their assumptions regarding equivalence or non-inferiority between treatments. Specifically, can the company confirm whether any formal statistical testing has taken place to support the company's assumptions of equivalence? As

this is not discussed in the company submission, the EAG has concerns regarding claims of treatment equivalence.

In the Company submission, conclusions of clinical equivalence were primarily based on the observed results of the NMA, which demonstrated no statistically significant differences between atogepant and rimegepant across the primary and all but one of the secondary outcomes evaluated. In addition to the NMA findings, this interpretation is supported by the judgement of clinical experts in migraine, who, upon review of the evidence base, concurred that the treatments demonstrated comparable clinical efficacy and safety profiles.[2] While the Company submission refers to comparability and similarity, any mention of 'equivalence' should be interpreted in the context of observed similarity consistent with clinical expert opinion, rather than formal statistical confirmation. This approach is consistent with established precedent. For example, Lee *et al*. 2024 identified 33 cost-comparison technology appraisals (TAs) based on an indirect treatment comparison (ITC), none of which applied formal statistical methods to demonstrate equivalence; instead, often relied on the absence of statistically significant differences.[3]

Based on the results of the NMA and unanimous clinical expert opinion, the conclusion is that atogepant is associated with similar overall health benefits compared with rimegepant.

A3. Priority question: The EAG notes that the company's NMAs selected as the primary analyses were conducted using random-effects (RE) models with informative priors. Please:

a) **Describe the source, derivation and justification for the informative priors used in each of the NMAs (including whether they were based on external data, previous meta-analyses, expert elicitation, or other assumptions);**

The informative prior distribution placed on the between-trial heterogeneity parameter was sourced from example 5 of NICE Decision Support Unit (DSU) Technical Support Document (TSD) 3, which uses an informative prior of half-normal (0, 0.32^2) for an odds ratio (OR) NMA.[4]

This choice is derived from empirical distributions of heterogeneity observed across meta-analyses of binary outcomes and implemented as recommended in TSD 3 for OR-scale models. The 95th percentile of this prior is ~0.63, which permits moderate heterogeneity while constraining implausibly large τ (representing between-study standard deviation [heterogeneity]). We selected this external, empirically based prior (not expert-elicited) because our networks use binary efficacy outcomes with similar trial designs and clinical contexts, where moderate heterogeneity is expected. The same prior was applied across NMAs with binary outcomes; for any continuous outcomes, τ was defined on the standardised mean-difference scale and assigned a separate Half-Normal prior appropriate to that scale.

b) **Provide the exact prior distributions and parameter values used for heterogeneity and treatment effects in each NMA;**

As mentioned above, the informative prior is:

$$\sigma \sim Half - Normal(0, 0.32^2)$$

The vague priors are:

$$\mu_i \sim N(0, 10000)$$

$$\sigma \sim U(0.0001, 5)$$

$$d_j \sim N(0, 10000)$$

With μ_i the i[th] trial specific mean, σ the between-trial heterogeneity, and d_j the j[th] treatment effect.

These prior distributions can all be observed directly in the provided WinBUGS models.

c) Explain the rationale for preferring RE models with informative priors over RE models with vague priors, given the apparent similarity in model fit;

The use of an informative prior allows for the incorporation of external evidence which leads to an improved estimation of relative effects, particularly with smaller sample sizes. This increases reliability in situations where data are limited; given this NMA is based on a sparse network, it was determined that a vague prior distribution was not appropriate.

RE models with a vague prior distribution are not considered reliable in the absence of repeated treatment effects, as it lacks sufficient information to accurately estimate between-study variance (as outlined in Section 3.9.4 of the Company submission).[4] Even if RE models with informative priors and vague priors show similar outputs and fit statistics, page 16 of NICE DSU TSD 2 recommends the use of informative priors, particularly where networks are small.[5] As demonstrated by the results presented in response to A3 d), the models using vague priors are highly comparable to the informative prior models with respect to point estimates, and likely overestimate uncertainty.

Therefore, the RE model with an informative prior distribution was consistently selected as the primary analytical approach for all networks. This approach provides a conservative and robust way to account for anticipated heterogeneity in sparse networks, without producing unrealistically wide credible intervals (CrIs).[4]

d) Comment on the impact of using informative versus vague priors on the estimated treatment effects and uncertainty across key outcomes.

Where possible, the results of the RE models with vague priors and an informative prior have been presented in Table 2 (as shown in Table 22 of the Company submission and Table 17 of the accompanying Appendix C). Across key outcomes, the choice of prior did not impact the ORs, which were almost identical between the two models and only impacted the level of uncertainty as demonstrated by the increased width of the CrI. Therefore, the overall conclusion that atogepant and rimegepant demonstrate comparable efficacy and safety remains unchanged. NMAs are not available for other outcomes for the RE model with vague priors for the reasons explained below in response to A3 c).

Table 2. RE model with an informative prior and vague priors

	Atogepant vs. rimegepant OR (95% CrI)	
	RE model with VP	RE model with IP
Pain freedom at two hours (primary endpoint)	[redacted]	[redacted]
Absence of MBS at two hours	[redacted]	[redacted]
Pain relief at two hours	[redacted]	[redacted]
Sustained pain relief from 2 to 24 hours	[redacted]	[redacted]
Sustained pain freedom from 2 to 24 hours	[redacted]	[redacted]

Abbreviations: CrI: credible interval; IP: informative prior; MBS: most bothersome symptom; OR: odds ratio; RE: random effects; VP: vague prior.

e) Please, can the company provide results using a random effects model with vague priors ('RE VP') for the outcomes of: sustained pain relief from 2 to 48 hours, use of rescue medication within 24 hours, ability to function normally at 2 hours, ability to function normally at 1 hour, sustained pain freedom from 2 to 48 hours and any AE. For each of the above outcomes, please, can they also clarify why the results of these RE VP NMAs had not been provided previously.

The RE models with VP have been presented in Table 3, alongside the RE models with IP, which as per Table 2, the choice of prior did not impact the ORs, which were again almost identical between the two models and only impacted the level of uncertainty as demonstrated by the increased width of the CrIs in some cases. These were not initially presented as they were not deemed key outcomes, and as per the response to A3 c), RE models with IP were deemed preferable.

Table 3. RE model with vague priors

	Atogepant vs. rimegepant OR (95% CrI)	
	RE model with VP	RE model with IP
Any AE	[redacted]	[redacted]
Use of rescue medication within 24 hours	[redacted]	[redacted]
Ability to function normally at two hours	[redacted]	[redacted]
Sustained pain relief from 2 to 48 hours	[redacted]	[redacted]
Sustained pain freedom from 2 to 48 hours	[redacted]	[redacted]

Footnotes: Bold denotes a statistically significantly lower and therefore favourable OR of the assessed outcome for treatment with atogepant compared with treatment with rimegepant.
Abbreviations: AE: adverse event; CrI: credible interval; IP: informative prior; OR: odds ratio; RE: random effects; VP: vague prior.

As per the response to A3 c), a lack of repeated treatment effects (only one rimegepant trial in the network) was noted and therefore the RE model with vague priors was not deemed viable for ability to function normally at 1 hour.

The use of an informative prior for the between-trial heterogeneity parameter results in very few statistically significant differences in between-trial heterogeneity. If it were technically feasible to run the vague prior model for ability to function normally at 1 hour, any changes to results would be minimal, other than the increased uncertainty shown by the larger CrIs (as seen in the results presented in A3 d), due to the fact that that a vague prior distribution can overestimate uncertainty in sparse networks. Overall, it is not expected that the use of a vague prior distribution would have any meaningful impact on the conclusions drawn. Given the use of vague prior distributions was not possible, this endpoint was modelled using informative prior distributions.

A4. Priority question: The EAG notes that two rimegepant trials included in the company's NMA were conducted exclusively in East Asian populations. Please conduct sensitivity analyses and provide the NMA results excluding BHV3000-313 and BHV3000-310.

The studies BHV3000-313 and BHV3000-310 are included within the NMA given that no treatment-effect modifiers (TEMs) were identified pertaining to race or any other characteristics in literature, nor through clinical expert engagement, as noted in Section 3.9.3 of the Company submission. The inclusion of these studies to the rimegepant network contributes to maximising the available evidence base to ensure robustness of results, and is aligned with the EAG and Committee preference in TA919 to include these studies.[6]

However, the results of the NMA excluding BHV3000-313 and BHV3000-310 from the network are presented in Table 4 below. Please note that these have been conducted as per the methodology in Section 3.9.4 of the Company submission, using the RE model with an informative prior for the reasons explained in clarification question A3 c). As with the original Company NMA, this analysis shows no significant difference between atogepant and rimegepant, other than use of rescue medication within 24 hours, supporting the conclusion of comparable efficacy between the two treatments.

Table 4. NMA sensitivity analysis excluding Asian studies (BHV3000-313 and BHV3000-310) for rimegepant from the network (RE with an informative prior model)

	Atogepant vs. rimegepant OR (95% CrI)
Pain freedom at two hours (primary endpoint)	[redacted]
Absence of MBS at two hours	[redacted]
Pain relief at two hours	[redacted]
Sustained pain relief from 2 to 24 hours	[redacted]
Sustained pain relief from 2 to 48 hours	[redacted]
Use of rescue medication within 24 hours	[redacted]
Ability to function normally at two hours	[redacted]
Sustained pain freedom from 2 to 24 hours	[redacted]

Sustained pain freedom from 2 to 48 hours	[redacted]
Any AE	[redacted]

Footnotes: Bold denotes a statistically significantly lower and therefore favourable OR of the assessed outcome for treatment with atogepant compared with treatment with rimegepant.
Abbreviations: AE: adverse event; CrI: credible interval; MBS: most bothersome symptom; NMA: network meta-analysis; OR: odds ratio; RE: random effects.

Rimegepant trials

A5. Priority question: In addition to the baseline characteristics already presented (age, sex, race, BMI, and monthly migraine days; Appendix C.1 in the company submission), for each rimegepant trial included in the NMAs:

a) **please provide baseline information aligned with that reported for the ECLIPSE trial: region, prior acute migraine treatment (including prior triptan failure, contraindication, or intolerance), current use of prophylactic concomitant medication, baseline migraine headache severity, migraine-associated symptoms, and most bothersome migraine-associated symptom.**
b) **In addition to the figure format currently presented, please provide numerical tables presenting all baseline characteristics for each of the rimegepant studies (including the summary statistic used and variance where appropriate, and sample size contributing to each estimate).**

Please see the file labelled '**NICE Q A5a, A5b.xlsx'** in the reference pack for new extractions requested in question A5 a) and the file '**NICE Q A5b.docx'** for tabular form of previously provided baseline characteristics requested in question A5 b).

For A5 a), there is consistency across all reported baseline information amongst the rimegepant trials and correspondingly between the rimegepant trials and ECLIPSE.

A6. Priority question: The EAG notes that the NMA includes rimegepant trials conducted across different phases (including Phase II, Phase III and Phase IV), time periods and geographical settings. To help us assess the consistency and robustness of the rimegepant evidence base, please provide a meta-analysis of all rimegepant trials included in the NMA for each outcome.

For each outcome, please:

a) **Specify which rimegepant trials are included and provide a clear justification for inclusion (e.g. earlier phase trials such as Marcus 2014 alongside more recent Phase III and Phase IV trials);**

b) Report pooled effect estimates with confidence intervals and p-values;

c) Comment on the between-study heterogeneity and any observed differences related to trial phase, publication year or geographical location.

As described in the feasibility assessment conducted for the NMA in the original Company submission (Section 3.9.3), the studies included in the NMA were meticulously reviewed for their suitability to inform indirect comparisons between atogepant and rimegepant. As a part of this assessment a search for prognostic factors and/or TEMs was conducted, with no conclusive evidence of TEMs found in the literature. This conclusion was also supported by UK clinicians at an advisory board. The comparability of the inclusion criteria of the studies included in the NMA, as well as key baseline characteristics (e.g., baseline migraine severity) and outcome definitions, meant that there was no strong rationale to exclude any of the included studies due to concerns of heterogeneity. While it is noted that statistical heterogeneity may be observed in some outcomes (see sections below), the degree of the heterogeneity is clearly not impactful on the interpretational level, and is therefore indicative of the consistency and robustness of the original NMA evidence base, including the rimegepant studies that informed the NMA.

Summary of approach

Under the specifications of the NMAs discussed in the Company submission (Section 3.9), namely:

- Vague priors on all treatment effects
- A single atogepant vs placebo study
- No head-to-head evidence of atogepant vs rimegepant

New meta-analyses for rimegepant vs placebo would not provide any practical benefits. The Company consider the extracted results of rimegepant vs placebo from the original NMA to effectively be equivalent to a Bayesian meta-analysis of rimegepant vs placebo (with the same assumed prior on the between-trial heterogeneity parameter).

As only a single trial of atogepant vs placebo (ECLIPSE) is available, there is no information related to the between trial heterogeneity for atogepant. Therefore, the estimate of the between trial heterogeneity in the NMA was dependent on the variation in the rimegepant trials only. As there is also no direct evidence of atogepant vs rimegepant, the rimegepant vs placebo comparisons extracted from the NMAs are considered to estimate both the between trial heterogeneity and the aggregate treatment effect of rimegepant.

For completeness, a Bayesian meta-analysis of pain freedom at 2 hours was conducted using the same FE, RE (with vague prior), and RE (with informative prior) models used in the NMAs to empirically demonstrate this. Please see '**A6 PF 2hr MA**' zip file in the reference pack for the source of these results. Given the similarity between the results of the meta-analysis and the NMA, the remainder of this response focuses on the outputs of the NMA described in the Company submission.

Table 5: Bayesian meta-analysis of pain freedom at two hours

Pain Freedom at 2 hours Model		Rimegepant vs Placebo Odds Ratio (95% CrI)	DIC Difference vs FE model
Meta-analysis	FE	2.11 (1.84, 2.43)	-
	RE IP	2.19 (1.73, 2.91)	-3.34
	RE VP	2.21 (1.64, 3.13)	-3.46
NMA	FE	2.11 (1.84, 2.43)	-
	RE IP	2.19 (1.73, 2.91)	-3.37
	RE VP	2.21 (1.64, 3.13)	-3.35

Footnote: Effect estimates, 95% CrIs, and relative difference in DIC between models are all within the order of the Monte Carlo error.
Abbreviations: CrI: credible interval; DIC: deviance information criterion; FE: fixed effects; IP: informative prior; NMA: network meta-analysis; RE: random effects; VP: vague prior.
Source: AbbVie Data on File. A6 PF 2hr MA.

a) Specify which rimegepant trials are included and provide a clear justification for inclusion (e.g. earlier phase trials such as Marcus 2014 alongside more recent Phase III and Phase IV trials);

As previously noted in the Company submission, and as confirmed by UK clinical experts at an advisory board (previously detailed in the Company submission), no treatment effect modifiers were identified for the acute treatment of migraine.[2] Furthermore, the inclusion criteria, baseline migraine severity and outcome definitions were highly comparable across all identified rimegepant studies, which again was confirmed by clinical and health economic experts. As such, there was no strong justification for excluding any specific rimegepant trial as long as it included the dose of interest (75mg). Therefore each outcome included all trials evaluating rimegepant 75mg reporting that endpoint. This is explicitly specified in Table 6 below.

Table 6: Trials included in the Bayesian NMA, by outcome

Outcome	Included Trials
Pain freedom at 2 hours	Lipton 2019; Marcus 2014; Lipton 2024; Yu 2023; Croop 2019; Ashina 2025; Ikeda 2025; ECLIPSE
Absence of MBS at 2 hours	Lipton 2019; Lipton 2024; Yu 2023; Croop 2019; Ashina 2025; Ikeda 2025; ECLIPSE
Pain relief at 2 hours	Lipton 2019; Marcus 2014; Lipton 2024; Yu 2023; Croop 2019; Ashina 2025; Ikeda 2025; ECLIPSE
Sustained pain relief from 2 to 24 hours	Lipton 2019; Marcus 2014; Lipton 2024; Croop 2019; Ashina 2025; Ikeda 2025; ECLIPSE
Sustained pain relief from 2 to 48 hours	Lipton 2019; Lipton 2024; Croop 2019; Ashina 2025; Ikeda 2025; ECLIPSE
Use of rescue medication within 24 hours	Lipton 2019; Lipton 2024; Yu 2023; Croop 2019; Ashina 2025; Ikeda 2025; ECLIPSE
Ability to function normally at 2 hours	Lipton 2019; Lipton 2024; Yu 2023; Croop 2019; Ashina 2025; Ikeda 2025; ECLIPSE
Sustained pain freedom from 2 to 24 hours	Lipton 2019; Marcus 2014; Lipton 2024; Yu 2023; Croop 2019; Ashina 2025; Ikeda 2025; ECLIPSE
Sustained pain freedom from 2 to 48 hours	Lipton 2019; Marcus 2014; Lipton 2024; Yu 2023; Croop 2019; Ashina 2025; Ikeda 2025; ECLIPSE

Any AE	Lipton 2019; Marcus 2014; Lipton 2024; Yu 2023; Croop 2019; Ashina 2025; Ikeda 2025; ECLIPSE

Abbreviations: AE: adverse event; MBS: most bothersome symptom.

b) Report pooled effect estimates with confidence intervals and p-values;

The pooled effect of rimegepant vs placebo is extracted from each of the NMAs and reported in Table 7 below.

Table 7: Pooled effect estimates for the Bayesian NMA of rimegepant versus placebo

Outcome – Model		Rimegepant vs Placebo Odds Ratio (95% CrI)	Bayesian p-value (2-sided)
Pain freedom at 2 hours	FE	2.11 (1.84, 2.43)	<0.001
	RE IP	2.19 (1.73, 2.91)	<0.001
	RE VP	2.21 (1.64, 3.13)	0.001
MBS free at 2 hours	FE	1.69 (1.51, 1.88)	<0.001
	RE IP	1.69 (1.47, 1.98)	<0.001
	RE VP	1.70 (1.45, 2.00)	0.001
Pain relief at 2 hours	FE	1.99 (1.79, 2.20)	<0.001
	RE IP	2.04 (1.72, 2.52)	<0.001
	RE VP	2.05 (1.69, 2.62)	<0.001
Sustained pain relief at 2 hours	FE	2.36 (2.09, 2.67)	<0.001
	RE IP	2.55 (1.91, 3.55)	<0.001
	RE VP	2.57 (1.72, 4.04)	0.003
Sustained pain relief at 2–48 hours	FE	2.27 (1.99, 2.59)	<0.001
	RE IP	2.51 (1.72, 3.82)	<0.001
Rescue medication use at 24 hours	FE	0.41 (0.36, 0.46)	<0.001
	RE IP	0.40 (0.31, 0.50)	<0.001
Ability to function normally at 2 hours	FE	1.92 (1.70, 2.16)	<0.001
	RE IP	1.94 (1.64, 2.37)	<0.001
Sustained pain freedom at 2–24 hours	FE	2.54 (2.14, 3.02)	<0.001
	RE IP	2.65 (2.03, 3.64)	<0.001
	RE VP	2.68 (1.89, 4.08)	0.001
Sustained pain freedom at 2–48 hours	FE	2.51 (2.10, 3.02)	<0.001
	RE IP	2.66 (1.98, 3.80)	<0.001
Any AE	FE	1.21 (1.04, 1.40)	0.013
	RE IP	1.21 (1.02, 1.46)	0.033

Abbreviations: AE: adverse event; FE: fixed effects; IP: informative prior; MBS: most bothersome symptom; RE: random effects; VP: vague prior.

c) Comment on the between-study heterogeneity and any observed differences related to trial phase, publication year or geographical location.

As seen in reported DIC statistics for the NMAs, the following outcomes demonstrated meaningful heterogeneity when using an approximate benchmark of 3 or 5 points of

improvement in the RE model(s) compared to the FE model which is the suggested breakpoint in NICE TSD3:

- PF 2hr (DIC difference between 3 and 5)
- SUS PR 2-24hr (DIC difference > 5)
- SUS PR 2-48hr (DIC difference > 5)
- SUS PF 2-48hr (DIC difference between 3 and 5)

It is noteworthy that 3 of the 4 outcomes highlighted above are sustained outcomes. This suggests that outcomes defined over shorter time intervals are more consistent across the included rimegepant studies. We can now inspect the leverage plots of those NMAs we have flagged here to identify which studies were outliers. Note that leverage plots for all NMAs are provided in response to A1, but the FE leverage plots with potentially "meaningful" heterogeneity have been highlighted here for discussion, as these plots help clearly identify which trials may be outliers. Please note these plots include ECLIPSE, as new meta-analyses excluding ECLIPSE were not run for the reasons explained in the response to A6 above, hence these plots were extracted from the existing NMAs. Given that ECLIPSE does not contribute to heterogeneity assessments as it is the only atogepant trial, the points in the plots below can be ignored (always on (±1,1)).

Pain freedom at 2 hours:

As presented in Figure 1, Lipton 2024, Ashina 2025 (NCT05509400), and Ikeda 2025 appear to be the most significant outliers, with Lipton 2024 showing a very weak treatment effect for rimegepant, and Ashina 2025 (NCT05509400) and Ikeda 2025 showing a strong treatment effect. This can be distinguished by placement of the placebo and active arm on the plot, and can be confirmed by consultation with the input data.

Figure 1: FE leverage plots for pain freedom at two hours

Abbreviations: FE: fixed effects

Sustained pain relief from 2 to 24 hours:

Pain freedom from 2 to 24 hours is similar to the results seen above for pain relief at 2 hours, Lipton 2024, Ashina 2025 (NCT05509400), and Ikeda 2025 appear to be the most significant outliers, with Lipton 2024 showing a very weak treatment effect for rimegepant, and Ashina 2025 (NCT05509400) and Ikeda 2025 showing a strong treatment effect. In this outcome, Lipton 2024 is flagged as a notably extreme outlier (Figure 2).

Figure 2: FE leverage plot for sustained pain relief from 2 to 24 hours

Abbreviations: FE: fixed effects

Sustained pain relief from 2 to 48 hours:

The FE leverage plot for sustained pain relief from 2 to 48 hours is presented in Figure 3. Again, Lipton 2024, Ashina 2025 (NCT05509400), and Ikeda 2025 appear to be the most significant outliers, with Lipton 2024 showing a very weak treatment effect for rimegepant, and Ashina 2025 (NCT05509400) and Ikeda 2025 showing a strong treatment effect.

Figure 3: FE leverage plot for sustained pain relief from 2 to 48 hours

Abbreviations: FE: fixed effects

Sustained pain freedom from 2 to 48 hours:

Figure 4 does not flag any outliers to same degree as those previously discussed. It appears that most trials have moderate dispersion from the expected mean beyond what would be expected due to sampling error within a trial. Lipton 2024 is still a somewhat notable outlier with respect to a weak treatment effect.

Figure 4: FE leverage plot for sustained pain freedom from 2 to 48 hours

Abbreviations: FE: fixed effects

Conclusions

Whilst in most of the plots just discussed, the most recent studies appear to be outliers, the fact that they are outliers in *different directions* suggests that publication year cannot explain the differences between rimegepant studies as there does not appear to be a monotonic trend related to publication year. It should be further noted that while Ikeda 2025 was often flagged as an outlier, Yu 2023 was not, thus racial demographics are also insufficient to explain heterogeneity. This is supported by the sensitivity analyses reported in response to question A4. Recall that over many outcomes, there was little evidence of meaningful heterogeneity, so the heterogeneity that is present may plausibly be dependent on the specific outcome in question.

Ultimately, while it is difficult to identify any conceptual baseline characteristic or difference in outcome definition that would explain this observed heterogeneity, it is not necessary to do so for these analyses. While it is noted that statistical heterogeneity may be observed in some outcomes, the degree of the heterogeneity is clearly not impactful on the interpretational level. The RE models naturally incorporate the between-trial heterogeneity, and the significance conclusions in the rimegepant vs placebo outcomes clearly do not change between the FE and RE models (as shown in Table 7 above). This was also true for the majority of the comparisons between atogepant and rimegepant.

A7. The EAG notes that an NMA was conducted for the use of rescue medication. Please specify:

a) **If the type/class of rescue medications used in ECLIPSE were similar to those used in rimegepant trials;**

There is overlap in the type of rescue medications used in ECLIPSE compared to those used in the rimegepant phase III trials (BHV3000-301, BHV3000-302, BHV3000-303). ECLIPSE permitted a broad range of rescue medications, including any triptan, ditan, ergot derivative, opioid, non-steroidal anti-inflammatory drug (NSAID), other analgesic or antiemetic. The rimegepant trials allowed use of aspirin, ibuprofen, acetaminophen (up to 1000mg / day), naproxen or antiemetics. In the in BHV3000-301 and BHV3000-303 trials, triptans were also permitted, but only if subjects were in need of migraine relief 48 hours after dosing with study medication (but before the End of Treatment Visit). The rimegepant trials did not permit use of opioids, ergotamins, butalbital compounds or muscle relaxants (except for baclofen) as rescue medication.

The ECLIPSE trials therefore permitted a wider range of rescue medication than the rimegepant trials. However, despite this, fewer patients on atogepant required rescue medications at 24 hours compared with patients on rimegepant, thereby demonstrating that atogepant can lessen the need for additional therapies (as shown in Table 22 of the Company submission).

b) **If the criteria for allowing rescue medications in ECLIPSE were the same as those used in the rimegepant trials (if not, please provide details of the differences and consider the impact these might have on the results).**

The criteria for allowing rescue medication were similar across both the ECLIPSE and BHV3000 trials, with rescue medication use allowed starting at 2 hours post study drug administrations.

As described above, ECLIPSE permitted a broader range of rescue medications options after 2 hours post-dose. Both ECLIPSE and the rimegepant trials applied the same criteria for rescue medications: any rescue medication taken before the 2-hour timepoint counted as a treatment failure for that specific attack. As the treatment-failure definition is identical between the atogepant and rimegepant trials, the outcomes also remain comparable. Additionally, clinical experts consulted by the Company while responding to clarification questions confirmed that, given that the outcome measures are the same across trials, the difference in the available rescue medications would not impact the relative effect in use of rescue medications between atogepant and rimegepant.

c) **If any difference in the type/class of rescue medication would be expected between atogepant and rimegepant.**

It was determined through clinical expert engagement that there would be no difference in the type/class of rescue medication usage in clinical practice.

Adverse events

A8. Priority question: The EAG notes that the network meta-analysis includes results for the outcome of 'any adverse events'. Please:

a) Clarify the definition of 'any adverse events'; and

The definition of "any adverse event" is synonymous with "treatment-emergent adverse event." It includes all adverse events regardless of intensity (mild, moderate, or severe), whether they are serious or nonserious adverse events, and whether or not they are potentially related to treatment.

b) Conduct an NMA for treatment-related adverse events.

The results of the NMA for treatment-related adverse events are presented in Table 8 below. There was no statistically significant difference for atogepant 60 mg compared with rimegepant 75 mg. As per the rationale included in section 3.9.5.1 of the Company submission, as well as in the response to A3 c) for selecting the RE model with an informative prior, results are presented for this model below.

Table 8: Relative effect of atogepant 60 mg compared with rimegepant 75 mg: TRAEs NMA - all studies for Rimegepant

TRAEs	Atogepant 60 mg vs. comparator Odds ratio (95 % CrI)
	RE IP
Placebo	[redacted]
Rimegepant 75 mg	[redacted]

Abbreviations: CrI: credible interval; RE IP: random effects with an informative prior distribution; TRAE: treatment-related adverse event

ECLIPSE trial

A9. Priority question. Please provide a breakdown of the type of current prophylactic concomitant medication for migraine used in each treatment arm of ECLIPSE for the mITT population (for attack 1) at baseline.

For reference, a summary of the population sizes from ECLIPSE that will be relevant for each population-related question within this clarification response, is presented in Table 9 below.

Table 9: Trial population sizes in ECLIPSE

Population	N of patients
ITT	[redacted]
Attack 1 ITT	[redacted]
Overall mITT	1,223
Attack 1 mITT	[redacted]

Abbreviations: ITT: intent-to-treat modification; mITT: modified intent-to-treat.
Source: AbbVie Data on File. ECLIPSE CSR (2025).[7]

For Attack 1, [redacted] of patients in the atogepant arm, and [redacted] of patients in the placebo arm, were using prophylactic concomitant medication. The most common (>1%) types of medication were [redacted], a breakdown of these medications are included in Table 10. The full list of other medications received by patients in ECLIPSE is provided in the reference pack.

Table 10. Current use of prophylactic concomitant medication; Attack 1 (mITT population)

Drug class and generic name	Atogepant ([redacted])[a] n/N1, (%)[b]	Placebo ([redacted])[a] n/N1, (%)[b]
Any prophylactic concomitant medication	[redacted]	[redacted]
Other antimigraine preparations	[redacted]	[redacted]
Amitriptyline hydrochloride	[redacted]	[redacted]
Botulinum toxin type A	[redacted]	[redacted]
Flunarizine dihydrochloride	[redacted]	[redacted]
Lomerizine hydrochloride	[redacted]	[redacted]
Propranolol hydrochloride	[redacted]	[redacted]
Topiramate	[redacted]	[redacted]
Valproate sodium	[redacted]	[redacted]
Other	[redacted]	[redacted]

Footnotes: [a]N= number of subjects in the mITT population; [b]n=Number of responders/N1=number of patients who received the treatment for the specified attack and had baseline headache severity for that attack. Missing data were imputed as non-responder. The total mITT population includes 1,223 patients; the mITT efficacy Attack 1 population includes [redacted] patients. Terms are listed as Not coded if a matching Anatomical Therapeutic Chemical Classification System (ATC) Level 4 - Chemical Subgroup is not available. Subjects are counted only once within each ATC class and preferred term. Placebo: subjects who were randomised to placebo for attack 1. Atogepant: subjects who were randomised to atogepant for attack 1.
Abbreviations: mITT: modified intent-to-treat.
Source: AbbVie Data on File. ECLIPSE Supplementary Data.[8]

A10. Priority question. Please provide baseline mean (and standard deviation) and median (with range) in each treatment arm of ECLIPSE for the mITT population (for attack 1) and for the overall mITT attack 1 population for:

a) monthly migraine days; and

b) monthly migraine attacks.

Data on baseline monthly migraine days and monthly migraine attacks were not routinely collected in the ECLIPSE trial. However, the average number of mild, moderate, or severe migraine attacks per month over the 3 months prior to screening were collected and are detailed in Table 11.

Table 11. Migraine history in Attack 1 mITT population and overall mITT population

	Attack 1 mITT (N=[redacted])		Overall mITT (N=1,223)	
Migraine history	**Atogepant ([redacted])**	**Placebo ([redacted])**	**Atogepant (N=605)**	**Placebo (N=618)**
Average number of mild, moderate, or severe migraine attacks per month over the past 3 months				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
Average number of moderate to severe migraine attacks per month over the past 3 months				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: The total mITT population includes 1,223 patients; the mITT efficacy Attack 1 population includes [redacted] patients. N = Number of subjects in the Population. N1 = Number of subjects who answered the question. n = Number of subjects with non-missing values in the specific category. Placebo: subjects who were randomised to placebo for attack 1. Atogepant: subjects who were randomised to atogepant for attack 1.
Abbreviations: mITT: modified intent-to-treat; SD: standard deviation.
Source: AbbVie. Data on File. ECLIPSE Supplementary Data,[8] Van Dycke et al. (2025).[9]

A11. Priority question. It is noted that an exclusion criterion in ECLIPSE was, "Taken medication for acute treatment of headache (including acetaminophen, NSAIDs, triptans, ditans, ergotamine, opioids, gepants, or combination analgesics) 10 or more days per month in any of the 3 months prior to Visit 2/Randomisation". Please clarify if this aligns with the anticipated population in which atogepant is expected to be used in, and if not, what impact this potential discrepancy may have on the generalisability of the results from ECLIPSE.

In accordance with clinical feedback, atogepant is anticipated to be used in the UK for the acute treatment of migraine in adults who have either tried at least two triptans and they did not work well enough, or have contraindications or intolerance to triptans and have tried NSAIDs and paracetamol without adequate response.[2] To clarify, there is no expected impact of this exclusion criterion on the relevance of the trial population to the anticipated population.

The exclusion of patients who have taken medication for acute treatment on 10 or more days per month in any of the prior 3 months was implemented to ensure a clear assessment of the acute efficacy of atogepant and to reduce potential confounding factors such as medication overuse headache (MOH). This approach follows the recommendation in the International Headache Society Guidelines for controlled trials of acute migraine attacks, Fourth Edition Section 1.1.3 and is consistent with precedent in acute treatment of migraine trials.[1] The rimegepant phase 3 acute trials (BHV3000-301/-302/-303) applied exclusion criteria and prohibited medications that effectively excluded patients with MOH, and the lasmiditan acute trials also excluded patients with MOH with >15 headache days per month.[10] Clinical experts consulted during this

clarification question stage stated they do not expect this discrepancy to have an impact on the generalisability of the results.

A12. Priority question. Please provide a breakdown of the type of rescue medication for migraine used in each treatment arm of ECLIPSE for the mITT population (for attack 1).

For Attack 1, [redacted] of patients in the atogepant arm and [redacted] of patients in the placebo arm used rescue medication within 24 hours after the double-blind dose. The most common (>3%) types of rescue medication are presented in Table 12. The full list of other rescue medications used is provided in the reference pack.[8]

Table 12. Use of rescue medication within 24 hours after the DB dose; Attack 1 (mITT population)

Reported name of drug, medication, or therapy	Atogepant ([redacted])[a] n/N1, (%)[b]	Placebo ([redacted])[a] n/N1, (%)[b]
Use of any rescue medication within 24 hours	[redacted]	[redacted]
Acetaminophen / Paracetamol	[redacted]	[redacted]
Almotriptan	[redacted]	[redacted]
Diclofenac	[redacted]	[redacted]
Domperidone	[redacted]	[redacted]
Eletriptan	[redacted]	[redacted]
Ibuprofen	[redacted]	[redacted]
Indomethacin	[redacted]	[redacted]
Ketoprofen	[redacted]	[redacted]
Naproxen	[redacted]	[redacted]
Naratriptan	[redacted]	[redacted]
Other not listed	[redacted]	[redacted]
Other NSAID or analgesic	[redacted]	[redacted]
Other NSAID or analgesic combination medication excluding opioid or ergot combination	[redacted]	[redacted]
Rizatriptan	[redacted]	[redacted]
Sumatriptan	[redacted]	[redacted]
Zolmitriptan	[redacted]	[redacted]

Footnotes: [a]N= number of subjects in the mITT population; [b]n=Number of responders/N1=number of patients who received the treatment for the specified attack and had baseline headache severity for that attack. Missing data were imputed as non-responder. The total mITT population includes 1,223 patients; the mITT efficacy Attack 1 population includes [redacted] patients. Subjects are counted only once within each reported name. Placebo: subjects who were randomised to placebo for attack 1. Atogepant: subjects who were randomised to atogepant for attack 1.Percentages are calculated as 100 x n/N1.
Abbreviations: DB: double blind; mITT: modified intent-to-treat; NSAID: Non-steroidal anti-inflammatory drug
Source: AbbVie. Data on File. ECLIPSE Supplementary Data.[8]

A13. It is noted that exposure to any gepant class of drug within 30 days prior to Visit 2/Randomisation was part of the exclusion criteria in ECLIPSE. Please

provide the number of patients in each trial arm in the mITT population (for attack 1) of ECLIPSE who had any history of prior exposure to:

a) **any gepant; and**

b) **atogepant.**

The number of patients in each trial arm in the modified intent-to-treat (mITT) population for Attack 1 of the ECLIPSE trial who had history of prior exposure to any gepant, including atogepant, is presented in Table 13. The proportion of patients with prior gepants exposure is comparable between the two treatment arms.

Table 13. Prior exposure to gepants for Attack 1 (mITT population)

Reported name of drug, medication, or therapy	Atogepant ([redacted])[a] n/N1, (%)[b]	Placebo ([redacted])[a] n/N1, (%)[b]
Gepants	[redacted][c]	[redacted]
Atogepant	[redacted]	[redacted]
Rimegepant	[redacted]	[redacted]
Rimegepant sulfate	[redacted]	[redacted]
Zavegepant	[redacted]	[redacted]

Footnotes: aN= number of subjects in the mITT population; bn=Number of responders/N1=number of patients who received the treatment for the specified attack and had baseline headache severity for that attack. c One patient in the atogepant arm had prior exposure to more than one gepant therapy.
Missing data were imputed as non-responder. The total mITT population includes 1,223 patients; the mITT efficacy Attack 1 population includes 1,214 patients. Subjects are counted only once within each reported name. Placebo: subjects who were randomised to placebo for Attack 1. Atogepant: subjects who were randomised to atogepant for Attack 1. Percentages are calculated as 100 x n/N1.
Abbreviations: mITT: modified intent-to-treat
Source: AbbVie. Data on File. ECLIPSE Supplementary Data.[8]

A14. Please provide baseline migraine-related characteristics for the ITT population (including migraine severity, associated symptoms, triptan use response) in ECLIPSE (for attack 1), to allow full comparison with the mITT population (for attack 1).

The baseline migraine-related characteristics for the intent-to-treat (ITT) population in the ECLIPSE trial for Attack 1 are presented in Table 14. When compared to the baseline characteristics of the mITT population (presented in Table 6 of the Company submission), these data demonstrate that the two patient populations are comparable with minimal differences seen across the migraine-related characteristics. To note, other baseline demographics are also closely aligned between the mITT and ITT populations (presented in Table 6 of the Company submission and Table 36 of the appendices).

Table 14. Baseline migraine-related characteristics of patients for Attack 1 (ITT population)

Baseline characteristic	Atogepant ([redacted])[a] n/N1, (%)[b]	Placebo ([redacted])[a] n/N1, (%)[b]
Triptan use response (actual)		
Triptan unsuitable[c]	[redacted]	[redacted]

Triptan experienced[d]	[redacted]	[redacted]
Triptan naïve	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Migraine headache severity		
Moderate pain	[redacted]	[redacted]
Severe pain	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Migraine-associated symptoms		
Photophobia	[redacted]	[redacted]
Phonophobia	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Most bothersome migraine-associated symptom		
Photophobia	[redacted]	[redacted]
Phonophobia	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Missing	[redacted]	[redacted]

Footnotes: [a]N= number of subjects in the population; [b]n=Number of subjects within category/N1=number of patients who received the treatment for the specified attack and had available assessments during the DB treatment period. [c]Defined as a subject who meets one of the two following criteria: Has a contraindication to triptans based upon local label and investigator judgment, irrespective of prior triptan use OR meets the following triptan failure definition for ≥2 different triptans: Currently uses a triptan or has used a triptan in the past and has not achieved pain relief at two hours post-dose in ≥2 out of 4 attacks based upon subject interview and investigator judgment OR used a triptan in the past but no longer uses a triptan due to AEs based upon subject interview and investigator judgment. [d]Defined as a subject who currently uses a triptan or has used ≥1 triptan in the past and does not meet the criterion for the 'Triptan Unsuitable' subgroup.
The ITT population includes [redacted] patients. Placebo: subjects who were randomised to placebo for Attack 1. Atogepant: subjects who were randomised to atogepant for Attack 1. Percentages are calculated as 100 x n/N1.
Abbreviations: AE: adverse events; ITT: intent-to-treat.
Source: AbbVie. Data on File. ECLIPSE Supplementary Data.[8]

Population

A15. Please clarify if atogepant in this indication for acute treatment of migraine is expected to be used in patients with both episodic and chronic migraine, similar to rimegepant. If so, please clarify if there are any clinical data for atogepant in the chronic migraine population and provide full details.

Similar to rimegepant, atogepant is expected to be used in patients with both episodic migraine (EM) and chronic migraine (CM).[11] This is aligned with the NICE recommendation for rimegepant as an acute treatment of migraine in TA919.[6]

In TA919, all relevant clinical trials for rimegepant for the acute treatment of migraine included in the Company submission enrolled individuals with EM experiencing two to eight migraine attacks per month.[6] During the TA919 appraisal, in light of the clinical and patient expert feedback, the Committee decided that the trial results were generalisable to both EM and CM populations.[6] Similar to the rimegepant trials, ECLIPSE also enrolled patients with a history of two to eight migraine attacks per month. Importantly, atogepant has been extensively studied and used in CM

patients for the prevention of migraine and has demonstrated a favourable efficacy and safety profile in this patient group, supporting its use across the migraine spectrum for acute treatment.[12]

A16. The EAG notes that the ECLIPSE trial included patients with episodic migraine only. The rimegepant trials included in the network meta-analysis also primarily included patients with episodic migraine. Please:

a) Confirm the migraine classification criteria used (for chronic vs episodic) in each rimegepant trial included in the NMA);

All rimegepant trials for the acute treatment of migraine included patients with <15 monthly headache days, which is the standard cut-off that distinguishes EM from CM. Thus, all rimegepant trials for the acute treatment of migraine included patients with EM.

b) Confirm whether any patients with chronic migraine were included, or whether all contributing trials were restricted to episodic migraine populations;

All rimegepant trials for the acute treatment of migraine were restricted to EM patients. This can be verified in the provided '**NICE Q A5a, A5b**' excel spreadsheet provided in the reference pack, which presents detailed inclusion criteria for each trial included in the NMAs.

c) Comment on the comparability of the rimegepant trial populations with the ECLIPSE population in terms of migraine type and baseline migraine frequency, and whether any differences are likely to meaningfully affect the NMA results.

In addition to the uniform EM requirement, all rimegepant trials for the acute treatment of migraine were assessed as having very similar baseline migraine frequency. The inclusion criteria of all trials required individuals to experience 2-8 moderate to severe migraine attacks per month, except for Marcus 2014 and Ashina 2025 (also referenced as NCT05509400).[13, 14] Marcus 2014 required 2-7 moderate to severe migraine attacks per month, which is highly comparable with the other trials, while Ashina 2025 required 4-14 moderate to severe migraine *days* per month.[13, 14] Given that migraine attacks are assumed to last 48 hours, this translates to 2-7 moderate to severe migraine attacks per month. Therefore, the distinction in Ashina 2025 was not considered meaningfully different from other included studies. It was therefore determined that the small differences in baseline migraine severity and frequency across trials were unlikely to meaningfully impact results. This was further confirmed by clinical and economic experts at an advisory board who did not consider there to be any meaningful differences between the studies.[2] Additionally, there were no meaningful differences in migraine type and baseline migraine frequency between the rimegepant trials and the ECLIPSE trial.

A17. Please clarify if the handling of missing data within each study was similar for each outcome among the studies included in the NMAs. If not,

please provide further details, including a discussion of the likely impact on the results of each of the NMAs.

Missing data was handled similarly for the majority of included studies. Within each given study, the method used for handling missing data was consistent across efficacy outcomes. As shown in Table 15, seven of the eight studies handled patients with missing data as failing treatment or equivalently, imputing as non-responders. The remaining study used the Last Observation Carried Forward (LOCF) data set for its analyses (Marcus 2014).[13]

LOCF can result in higher estimated response rates compared to a non-responder or treatment failure imputation as it is a less conservative method of handling missing data. The response rates in Marcus 2014 are higher than average for both the placebo and rimegepant arms across all outcomes.[13] However, the proportion of missing data in Marcus 2014 was considered modest and broadly similar across treatment arms, and the observed response rates are generally quite similar to those of Ikeda 2025.[15] Marcus 2014 was therefore judged sufficiently comparable to contribute to the network and was therefore included within the NMA. The inclusion of Marcus 2014 was deemed to be a conservative approach as the higher response rates would, if anything, bias results towards rimegepant.

Table 15: Handling of missing data in the studies included in the NMAs

Study	Missing data handling
ECLIPSE[7]	Subjects with missing data are treated as treatment failures
Lipton 2019[16]	Patients with missing data were considered to have treatment failure
Marcus 2014[13]	LOCF
Lipton 2024[17]	Patients with missing data were imputed as failures
Yu 2023[18]	Missing data imputed as treatment failures
Croop 2019[19]	Missing data imputed to be failure
Ikeda 2025[15]	Participants with missing data were classified as non-responders
Ashina 2025[14]	Participants with missing data were imputed as failures

Abbreviations: LOCF: last observation carried forward; NMA: network meta-analysis.

Subgroups

A18. Priority question. Please provide forest plots along with odds ratios, 95% confidence intervals and p-values for the prespecified subgroups (Region [Europe, China, Japan, or other], Current use of prophylactic concomitant medication for migraine [yes or no], Previous response to and use of triptans [triptan unsuitable, triptan experienced, or triptan naïve]) of ECLIPSE (using the mITT for attack 1) for the following outcomes:

a) **Pain freedom at two hours after the double-blind dose for the first attack;**

Overall, across all subgroups, atogepant shows consistently improved results compared with placebo in the ECLIPSE trial.[8]

As shown in Figure 5, atogepant demonstrates [redacted] odds of achieving pain freedom at 2 hours versus placebo in Europe, China, and Japan. The 'Other' subgroup was also [redacted]; the lower bound of the 95% confidence interval (CI) [redacted]. These subgroup results demonstrate that the treatment effect of atogepant on pain freedom is not impacted by patient region. With regard to the result for the "Other" subgroup, it is anticipated that [redacted] may be due uncertainties introduced to the data due to the relatively small subgroup size given that clinical experts in the advisory board revealed there are no TEMs, as detailed in Section 3.9.3.1 of the Company submission.[2]

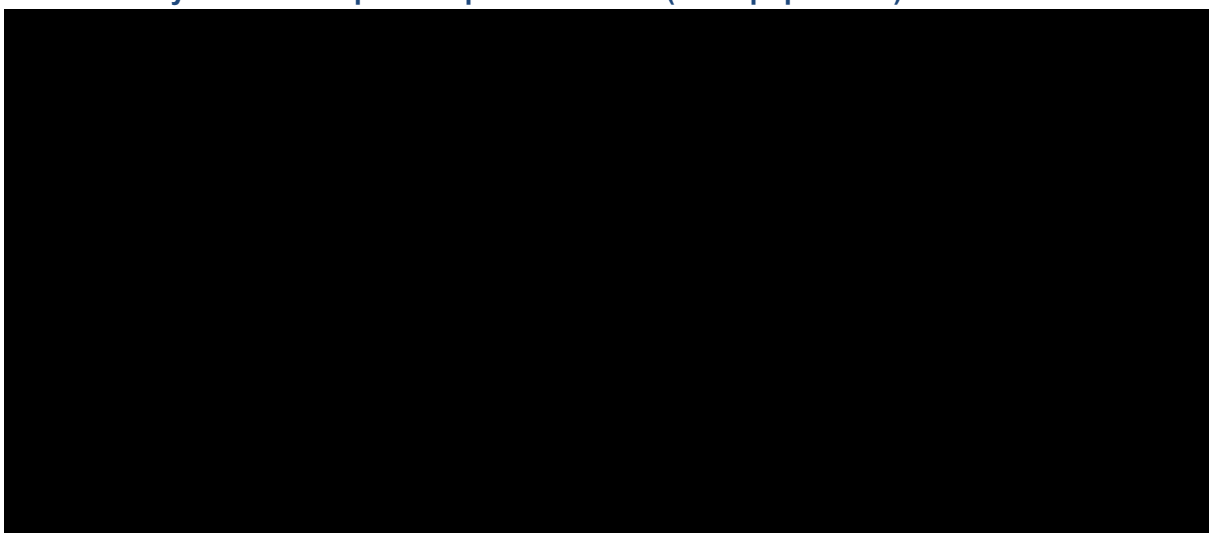
Similarly, across the triptan unsuitable, triptan experienced and triptan naïve subgroups, atogepant is generally associated with [redacted], as shown in Figure 6. Atogepant shows a [redacted] result in the triptan unsuitable and triptan experienced subgroups. In the triptan naïve subgroup, [redacted], which, again, is likely explained by the small subgroup sizes introducing uncertainty.

Lastly, as shown in Figure 7, atogepant demonstrates [redacted] pain freedom at 2 hours compared with placebo, irrespective of preventive migraine medication use.

Figure 5. Forest plot of subgroup analysis of pain freedom at 2 hours after the DB dose for the first attack by region (mITT population)

Abbreviations: CI: confidence interval; DB: double-blind; n1: responder; n2: responder; N1: treatment; N2: placebo.
Source: AbbVie. Data on File. ECLIPSE Supplementary Data.[8]

Figure 6. Forest plot of subgroup analysis of pain freedom at 2h after the DB dose for the first attack by historical triptan-response stratum (mITT population)



Abbreviations: CI: confidence interval; DB: double-blind; n1: responder; n2: responder; N1: treatment; N2: placebo.
Source: AbbVie. Data on File. ECLIPSE Supplementary Data.[8]

Figure 7. Forest plot of subgroup analysis of pain freedom at 2h after the DB dose for the first attack by preventive migraine medication use (mITT population)

Abbreviations: CI: confidence interval; DB: double-blind; n1: responder; n2: responder; N1: treatment; N2: placebo.
Source: AbbVie. Data on File. ECLIPSE Supplementary Data.[8]

b) Pain relief at two hours after the double-blind dose for the first attack; and

As shown in Figure 8, atogepant is associated with [redacted] in the Europe and Japan subgroups, and [redacted]. As noted above, small subgroup sizes may be contributing to increased uncertainty, as clinical experts

determined in the advisory board that there were no TEMs identified, detailed in Section 3.9.3.1 of the Company submission.

In the triptan-response subgroups, pain relief at 2 hours demonstrates similar findings to pain freedom at 2 hours, as shown in Figure 9. Atogepant is associated with [redacted] odds of achieving pain relief at 2 hours in the triptan unsuitable and triptan experienced groups, [redacted] for the triptan naïve group [redacted] by the lower bound of the 95% CI.

As with pain freedom at 2 hours, atogepant is associated with [redacted] odds of achieving pain relief at 2 hours compared with placebo, irrespective of preventive migraine medication use (Figure 10).

Figure 8. Forest plot of subgroup analysis of pain relief at 2h after the DB dose for the first attack by region (mITT population)

Abbreviations: CI: confidence interval; DB: double-blind; n1: responder; n2: responder; N1: treatment; N2: placebo.
Source: AbbVie. Data on File. ECLIPSE Supplementary Data.[8]

Figure 9. Forest plot of subgroup analysis of pain relief at 2h after the DB dose for the first attack by historical triptan-response stratum (mITT population)

Abbreviations: CI: confidence interval; DB: double-blind; n1: responder; n2: responder; N1: treatment; N2: placebo.
Source: AbbVie. Data on File. ECLIPSE Supplementary Data.[8]

Figure 10. Forest plot of subgroup analysis of pain relief at 2h after the DB dose for the first attack by preventive migraine medication use (mITT population)

Abbreviations: CI: confidence interval; DB: double-blind; n1: responder; n2: responder; N1: treatment; N2: placebo.
Source: AbbVie. Data on File. ECLIPSE Supplementary Data.[8]

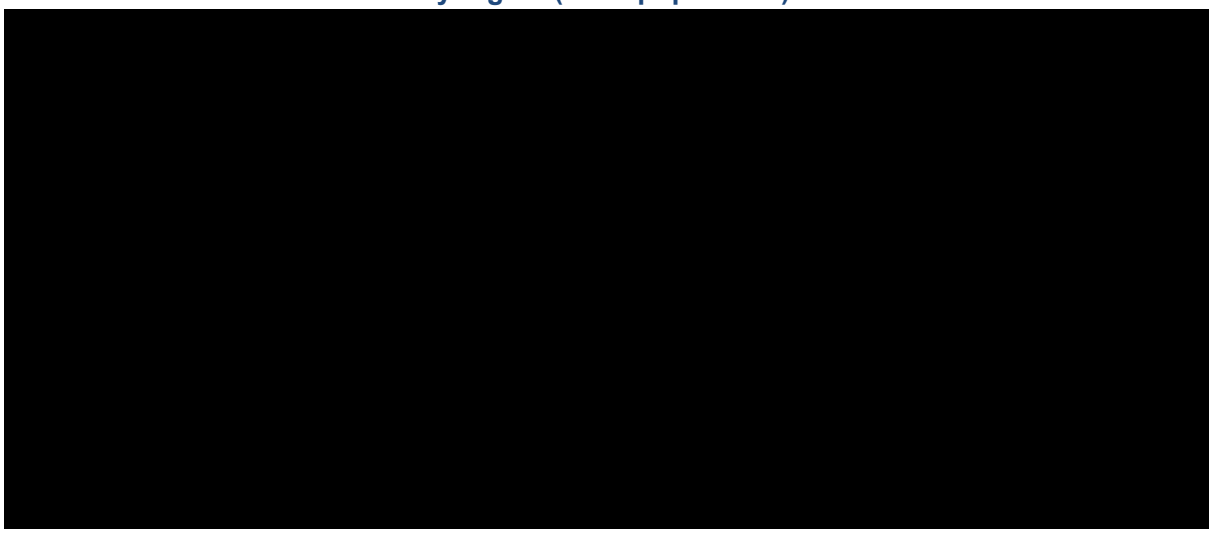
c) Sustained pain freedom 2 to 24 hours.

Consistent with pain freedom and pain relief at 2 hours, atogepant demonstrates [redacted] odds of sustained pain freedom from 2 to 24 hours in the Europe, China and Japan subgroups (Figure 11). As above, the [redacted], which may be explained by small sample sizes introducing uncertainty.

As shown in Figure 12, atogepant demonstrates [redacted] odds of achieving sustained pain freedom from 2 to 24 hours than placebo in all triptan-response subgroups.

Similarly, atogepant shows [redacted] sustained pain freedom from 2 to 24 hours compared with placebo (Figure 13), irrespective of preventive migraine medication use.

Figure 11. Forest plot of subgroup analysis of sustained pain freedom from 2–24h after the DB dose for the first attack by region (mITT population)



Abbreviations: CI: confidence interval; DB: double-blind; n1: responder; n2: responder; N1: treatment; N2: placebo.
Source: AbbVie. Data on File. ECLIPSE Supplementary Data.[8]

Figure 12. Forest plot of subgroup analysis of sustained pain freedom from 2–24h after the DB dose for the first attack by historical triptan-response stratum (mITT population)

Abbreviations: CI: confidence interval; DB: double-blind; n1: responder; n2: responder; N1: treatment; N2: placebo.
Source: AbbVie. Data on File. ECLIPSE Supplementary Data.[8]

Figure 13. Forest plot of subgroup analysis of sustained pain freedom from 2–24h after the DB dose for the first attack by preventive migraine medication use (mITT population)

Abbreviations: CI: confidence interval; DB: double-blind; n1: responder; n2: responder; N1: treatment; N2: placebo.
Source: AbbVie. Data on File. ECLIPSE Supplementary Data.[8]

Summary

In summary, atogepant demonstrated consistently improved pain freedom at 2 hours, pain relief at 2 hours and sustained pain freedom from 2 to 24 hours compared with placebo across all subgroups in the ECLIPSE trial, in line with findings in the full mITT population. Any non-statistically significant improvements are likely attributable to small subgroup sizes introducing increased uncertainty, rather than a true difference in treatment effect; as noted in Section 3.9.3.1 of the Company submission, where clinical experts determined that there are no TEMs. Therefore, atogepant is expected to deliver superior efficacy regardless of patient region, previous triptan response or concomitant preventive migraine medication use.

A19. Please provide the results for all outcomes in the NMAs for the following subgroups of ECLIPSE (mITT population for attack 1):

a) **Europe;**
b) **China, Japan and Other.**

The results for the Europe and China, Japan and Other subgroups for the mITT population (Attack 1) from the ECLIPSE trial for all outcomes that are presented in the NMA are presented in Table 16. The direction of effect across the outcomes was consistent with that observed in the mITT population (see Section 3.6 of the Company submission), favouring atogepant over placebo with the majority of outcomes remaining statistically significant across regional subgroups.[7, 8] Additionally, clinical experts consulted at an advisory board did not consider that geography or ethnicity would be a TEM; as such, any results that lack statistical significance are anticipated to be due to the relatively small subgroup sizes compared to the mITT population.[2] As such, data from the mITT population continues to provide the most robust estimate of treatment effect for atogepant versus placebo as they include the largest number of patients available, minimising uncertainty.

Table 16: Regional subgroup analyses from the ECLIPSE trial for Attack 1 (mITT population)

Outcomes	Subgroup	Treatment	Responder n/N1[a] (%)	OR (95% CI)	P-value
Pain freedom at 2 hours	Europe	Atogepant	[redacted]	[redacted]	[redacted]
		Placebo	[redacted]		
	China, Japan and other	Atogepant	[redacted]	[redacted]	[redacted]
		Placebo	[redacted]		
MBS free at 2 hours	Europe	Atogepant	[redacted]	[redacted]	[redacted]
		Placebo	[redacted]		
	China, Japan and other	Atogepant	[redacted]	[redacted]	[redacted]
		Placebo	[redacted]		
Pain relief at 2 hours	Europe	Atogepant	[redacted]	[redacted]	[redacted]
		Placebo	[redacted]		
	China, Japan and other	Atogepant	[redacted]	[redacted]	[redacted]
		Placebo	[redacted]		
Use of rescue medication within 24 hours	Europe	Atogepant	[redacted]	[redacted]	[redacted]
		Placebo	[redacted]		
	China, Japan and other	Atogepant	[redacted]	[redacted]	[redacted]
		Placebo	[redacted]		
Sustained pain freedom from 2 to 24 hours	Europe	Atogepant	[redacted]	[redacted]	[redacted]
		Placebo	[redacted]		
	China, Japan and other	Atogepant	[redacted]	[redacted]	[redacted]
		Placebo	[redacted]		
Sustained pain freedom from 2 to 48 hours	Europe	Atogepant	[redacted]	[redacted]	[redacted]
		Placebo	[redacted]		
	China, Japan and other	Atogepant	[redacted]	[redacted]	[redacted]
		Placebo	[redacted]		
Sustained pain relief from 2 to 24 hours	Europe	Atogepant	[redacted]	[redacted]	[redacted]
		Placebo	[redacted]		
	China, Japan and other	Atogepant	[redacted]	[redacted]	[redacted]
		Placebo	[redacted]		
Sustained pain relief from 2 to 48 hours	Europe	Atogepant	[redacted]	[redacted]	[redacted]
		Placebo	[redacted]		
	China, Japan and other	Atogepant	[redacted]	[redacted]	[redacted]
		Placebo	[redacted]		
Ability to function normally at 2 hours	Europe	Atogepant	[redacted]	[redacted]	[redacted]
		Placebo	[redacted]		
	China, Japan and other	Atogepant	[redacted]	[redacted]	[redacted]
		Placebo	[redacted]		

Any AE	Europe	Atogepant	[redacted]	[redacted]	[redacted]
		Placebo	[redacted]		
	China, Japan and other	Atogepant	[redacted]	[redacted]	[redacted]
		Placebo	[redacted]		

Footnotes: [a]n=Number of responders/N1= Number of patients in the subgroup for whom endpoint data were available. [b]P-value <=0.05. [c]P-value <=0.001.
Abbreviations: AE: adverse event; CI: confidence interval; MBS: most bothersome symptom; mITT: modified intent-to-treat; OR: odds ratio.
Source: AbbVie. Data on File. ECLIPSE Supplementary Data.[8]

Section B: Clarification on cost-effectiveness data

Drug acquisition costs

B1. Priority question: The EAG considers that, as the only difference in cost is based on the acquisition costs of the two treatments, a simplified analysis would be useful to validate and demonstrate that the company's more complex approach to modelling of costs is not a concern. Therefore, please provide a scenario analysis that estimates total costs for each treatment based on the treatment cost per migraine attack (assuming the duration is two days) and the mean number of migraine attacks over a 2-year period and present the incremental costs. Please describe the analysis fully, including any assumptions made.

As discussed in the Company submission, although only the drug acquisition costs are expected to differ between atogepant and rimegepant, a full cost-comparison model aligned to the model in TA919 was provided to ensure robustness of the analysis.[6] However, in line with the EAG's request, a simplified analysis that estimates the total costs for each treatment based on the treatment cost per migraine attack, assuming a two-day duration, and the mean number of migraine attacks over a two-year period has been conducted.

The calculations for the simplified analysis are presented in Table 17 below. As in the submitted cost-comparison model, it is assumed that 100% of patients in both arms are prescribed a 2-pack of either atogepant or rimegepant. In line with their dosing regimens, patients are to take up-to one tablet a day, *pro re nata*, for each migraine attack. The treatment cost per migraine attack is, therefore, the cost of each 2-pack divided by the number of tablets per pack.

At baseline, the monthly migraine days from the ECLIPSE trial mITT population was [redacted] days. Assuming a migraine lasts for 48 hours, this corresponds to [redacted] migraine attacks per month, and therefore [redacted] migraine attacks per year. As such, the total cost of atogepant over a 2-year time period is [redacted]; the total cost of rimegepant over a 2-year time period is [redacted].

The simplified incremental acquisition cost differential of atogepant compared with rimegepant is therefore -£[redacted] (Table 18) demonstrating that atogepant remains a cost-saving use of NHS resources in the EAG-requested analysis.

Table 17: Simplified analysis calculations

	Atogepant	Rimegepant
Cost of 2-pack	£25.78	£25.80
Cost per migraine attack	£25.78 ÷ 2 = £12.89	£25.80 ÷ 2 = £12.90
Total cost per patient over 2 years	[redacted]	[redacted]
Incremental costs per patient (for atogepant)	[redacted]	

Table 18: Simplified analysis results

Technology	*Base case total costs*	Simplified analysis total costs
Atogepant	[redacted]	[redacted]
Rimegepant	[redacted]	[redacted]
Incremental costs per patient (for atogepant)	[redacted]	[redacted]

Overall, in line with the results of the analysis presented in the Company submission, the results of this simplified analysis demonstrate that atogepant is an effective, well-tolerated, cost-saving treatment option in an underserved patient population that would provide effective acute treatment for migraine patients in the UK, with potential to enhance health-related quality of life (HRQoL) and improve work productivity.

B2. Please clarify why a non-flat pricing structure has been proposed for the 2-tablet and 7-tablet pack sizes?

The 2- and 7-tablet packs developed to support acute migraine treatment in UK will offer greater convenience for people suffering from migraine, who only require medication as needed and at the onset of a migraine attack, rather than a daily treatment regimen for preventing migraine. The list prices for the 2-tablet and 7-tablet packs have been provisionally approved by the Department of Health and Social Care.

B3. Priority question: A model cycle is assumed to be 48 hours (2 days). All patients are given treatment in the first cycle and then response is assessed. Non-responders incur the cost of two tablets, reflective of a two-tablet pack of either atogepant or rimegepant and assumes one tablet wastage. However, responders only incur the cost of a single tablet and a single migraine attack for each model cycle is assumed to last two days.

a) **Please clarify if a patient responds to treatment after one dose but experiences pain relief (definition of response in the model) rather than**

pain freedom, is it recommended to take another dose on the following day?

The ECLIPSE protocol specifies that patients should take one tablet per migraine attack.[20] Additionally, as results from the ECLIPSE trial demonstrate that atogepant was statistically significantly superior to placebo in the sustained pain relief up to 48 hours endpoint, meaning that pain relief on atogepant was experienced up to 48 hours after initial dosing, it is not anticipated that patients would require an additional dose of atogepant on the second day. Clinical experts noted that for a small proportion of patients who did require additional pain relief on the second day, they would advise patients to take their gepant treatment once daily as needed therefore a patient would be able to take an additional tablet (atogepant or rimegepant).

b) Please provide a scenario where the cost of a 2-pack of tablets is assumed for all patients in the first cycle and the cost of two tablets is assumed for responders who experience a migraine attack for the remaining cycles of the model.

In line with the response to part a), AbbVie do not anticipate that two tablets would be required to treat a single migraine attack. However, to examine the uncertainty, a scenario analysis has been provided assuming that every patient accrues the cost of a 2-pack of tablets in the first cycle and subsequently responders accrue the cost of two tablets per migraine attack for the remainder of the model time horizon in both treatment arms.

The results of this scenario analysis are presented in Table 19. As shown below, by doubling the number of tablets administered per migraine attack for both atogepant and rimegepant, the total acquisition cost associated with both treatments doubles. Therefore, the incremental cost savings for atogepant are double that of the base case analysis. As such, atogepant remains a cost-saving use of NHS resources in the acute treatment of migraine.

Table 19: Two tablets per migraine attack scenario results

Technology	*Base case (total costs)*	Scenario analysis		
		Drug acquisition costs	Healthcare resource use costs	Total costs
Atogepant	[redacted]	[redacted]	[redacted]	[redacted]
Rimegepant	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs per patient (for atogepant)	[redacted]	[redacted]	[redacted]	[redacted]

B4. Priority question: The EAG notes that the cost per tablet for the 28 tablet-pack size of atogepant is substantially less expensive than the proposed cost per tablet of the 2 tablet- and 7 tablet-pack size. Given that the baseline mean monthly migraine days from ECLIPSE was [redacted] days, the smaller pack sizes may be less frequently used in clinical practice. Additionally, the EAG's

clinical expert advised that if a patient responds to treatment, then a number of tablets are prescribed rather than a whole pack. As such, hospital prescribing may take tablets from the least expensive pack size of a medicine to give to patients. Therefore, please provide a scenario analysis using the cost per tablet of the 28 tablet-pack size of atogepant.

In the Company submission, 2-pack sizes were selected in the base case for both atogepant and rimegepant to model the most comparable pack sizes. In addition, clinical experts consulted at an advisory board (n=5) stated that the 2-tablet pack would be considered a 'trial pack size' in practice and would likely be given to first-time patients to assess whether they were treatment responders and tolerated the treatment well.[2] Furthermore, the baseline mean monthly migraine days from ECLIPSE was [redacted] days; given a migraine attack is assumed to last 48 hours, and patients are to take up-to one tablet a day, *pro re nata*, for each migraine attack, as per the summary of product characteristics (SmPC), this translates into [redacted] tablets per month.[21] Clinical experts considered that the 28-pack size of atogepant would primarily be used for the preventative treatment of migraine and the 2- and 7-packs will primarily be used for acute treatment.

However, in line with the EAG's request, a scenario analysis has been conducted using the cost per tablet of the 28-pack of atogepant. In line with clinical expert feedback, all patients in both treatment arms were modelled to receive a 2-pack on day 1; those who did not respond accrued the cost of a wasted 2-pack.[2] Patients in the atogepant arm who responded subsequently continued to accrue the per-tablet cost from the 28-pack (£6.51) per migraine attack for the remainder of the model time horizon. Note this approach conservatively overestimates the total acquisition cost within the atogepant arm by counting an additional 28-pack tablet cost that would be used by patients who in practice would receive the second tablet from their initial 2-pack. Patients in the rimegepant arm who responded accrued the cost of the second tablet within the 2-pack, and subsequently continued to accrue the per-tablet cost from the 2-pack, as in the base case.

The results of this scenario analysis are presented in Table 20. As expected, the lower cost per tablet for atogepant reduced the total atogepant acquisition costs, without impacting the rimegepant acquisition costs; therefore, the incremental cost-savings associated with atogepant increased substantially. As such, atogepant remains a cost-saving use of NHS resources, while representing an effective, well-tolerated and much needed treatment for acute migraine.

Table 20: Atogepant 28-pack cost per tablet scenario results

Technology	*Base case (total costs)*	Scenario analysis		
		Drug acquisition costs	Healthcare resource use costs	Total costs
Atogepant	[redacted]	[redacted]	[redacted]	[redacted]
Rimegepant	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs per patient (for atogepant)	[redacted]	[redacted]	[redacted]	[redacted]

B5. Priority question: The annual discontinuation rate of 13.5% was cited as obtained from Johnston *et al*. 2024, but the value in the paper is 9.7%. Please explain the discrepancy and amend the model if necessary.

In Johnston *et al.* 2024, the 9.7% value refers to the annual discontinuation rate specifically for the population of patients who discontinued ≥2 triptans. As all clinical inputs in the model are based on the mITT population, the annual discontinuation rate for the mITT population from Johnston *et al*. 2024 has been applied, which is 13.5%.[22] This value was sourced from the supplementary appendix, which is included in the reference pack.[22]

Care setting

B6. In the submission, the company states that some NHS organisations allow initiation and/or follow-up of rimegepant in the primary care setting. Please can you clarify the source of the information and provide data to substantiate the claim?

Several NHS Integrated Care Board (ICB) formularies and local commissioning documents allow rimegepant to be initiated and/or followed up in primary care for the acute treatment of migraine. This is indicated by a 'Green' (or equivalent) traffic-light status in the formulary. While definitions vary between formularies, 'Green' status generally denotes that the medicine is suitable for initiation and prescribing in all care settings, including primary care.

Please find examples of local formularies permitting primary care use for rimegepant below:

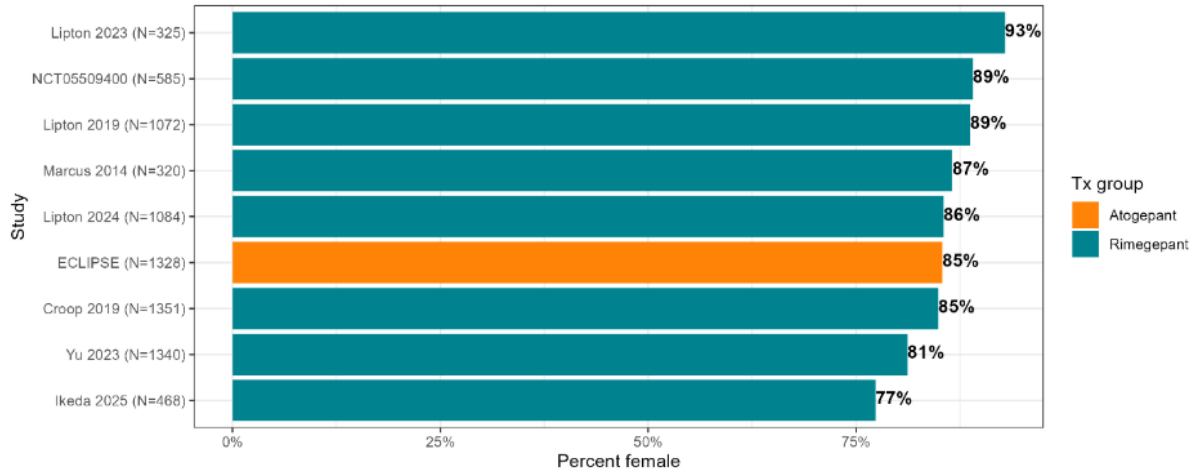
- NHS North Central London formulary[23]
- NHS Somerset formulary[24]
- NHS North East and North Cumbria formulary[25]

Section C: Textual clarification and additional points

C1. Please clarify what baseline characteristics data are reported in the company submission appendix Figure 13: Baseline sex of included studies.

The figure reports the percentage of female patients at baseline. This has been updated in Figure 14 below to clarify.

Figure 14: Baseline sex of included studies



Abbreviations: Tx: treatment.

C2. Priority question: In the model, the baseline MMD is [redacted] days, based on ECLIPSE. However, in Figure 16 of the company submission appendix, the value reported is [redacted] days. Please clarify whether the data presented in Figure 16 represent baseline monthly migraine attacks rather than monthly migraine days (MMD).

The data in Figure 16 of the Company submission appendix represent moderate to severe monthly migraine attacks or days, depending on study-specific reporting. Because most studies specified moderate to severe migraine attacks rather than days, the plot has been regenerated in Figure 15 below with corrected labelling and clarifying footnotes.

Figure 15: Baseline MMD of included studies

[redacted]

Footnotes: The data for study NCT05509400 represent moderate to severe migraine days per month at baseline.[14] For all other studies, the data represent moderate to severe migraine attacks per month at baseline.
Abbreviations: MMD: monthly migraine days; Tx: treatment.

References

1. Diener HC, Tassorelli C, Dodick DW, et al. Guidelines of the International Headache Society for controlled trials of acute treatment of migraine attacks in adults: Fourth edition. Cephalalgia 2019;39:687-710.
2. AbbVie Data on File [CONFIDENTIAL]. Atogepant in Migraine UK Advisory Board Meeting Report, 2025.
3. Dawn Lee AA, Alan Lovell, Ahmed Abdelsabour, Edward C. F. Wilson, G. J. Melendez-Torres. How similar is similar enough? Assessment of indirect treatment comparisons to support similarity for NICE's cost comparison route. Available at: https://www.ispor.org/docs/default-source/euro2024/how-similar-is-similar-enough-cost-comparison-poster-ispor142603-pdf.pdf?sfvrsn=21e7eb7b_0. [Last accessed: February 2026].
4. National Institute for Health and Clinical Excellence (NICE). NICE DSU Technical Support Document 3: Heterogeneity: Subgroups, Meta-Regression, Bias and Bias-Adjustment. Available at: https://www.ncbi.nlm.nih.gov/books/NBK395886/pdf/Bookshelf_NBK395886.pdf. [Last accessed: 18 December 2025].
5. Dias S, Welton NJ, Sutton AJ, et al. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. Available at: https://www.ncbi.nlm.nih.gov/books/NBK310366/. [Last accessed: February 2026].
6. National Institute for Health and Care Excellence (NICE). Rimegepant for treating migraine (TA919). Available at: https://www.nice.org.uk/guidance/ta919 [Last accessed: October 2025].
7. AbbVie Data on File [CONFIDENTIAL]. ECLIPSE Clinical Study Report, 2025.
8. AbbVie Data on File [CONFIDENTIAL]. ECLIPSE Supplementary Data.
9. Dycke AV, Brand-Schieber E, Ornello R, et al. Efficacy, Safety, and Tolerability of Atogepant for the Acute Treatment of Migraine: Results from the ECLIPSE Trial, In 19th European Headache Congress (EHC), Lisbon, Portugal, 2025.
10. Kuca B, Silberstein SD, Wietecha L, et al. Lasmiditan is an effective acute treatment for migraine: A phase 3 randomized study. Neurology 2018;91:e2222-e2232.
11. Rimegepant (Vydura). Summary of product Characteristics. Available at: https://ec.europa.eu/health/documents/community-register/2022/20220425155292/anx_155292_en.pdf. [Last accessed: October 2025].
12. Pozo-Rosich P, Ailani J, Ashina M, et al. Atogepant for the preventive treatment of chronic migraine (PROGRESS): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2023;402:775-785.
13. Marcus R, Goadsby PJ, Dodick D, et al. BMS-927711 for the acute treatment of migraine: a double-blind, randomized, placebo controlled, dose-ranging trial. Cephalalgia 2014;34:114-25.
14. Messoud Ashina et al., "A Phase 4 Randomized Double-blind Placebo-Controlled Study of Rimegepant for Acute Treatment of Migraine in Adults Unsuitable for Triptan Use," in Annual Metting of the American Headache Society, Minneapolis, 2025.
15. Ikeda K, Matsumori Y, Kudo M, et al. Efficacy and safety of rimegepant for the acute treatment of migraine in Japan: A dose-ranging, double-blind, randomized controlled trial. Headache 2025.
16. Lipton RB, Croop R, Stock EG, et al. Rimegepant, an Oral Calcitonin Gene-Related Peptide Receptor Antagonist, for Migraine. N Engl J Med 2019;381:142-149.
17. Lipton RB, Thiry A, Morris BA, et al. Efficacy and Safety of Rimegepant 75 mg Oral Tablet, a CGRP Receptor Antagonist, for the Acute Treatment of Migraine: A Randomized, Double-Blind, Placebo-Controlled Trial. J Pain Res 2024;17:2431-2441.

18. Yu S, Kim BK, Guo A, et al. Safety and efficacy of rimegepant orally disintegrating tablet for the acute treatment of migraine in China and South Korea: a phase 3, double-blind, randomised, placebo-controlled trial. Lancet Neurol 2023;22:476-484.
19. Croop R, Goadsby PJ, Stock DA, et al. Efficacy, safety, and tolerability of rimegepant orally disintegrating tablet for the acute treatment of migraine: a randomised, phase 3, double-blind, placebo-controlled trial. The Lancet 2019;394:737-745.
20. AbbVie Data on File [CONFIDENTIAL]. ECLIPSE Protocol, 2023.
21. AbbVie Data on File [CONFIDENTIAL]. Atogepant Summary of Product Characteristics. .
22. Johnston K, Powell LC, Popoff E, et al. Cost-effectiveness of rimegepant oral lyophilisate compared to best supportive care for the acute treatment of migraine in the UK. J Med Econ 2024;27:627-643.
23. NHS. North Central London ICB. Available at: https://www.ncl-jointformulary.nhs.uk/chaptersSubDetails.asp?FormularySectionID=4&SubSectionRef=04.07.04.02&SubSectionID=A100&drugmatch=6160#6160. [Last accessed: February 2026].
24. NHS. Somerset ICB. Available at: https://www.somersetformulary.nhs.uk/chaptersSubDetails.asp?FormularySectionID=4&SubSectionRef=04.07.04&SubSectionID=A100. [Last accessed: February 2026].
25. NHS. North East and North Cumbria ICB. Available at: https://www.northeastnorthcumbriaformulary.nhs.uk/chaptersSubDetails.asp?FormularySectionID=4&SubSectionRef=04.07.04.02&SubSectionID=A100&drugmatch=5917#5917. [Last accessed: February 2026].

NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal
Atogepant for treating migraine [ID6615]
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].

Information on completing this submission

- 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
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	The Migraine Trust
3. Job title or position	[redacted]
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 in the UK affected by migraine. We are the only UK migraine charity providing information and support, campaigning for awareness and change, and funding and promoting research. 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 around 34,000 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.]	£29,969 from Abbvie to support our work around improved patient journeys and patient advocacy £46,100 from Pfizer to support the charity's work to put migraine higher up the work agenda

If so, please state the name of the company, amount, and purpose of funding.	
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 conduct regular research and surveys of people affected by migraine across the UK, to obtain information on their experiences of the impact of migraine and unmet needs. Our research from the last 3 years has primarily informed our responses. We also have regular contact through our range of support services with people affected by migraine, and we track the type of information and support that people are seeking and the challenges they face. Additionally, we have the facility for people to feed back on our information webpages, where they often describe their personal experiences. Our surveys often receive over 2,000 responses, therefore providing depth of insight, impact and quality of data.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Migraine is an often misunderstood and stigmatised condition, frequently being dismissed as 'just a headache'. We know from our regular surveys of people with migraine, and from those that contact our support services, that people consistently feel dismissed or invalidated across home, work, and healthcare settings. As a result, those living with migraine often tell us they don't receive the support, care and treatment they need. For many people, migraine symptoms are so debilitating that they have a serious impact on mental health, as well as daily living, work, relationships and ability to socialise. Over a quarter of the 5,000 people contacting our helpline in 2025 did so because of feelings of low wellbeing, with 12% mentioning feeling isolated or alone. **Research into gender, ethnicity and social grade – 'The Migraine Divide' 2025** Our most recent research released in December 2025 looked at the impact social grade, gender and ethnicity have on people's experience of migraine. These factors shaped how people felt they were perceived by others – which impacted on their willingness to disclose their migraine and seek help. Of the 2,200 people surveyed (with over-representation from ethnic minority groups), key findings included: • 92% of all participants said migraine affects their ability to work, and 95% said it impacts their education. Four in five (79%) reported a negative effect on their mental health • Women were more likely to not want to disclose their migraine for fear of being seen as "emotional" or unreliable, while men cited concerns about being perceived as weak • Those with Black heritage were most likely to fear discrimination or a negative impact on their career compared to white colleagues (37% v 26%) • 23% of mixed-ethnicity, 19% of Asian, and 16% of Black respondents said their ethnicity had negatively affected their care, compared with just 7% of white participants • 49% of those from lower-income backgrounds said they had worked through a migraine attack because they couldn't afford to take time off, compared to 33% of higher income groups. Fears of job security and lack of flexibility were significant barriers to disclosure among C2DE backgrounds, with ABC1 participants more likely to worry about their reputation and perceived reliability or impact on their career progression • Participants overwhelmingly described coping alone, developing personalised strategies due to inadequate support from health professionals or fear of judgement from others.

	Survey on workplace support – 'Challenging stigma' 2025 In 2025, we surveyed over 2,000 people with migraine about their experiences in the workplace. Key results included: • People with migraine report feeling that they are not believed (65%) and regularly have their migraine dismissed as an exaggeration or excuse (66%). • 91% had worked while experiencing migraine symptoms (often due to the fear of being disciplined or losing their job) • 15% had been forced to move from full-time to part-time work • 19% have had to leave a job entirely • 59% would not feel comfortable talking to their line manager about their migraine • 58% had avoided telling an employer about their migraine, due to the worry of not being hired, promoted or taken seriously. **Survey on impact of migraine on mental health – 'Migraine hurts' 2024** This survey exploring the impact of migraine in more than 2,000 people, found that: • 89% said their mental health had been affected as a result of their migraine, with 55% saying the impact is significant and 34% having thoughts of suicide due to migraine. • As a result of their migraine 80% participate less in social occasions, 59% have lost confidence and 48% feel isolated • Impact on work is significant. 49% say migraine has a negative impact on ability to work and 27% say it has caused significant financial difficulties • The physical pain of migraine, living with the unpredictable nature of attacks, feelings of guilt or letting people down and missing out on events are all aspects of migraine that affect mental health.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	We know that many people experience delays and challenges in accessing appropriate healthcare. There is also inequity in the provision of treatments, with many people finding treatments available on the NHS not available in their region. Provision of specialist headache clinics is patchy and waiting times for specialist care are often lengthy. Many people also report lack of understanding about migraine among healthcare professionals. People regularly tell us that receiving a correct diagnosis can be time-consuming, stressful and difficult. They can wait years for the right treatment and care, and feel that they are a burden or a nuisance asking for help. In our 2025 research, 'The Migraine Divide', many people reported misdiagnoses, inappropriate medication and difficulty accessing specialist care. Dismissive experiences led to mistrust in healthcare, hesitation to seek help, and worsening health outcomes. People from mixed, Asian and Black backgrounds were more likely to feel that ethnicity negatively affected their treatment. In 2023, we conducted a survey into access and use of CGRP mAbs. Of the 186 people who had 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. Our 2024 Migraine Treatment in Primary Care Survey in 284 people found that: • 78% (n=218/280) of migraine patients had seen a doctor between 1–10 times and 16% (n=45/280) greater than 10 times before their migraine was diagnosed • Patients feel it is up to them to manage their migraine (66% (n=188/284) said always & 23% (n=66/284) often) • 13% (n=37/283) were satisfied (completely or very) with the experience they've had of their care and treatment vs. 45% (n=128/283) slightly/not at all satisfied • Large numbers are visiting A&E or being referred to outpatient neurology services for unnecessary investigations and treatment.

8. Is there an unmet need for patients with this condition?	Yes. Many people do not have appropriate acute treatment for migraine. This is due to lack of efficacy, side effects or medication overuse from many of the current treatments, or medical comorbidities, such as cardiovascular disease, kidney and liver disease, that exclude or limit current acute treatment options. This is exacerbated by the current issue around access to medication already on the market. Access to an effective, well-tolerated acute medicine that can be used in the early stages of a migraine attack without fear of medication overuse, could avoid some of the debilitating symptoms that impact on activities and function. There is currently only one gepant available to be used as an acute treatment, and for some, this doesn't work or the side effects may be too great. This would represent an alternative, expanding the range of treatment options available. For people who have responded well to atogepant as a preventative, being able to take it when needed as an acute treatment may also represent an alternative option to potentially needing to stop the medication altogether. People with migraine have struggled for decades with ineffective or limited treatment options, that have been designed for other conditions. Now that we have migraine-specific treatments available, it is vital for patients to have access to all the relevant treatments they are eligible for, to ensure they can manage their health.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	People who completed our feedback survey on our Gepants information page had positive comments about another option being available to them if they are unable to take triptans (in relation to other gepants already on the market for acute treatment). People contacting our helpline have made similar comments, with many saying they are relieved to have another option available and reporting that it has helped. "Useful information if you can't take triptans especially" "I have had bad effects from triptans years ago and have subsequently had a heart attack. .....I am told these should help, I really hope they do" "I take Zolmitriptan at the onset of a migraine but for the past few weeks, nothing has worked! My neurologist has suggested Rimegepant and left it to me to research and get back to him. It is looking like a good option!"

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Overall, patients don't see any disadvantages of the technology. Any concerns are around access and ensuring healthcare professionals are aware of it. Considering feedback regarding other gepants on the market for acute treatment, comments from our information survey show there is some frustration about not having access to gepants in certain areas of the country or needing to wait for an appointment with a neurologist. From people contacting our helpline, it appears that GPs rarely mention gepants as an acute treatment option. Similar to treatments in general for all health conditions, we've had some people that contacted our helpline who were prescribed currently-available acute gepants who found it didn't help them or had some side effects such as severe nausea and stomach pain. There also appears to be an issue in some areas that only limited amounts can be prescribed and this is not enough to cover all attacks.

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 for the acute treatment of migraine would be particularly beneficial for people who have not found other acute medicines effective, or are unable to take them due to: • side effects • medication overuse • medical comorbidities, such as cardiovascular disease, kidney and liver disease. It may represent a better option for people over the age of 65 with certain cardiovascular risk factors. People who will benefit less include those with silent migraine, as acute medicines don't help with this type of migraine.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Please see above comments regarding our research into social grade, gender and ethnicity. These factors often impact experiences of people living with migraine, including accessing healthcare. As mentioned above, it is vitally important that there is equitable access to this treatment (if approved for acute).

Other issues

13. Are there any other issues that you would like the committee to consider?	It would be helpful to consider whether there is any evidence of potential benefits or contraindications to taking atogepant alongside other acute treatments, including painkillers, ant-emetics and triptans. It would be helpful to review whether there is evidence of safety supporting the use of atogepant as an acute treatment in people already taking rimegepant or CGRP mAbs as a preventer. It would be helpful to review whether there is any evidence to support people who have experienced a significant reduction in migraine frequency or severity using atogepant as a preventer being able to maintain this remission using atogepant on an (acute) as required basis only. A potential barrier is likely to be equity and ease of access. Any treatment approved by NICE and appearing in NICE guidance on migraine should be offered equitably across England and Wales. Currently, millions of people struggling with migraine are still unable to access life-changing treatments that have previously been approved. As an oral, acute treatment with good tolerability, ensuring access in the primary care setting would enable more equitable access, with fewer potential delays and costs incurred for specialist services. If the treatment is only available via a headache specialist, this is likely to create issues with access or treatment delays.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• People with migraine often have debilitating symptoms that impact many areas of life. An effective treatment that targets migraine symptoms with minimal side effects is crucial. • There is an unmet need for patients who are unable to tolerate other acute medicines, find these ineffective, experience medication overuse, or cannot take them for other reasons (such as comorbidities). • Many people with migraine experience issues with access to treatment and care, long waiting lists, inequity in provision of treatments and lack of understanding from healthcare professionals. This can be compounded by factors such as ethnicity, gender and social grade. • 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.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal
Atogepant for treating migraine [ID6615]
Professional 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 the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- 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
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	Association of British Neurologist (ABN)
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):
5a. Brief description of the organisation (including who funds it).	The Association of British Neurologists' is a professional membership organisation and its mission is to improve the health and well-being of people with neurological disorders by advancing the knowledge and practice of neurology in the British Isles. The ABN receives funding mainly from its member subscriptions and annual conference income. Additional funding from external charity organisations is received to solely fund fellowships. Additionally, the ABN receives sponsorship from pharmaceutical companies. Sponsoring companies have no input, control nor opportunity to influence the ABN.
5b. Has the organisation received any funding from the manufacturers 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.**	In the past 12 months, the ABN has received sponsorship from the following companies to support the ABN Annual Conference. Sponsorship companies have no editorial input, control over the agenda, speaker selection, content development nor opportunity to influence the conference. Sponsorship is £18,020 per company. • Abbvie • Alnylam • Angelini • argenx • Biogen • Eisai • Eli Lilly • Janssen • Pfizer • Roche • Sanofi • Teva • UCB

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Migraine is a highly prevalent condition that affects 15% of the general population. There is no cure but it can be well controlled through abortive and preventive treatment options. During an acute attack of migraine, a patient experiences moderate to severe throbbing headache with associated features of nausea, vomiting and sensitivity to light, sound and smell. The condition shows exacerbation with physical activity and hence most patients are unable to be productive during the attack that may last between 4-72 hours. An effective acute treatment, therefore, relieves pain and associated symptoms within 2 hours. Those with frequent migraine attacks are usually given preventive treatment to reduce the frequency and severity of acute attacks.
7. 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.)	In various clinical trials response to treatment at 2 hours is measured to evaluate the efficacy of the given therapy. The guidelines by the British Association for the Study of Headache (BASH) indicates any treatment ineffective if there is no response at 2 hours. For migraine treatments, a reduction in pain severity from severe/moderate to mild or pain free and relief from the most bothersome symptoms at two hours is regarded as an effective response.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Currently simple painkillers like paracetamol and non-steroidal anti-inflammatory drugs are recommended as first line treatment. Triptans are given in those with inadequate response to simple painkillers. Recently, one of the Calcitonin Gene Related Peptide (CGRP) receptor blocker, Rimegepant has been approved by NICE for acute treatment in those with lack of response to two triptans or where triptans are contraindicated. When it comes to abortive treatment, the choice remains between these three lines and there is a huge unmet need as many patients are unsuitable or have contraindications to the use of these choices.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	There are two approaches of treating an acute migraine attack. Stepped and Stratified. In stepped approach, treatment is recommended with simple painkillers and escalated to triptans if there is lack of response or inadequate response. Those with lack of response to two triptans or with contraindications to their use have recently been approved for Rimegepant, one of the CGRP receptor antagonist. In stratified approach patients are given the best possible option from the very start.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	In the UK there are three guidelines that are often consulted. These are NICE, SIGN and BASH. The first is NICE guidelines CG150 first published in 2012 and have been updated at three yearly intervals, although the overall guidelines require to be completely rewritten and many drugs have been introduced since its first publication. BASH guidelines published in 2019 by the British Association for the Study of Headache is currently being updated and is used by many headache specialists in England and Wales. SIGN guidelines have recently been updated and is followed mainly in Scotland, although widely used all over the UK.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Recommendations for abortive treatment is similar in all three guidelines, although there is considerable difference in the hierarchy of treatment when it comes to preventive options. NICE still recommends propranolol, amitriptyline and topiramate as first line treatment, although BASH and SIGN recommend amitriptyline, propranolol and candesartan being the first three options due to the recent guidance from the Medicine and Healthcare products Regulatory Agency (MHRA) on the use of topiramate in women less than 50 due to its teratogenicity.
9c. What impact would the technology have on the current pathway of care?	Atogepant will add another abortive treatment option along with Rimegepant in those with failure to respond to two triptans or those with contraindications to triptan.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes this will provide another abortive treatment option in those non-responsive to triptans or contraindications to their use.
10a. How does healthcare resource use differ	As another CGRP receptor antagonist is already being used as an abortive treatment in a selective group of patients, Atogepant will be used in the same category.

between the technology and current care?	
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Being an abortive treatment, primary care and those working in Accident and Emergency Department and acute medical unit will be prescribing the drugs more than tertiary or out-patient secondary care.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	It is a good idea to have a choice of two in triptan non-responders as not everyone will respond to Rimegepant.
11a. Do you expect the technology to increase length of life more than current care?	No
11b. Do you expect the technology to increase health-related quality of life more than current care?	No
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As recommended by NICE, this technology is suitable for those who have tried and failed two triptans or have contraindications to their use.

The use of the technology

13. 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.)	Very easy to use.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The treatment is recommended for acute attacks, and I suppose if there is lack of response in three acute attacks, there is little point in prescribing for further attacks.
15. 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?	This will certainly contribute in improving the quality of life of patients with migraine.

16. 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?	CGRP receptor antagonist are novel drugs recently introduced both for abortive and preventive treatment options. With the side effect profile similar to placebo and no major contraindications, it is innovative and will play substantial role in how the acute attacks are managed.
16a. Is the technology a 'step-change' in the management of the condition?	Not so as Rimegepant has already been approved in this group of patients.
16b. Does the use of the technology address any particular unmet need of the patient population?	Not everyone prescribed Rimegepant shows an adequate response, hence there is unmet need in those groups of patients.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effect profile of the drug is no different to placebo.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	The evidence comes from a single Phase 3 trial (ECLIPSE) presented as an abstract in recent European Headache Congress in Lisbon. It was a 24-wee multicentre, randomised, double-blind, placebo controlled multiple-attack study that enrolled 1223 patients. The primary end-point was achieved. At two hours pain freedom was seen in 24.3% compared to 13.1% in the placebo group. An important

	secondary end-point of relief from most bothersome symptom at two hours was also achieved. The trial included participants from the UK.
18a. If not, how could the results be extrapolated to the UK setting?	N/A
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Pain freedom rather than relief and absence of most bothersome symptoms rather than relief means the outcomes measured were more stringent than used in some of the trials.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The side effect profile was comparable to placebo. Nasopharyngitis and upper respiratory tract infections were reported in 2.3 – 4.6%.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	There is no head-to-head study with the currently used drug Rimegepant given in those with triptan failure or contraindications. However, it appears that the price of the current technology is almost half of what Rimegepant will cost.
20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology	None

appraisal guidance XXXX?	
21. How do data on real-world experience compare with the trial data?	No real world data is available

Add any topic-specific questions here or delete if not needed

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Migraine is three times more common in females.
22b. Consider whether these issues are different from issues with current care and why.	Not so

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Atogepant is a CGRP receptor antagonist effective as an abortive therapy in migraine. • The evidence comes from a single trial (ECLIPSE) recently presented at a European Congress as an abstract. • There are no head-to-head study with the other CGRP receptor antagonist Rimegepant, currently being used in those not responding to triptans or contraindications to their use. • The technology is half the price of Rimegepant. • The adverse events seen in 2-4% are mild and comparable to placebo.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal
Atogepant for treating migraine [ID6615]
Professional 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 the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- 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
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	British Association for the Study of Headache
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): Representative for national charity for headache sufferers and headache health care providers (BASH)
5a. Brief description of the organisation (including who funds it).	British Association for the Study of Headache (BASH) *BASH's mission is to reduce the impact of headache disorders by delivering world-class education, promoting best practice in headache care, and driving policy change that benefits people affected by headache across the UK*
5b. Has the organisation received any funding from the manufacturers 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.**	Yes sponsored educational events with parity across pharmaceutical companies
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Improve acute management of migraine to optimise individual function and quality of life
7. 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.)	Improvement in individual function and quality of life. Reduced days off work and increased work productivity Reduced emergency healthcare resource use
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, Triptans have the disadvantages that they are contraindicated in those with a history of cerebrovascular or cardiovascular ischaemic events or uncontrolled hypertension. There are also a proportion of individuals who do not tolerate or respond to triptans. There is also risk of triptan-overuse rebound headache with use on more than 10 days per month which can exacerbate headache conditions. Patients unresponsive to Rimegepant as rescue treatment.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	First line: Anti-inflammatories and paracetamol first line Second line: Triptans (oral tablets, nasal sprays, dissolvable tablets, injections) are specific migraine targeted analgesia. If the first one is ineffective or not tolerated as second or third choice of triptan should be tried. Third line: Rimegepant is available when triptans are contra indicated, triptans not tolerated, simple analgesics not effective We anticipate atogepant to be used in the same circumstances as Rimegepant and for those that do not respond to Rimegepant.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE criteria for the use Rimegepant for acute migraine treatment BASH Headache Management Guidelines SIGN 155: Pharmacological Management of Migraine
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is current variability in access to CGRP antagonists (gepants) including Rimegepant and Atogepant depending on the local formulary status which is creating health inequality between geographical regions. We would advise that access is supported with GREEN formulary status to allow initiation in Primary Care for the acute treatment of migraine without referral to secondary care. Ideally a national formulary would help reduce this geographical variability or 'postcode lottery'.
9c. What impact would the technology have on the current pathway of care?	Add additional treatment options for rescue treatment to patients suffering migraine within primary care which would reduce referrals to secondary care and emergency hospital admissions
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	We anticipate atogepant to be used in the same circumstances as Rimegepant as an acute treatment

10a. How does healthcare resource use differ between the technology and current care?	
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The GP/ Primary Care Health Professional is the first point of contact for an individual seeking help managing migraine. We would strongly recommend that atogepant as an acute migraine treatment is accessible and provided in primary care which is line with triptan and Rimegepant use, to avoid any barriers for people accessing effective rescue migraine treatment.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nil
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, on an individual basis depending on their history of triptan or Rimegepant tolerability or effectiveness.
11a. Do you expect the technology to increase length of life more than current care?	No
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes- an additional rescue treatment option may reduce unnecessary hospital admissions or further GP appointments
12. Are there any groups of people for whom the technology would be more or less effective (or	Yes- those with current contraindications, intolerances or lack of efficacy to triptan treatment as outlined in Q8

appropriate) than the general population?	

The use of the technology

13. 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.)	Just as easy as current care for patients and professionals. No monitoring or training required. SmPC outlines avoidance in severe renal and liver impairment. Not licences in pregnancy or breast feeding. Listed medication interactions clearly outlined in SmPC.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Anticipate atogepant to be an option if triptans are not effective, tolerated or contraindicated. No additional testing required.
15. Do you consider that the use of the technology will result in any	No

substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. 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?	Atogepant belongs to the class of gepants which is a migraine-specific acute treatment which does not have active vasoconstrictive actions so can be use in individuals with vascular disease where there has previously been no other treatment option other than anti-inflammatories and paracetamol. The gepants have also not been associated with the development of cutaneous allodynia which is a marker of medication overuse rebound headache in animal studies, making it a preferable option in those individuals with regular migraine. These unique pharmacological properties make atogepant an innovative acute migraine treatment for managing migraine attacks acutely including those that have contraindications, intolerances or do not respond to triptans, or are at risk of medication overuse
16a. Is the technology a 'step-change' in the management of the condition?	Yes in the same way as Rimegepant is a new option where there has not been an option before for people who have contraindications, intolerances or do not respond to triptan treatment.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, as above
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Constipation (10%) and nausea (2%) may be managed with usual first line medication if they occur and are not anticipated to be a reason that individuals stop taking using the medication, unless severe. We

	anticipate that the benefits of using atogepant as an acute treatment for migraine will outweigh the potential adverse events and improve quality of life.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	The ECLIPSE study involved a placebo-controlled trial of efficacy, safety and tolerability of atogepant as an acute treatment for migraine with relevant primary outcomes in line with UK clinical practice. It did not test individuals who have failed triptans previously.
18a. If not, how could the results be extrapolated to the UK setting?	N/A
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Time to pain relief which allows the individual to function is the most important putcome form a clinical point of view alongside tolerability.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not applicable : clinical trial data used standard primary and secondary endpoints
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Real-world data is limited at present so we are unable to comment.
19. Are you aware of any relevant evidence that	No

might not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance XXXX?	No
21. How do data on real-world experience compare with the trial data?	Real-world data is limited at present so we are unable to comment.

Add any topic-specific questions here or delete if not needed

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	We would advise that access is supported with GREEN formulary status to allow initiation in Primary Care for the acute treatment of migraine without referral to secondary care across England to minimise any geographical variation in access to treatment.
22b. Consider whether these issues are different from issues with current care and why.	Equity of access has been an existing problem with all advanced migraine treatments eg CGRP monoclonal antibodies, Botulinum toxin, gepants. This is due to variations in local formulary status, differences in headache service providers, and awareness/education of primary care providers (e.g some areas have access only via to a local specialist secondary care headache service which are not available in every region, others via community headache services or private providers)

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Low risk, well-tolerated, effective acute migraine medication • Provides an alternative option for when triptans are not an option • Access best placed in primary care • Recommend that it is supported by GREEN formulary status • Improves function and quality of life of individuals with migraine

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal
Atogepant for treating migraine [ID6615]
Professional 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 the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- 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
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	UK Clinical Pharmacy Association (UKCPA)
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? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The UK Clinical Pharmacy Association (UKCPA) is a leading professional membership body and registered non-profit dedicated to advancing clinical pharmacy practice and medicine management across the UK. Founded in 1981, it provides a platform for expert-led education and the development of national clinical standards through its specialist interest groups, such as the Neuroscience Committee. The organization is a key stakeholder for bodies like NICE and NHS England, coordinating expert responses to national consultations. UKCPA is primarily funded through annual member subscriptions and revenue from its specialized training events, alongside occasional educational grants provided under strict governance codes.
5b. Has the organisation received any funding from the manufacturers 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

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Atogepant in this appraisal will be evaluated as abortive treatment for migraine.
7. 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.)	reduction in headache pain and associated symptoms, speed of onset, improve patient's ability to function, limited and tolerated adverse effects of treatment, improve patients' quality of life.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, still many patients suffer from pain and other symptoms that limit their quality of life and impair their ability to contribute to society or to take care of their families.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	The migraine abortive options or treatment include NSAIDs, paracetamol, triptans and one gepant (Rimegepant).
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guideline CG150, SIGN guideline SIGN155, BASH guidelines.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Pathways vary across the country. It is accepted that gepants can be tried if triptans are controindicated or at least 2 triptans have failed.
9c. What impact would the technology have on the current pathway of care?	Will give another abortive treatment option to patients.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Likely in a similar way as Rimegepant for acute treatment of migraine.
10a. How does healthcare resource use differ between the technology and current care?	Currently we have only of gepant who can be offer to patients as abortive treatment either if triptans failed or are contraindicated. Atogepant will offer another option to patients.
10b. In what clinical setting should the technology be used? (For example,	Primary care, secondary care and specialist clinics

primary or secondary care, specialist clinics.)	
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No investment needed.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	There is no cure for migraine, but we can offer options to patients to manage their symptoms and conditions at the very best. Gepants compared to triptans offer the advantage of not being likely to cause medicaton overuse headaches which represent a significant burden in this patients' population and limit the efficacy of prophylactic options.
11a. Do you expect the technology to increase length of life more than current care?	No
11b. Do you expect the technology to increase health-related quality of life more than current care?	Not significantly
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No

The use of the technology

13. Will the technology be easier or more difficult to use for patients or	Same level of difficulties as current care.

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.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes we should define rules to start and stop. No additional testing needed.
15. 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?	No
16. 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	No, but will give another option of treatment.

way that current need is met?	
16a. Is the technology a 'step-change' in the management of the condition?	No
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, limited options available.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	No

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	n/a
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	reduction in headache pain (including freedom from pain), speed of onset, regain of normal functioning, health-related quality of life.

18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	n/a
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance XXXX?	No
21. How do data on real-world experience compare with the trial data?	It's a good reflection of the population being treated.

Add any topic-specific questions here or delete if not needed

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	n/a

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• There is no cure for migraine but atogepant can represent a good treatment option. • Atogepant is unlikely to cause medication overuse headaches which is a significant burden in this population • Outcome chosen are realistic and measurable • This treatment option should be allowed to be offered in primary care •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Atogepant for treating migraine [ID6615]

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.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

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 **27 April 2026.** 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.

Part 1: Treating migraine and current treatment options

Table 1 About you, aim of treatment, place and use of atogepant, sources of evidence and equality

1. Your name	Callum Duncan
2. Name of organisation	NHS Grampian
3. Job title or position	Consultant Neurologist
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 atogepant ? ☐ 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 ? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Acute treatment – to abort the migraine attack within 2 hours or to significantly reduce the severity of the (and disability associated with) attack. For the attack not to recur. Prevent Medication Overuse Headache Preventative treatment – to reduce the frequency and severity of attacks, to prevent the development of chronic migraine (prevent progression).

9. What do you consider a clinically significant treatment response?	Acute treatment: Headache freedom or significantly reduced headache severity at 2 hours. No recurrence of headache (usually assessed as headache freedom at 24 or 48 hours). Effective in 3 out of 4 attacks (as defined by EHF guidance on Triptans).
10. In your view, is there an unmet need for patients and healthcare professionals in migraine?	Yes. Triptans very effective, but a proportion of patients do not respond to or do not tolerate triptans and have failed other acute treatment options. Triptans are contraindicated in those with a history of cerebrovascular of cardiovascular events or uncontrolled hypertension. Medication Overuse Headache is a risk for all current acute treatments other than Rimegepant. Rimegepant is currently recommended for patients who have failed adequate trials of 2 triptans. This is not effective for all these patients, and a second CGRP antagonist option would be useful.
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 across the NHS? (Please state if your experience is from outside England.) • What impact would atogepant have on the current pathway of care?	NICE criteria for the use Rimegepant for acute migraine treatment BASH Headache Management Guidelines SIGN 155: Pharmacological Management of Migraine National Headache Pathway (Scotland – Centre for Sustainable Delivery) Neurology pathways | Right Decisions Yes pathways are well defined and the opinion of headache professionals across the UK is broadly similar. I am a headache neurologist based in Scotland and am chair of SIGN 155 and chair and stream lead for the National Headache Pathway. 1st line Aspirin 900mg or Ibuprofen 400-600mg as abortive treatment. Paracetamol 1g has a limited role in those who are pregnant or have mild attacks. 2nd line Triptans. The effect is idiosyncratic and if one fails then others should be used. At least 2 should be trialled, the mode of administration should be considered (oral, nasal, subcutaneous), and combination treatment should be considered. See National Headache Pathway for detail.

	3rd line Rimegepant when triptans not tolerated or contraindicated and 1st and 2nd line options not effective. I would envisage Atogepant being used as a 3rd line option with the same parameters as Rimegepant as an alternative to Rimegepant and where Rimegepant not effective.
12. Will atogepant 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 atogepant and current care? • In what clinical setting should atogepant be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce atogepant ? (for example, for facilities, equipment, or training)	Atogepant is already used as a preventative treatment option. It is not currently used for the acute treatment of migraine. Atogepant would be a second option to Rimegepant in patients who do not respond to simple analgesics (or where they are contraindicated / not appropriate) and not responded to 2 or more triptans where they have been appropriately used or where triptans are contraindicated. I suggest it would be an alternative option to Rimagepant and unless clinical evidence suggests otherwise they should both be options rather than mandating one is used ahead of the other. Atogepant (as an acute treatment) should be an option in primary care. Appropriate guidance can be given and if referral to secondary care is required this may increase waiting times etc. Atogepant (as an acute treatment) would be an additional treatment in an established pathway and no additional investment would be required.
13. Do you expect atogepant to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes. Rimegepant has been a useful additional treatment option in patients who do not respond to simple analgesics and triptans. It would be beneficial to have a second CGRP antagonist option to use in the same part of the pathway as Rimegepant. I would expect some patients to respond to Atogepant who do not respond to Rimegepant, in the same way we see with the triptans.
14. Are there any groups of people for whom atogepant would be more or less effective (or appropriate) than the general population?	Atogepant is more appropriate in patients with cardiovascular contraindications where triptans and NSAIDs are not appropriate. As Atogepant is also used as a preventative treatment, Medication Overuse Headache is not going to be a concern and CGRP antagonists may be more appropriate where MOH is a current issue.

15. Will atogepant 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)	It should be straight forward to use in established treatment pathways and straightforward to use in primary care. It would be an additional treatment. No specific measures or monitoring would be required.
16. Will any rules (informal or formal) be used to start or stop treatment with atogepant ? Do these include any additional testing?	I would envisage the same rules as for Rimegepant – after adequate trials of simple analgesia and at least 2 triptans. I would use as an additional option to Rimegepant. I would limit use to 10 days per month (if used and an acute treatment) in the same way as triptans. If not adequately effective it should be stopped. EHF suggests effectiveness in 3 out of 4 attacks. These rules are established and not extra testing required.
17. Do you consider that the use of atogepant 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	Not an expert on this, but no
18. Do you consider atogepant 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? • Does the use of the technology address any particular unmet need of the patient population?	Yes – I agree with the opinion set out in the BASH submission re innovation. CGRP antagonists are a step change in that we have a treatment option for patients who fail current treatment options up to and including triptans and for those with cardiovascular contraindications where current options are limited. It is important to have more than one option and atogepant would provide that second option.

19. How do any side effects or adverse effects of atogepant affect the management of migraine and the patient's quality of life?	The CGRP antagonists are well tolerated medications and have less side effects than triptans. Atogepant: Constipation (10%) and nausea (2%) may be managed with usual first line medication if they occur and are not anticipated to be a reason that individuals stop taking using the medication, unless severe. The benefits of using atogepant as an acute treatment for migraine will outweigh the potential adverse events and improve quality of life.
20. Do the clinical trials on atogepant 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?	The ECLIPSE study involved a placebo-controlled trial of efficacy, safety and tolerability of atogepant as an acute treatment for migraine with relevant primary outcomes in line with UK clinical practice. It did not test individuals who have failed triptans previously. 2 hour pain freedom / pain relief and 2 hour freedom from most bothersome symptom and 24 hour pain freedom. As per BASH – time to pain relief which allows the individual to function and tolerability are the most important clinical outcomes. Atogepant is used in the UK as a preventative treatment and no unexpected adverse events have emerged thus far.
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 since the publication of NICE technology appraisal guidance [TA919]?	No
23. How do data on real-world experience compare with the trial data?	Real world evidence currently limited and so not able to comment.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. 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	As per BASH, I would recommend access is recommended with GREEN formulary status. This would allow timely use (ie not wait for secondary care opinion), would not adversely affect secondary care waiting lists and would avoid unwanted geographical variation across the UK.

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.	I do not think there are any specific issues that will affect groups included in equality legislation over the general population.
25. Please comment on the clinical equivalence between atogepant and rimegepant (Link to TA919). • Do you anticipate them to be offered in a similar position of the treatment pathway? If not, where would they differ? • Do you consider them to be clinically equivalent? (for example, similar efficacy and safety for the	I think that atogepant and rimegepant should be considered in the same position in the treatment pathway as already outlined (Q12 and 16). I think they will be clinically equivalent (both effectiveness and safety), but some patients may respond to one when they do not respond to the other in the same way we see for triptans.

intended population) If not, please explain why they might be different?	There is currently more evidence for Rimegepant in the clinical domain and Rimegepant have specifically looked at triptan non-responders and those with triptan contraindications in post hoc analysis and a phase 4 trial.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Low risk, well tolerated effective acute treatment

Provides an alternative to triptans when they do not work or are not an option due to contraindications

Important to have a second CGRP antagonist option

Access is best in primary care via GREEN formulary status

An additional treatment to improve the function and quality of life in individuals with migraine, not currently served by available options

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Atogepant for treating migraine [ID6615]

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.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

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 **27 April 2026.** 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.

Part 1: Treating migraine and current treatment options

Table 1 About you, aim of treatment, place and use of atogepant, sources of evidence and equality

1. Your name	Olga Tanda
2. Name of organisation	UK Clinical Pharmacy Association
3. Job title or position	Standards and Consultations Lead
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 atogepant ? ☐ 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.	No links
8. What is the main aim of treatment for migraine ? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Migraine is a neurological condition with no definitive cure. The primary aim of treatment is to improve patients' quality of life and reduce the frequency of migraine attacks. In some cases, patients receiving effective prophylactic treatment may become migraine-free.

9. What do you consider a clinically significant treatment response?	- **Acute treatment:** reduction in pain at 2 hours, pain freedom at 2 hours, and a low recurrence rate. - **Prophylaxis:** • ≥50% reduction in monthly migraine days for episodic migraine • ≥30% reduction in monthly migraine days for chronic migraine
10. In your view, is there an unmet need for patients and healthcare professionals in migraine?	Yes, particularly regarding **oral treatment options** for both acute and preventive management.
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 across the NHS? (Please state if your experience is from outside England.) • What impact would atogepant have on the current pathway of care?	Relevant guidelines include: • NICE guideline CG150 • SIGN guideline 155 • British Association for the Study of Headache (BASH) guidelines There is significant **geographical variation and inconsistency** in migraine pathways across the NHS. In some areas, patients can access gepants in primary care, while in others access requires specialist recommendation and, in some cases, prolonged specialist assessment. Atogepant is currently used as a **prophylactic option** after failure of at least three lower-cost preventive treatments, each tried at an appropriate dose for at least three months. If approved for **acute treatment**, atogepant could provide an alternative to rimegepant, a drug from the same class with a similar mechanism of action.
12. Will atogepant 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 atogepant and current care? • In what clinical setting should atogepant be used? (for example, primary or secondary care, specialist clinic)	At present, atogepant is used solely as a preventive option following failure of primary-care prophylactic therapies. As an **acute treatment**, it would likely be used in **primary care**, similarly to rimegepant. No additional investment in facilities, equipment, or training would be required.

• What investment is needed to introduce atogepant ? (for example, for facilities, equipment, or training)	To improve migraine management at Integrated Care Board (ICB) level, consideration could be given to **community-based headache clinics** led by trained non-medical prescribers (e.g. pharmacists, advanced clinical practitioners, or specialist nurses).
13. Do you expect atogepant to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase health-related quality of life more than current care?	Atogepant is unlikely to offer substantially greater benefits than rimegepant but may provide an **alternative option** for patients who experience better tolerability or a different clinical response.
14. Are there any groups of people for whom atogepant would be more or less effective (or appropriate) than the general population?	Atogepant may be particularly beneficial for patients with **medication-overuse headache**, as evidence from prophylactic studies suggests good efficacy in this population. Gepants do not cause medication-overuse headache, which is a key advantage. (Goadsby PJ, Friedman DI, Holle-Lee D, Demarquay G, Ashina S, Sakai F, Neel B, Gandhi P, Dabruzzo B, Smith JH, Liu Y, Trugman JM. Efficacy of Atogepant in Chronic Migraine With and Without Acute Medication Overuse in the Randomized, Double-Blind, Phase 3 PROGRESS Trial. Neurology. 2024 Jul 23;103(2):e209584.)
15. Will atogepant 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)	Atogepant has a similar ease of use and practical profile to rimegepant, which is already established in practice.
16. Will any rules (informal or formal) be used to start or stop treatment with atogepant ? Do these include any additional testing?	1. Acute treatment with atogepant should be considered where: • At least two triptans, each used in a minimum of three attacks, have failed, **or** • The patient has cardiovascular or other contraindications to triptans.

17. Do you consider that the use of atogepant 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	No additional substantial benefits are anticipated beyond those captured by standard quality-of-life measures.
18. Do you consider atogepant 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? • Does the use of the technology address any particular unmet need of the patient population?	Atogepant offers similar benefits to rimegepant. However, in patients with chronic migraine, atogepant could potentially be used for both **preventive and acute treatment**, avoiding the need to combine separate gepants.
19. How do any side effects or adverse effects of atogepant affect the management of migraine and the patient's quality of life?	The most common adverse effects are constipation and nausea or other gastrointestinal symptoms, which may occasionally lead to discontinuation. Atogepant remains under **black triangle monitoring**, and all suspected adverse drug reactions should be reported.
20. Do the clinical trials on atogepant 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?	Clinical trials reflect UK practice for prophylactic use. However, class effects cannot be assumed, as rimegepant was ineffective in chronic migraine prophylaxis, whereas atogepant demonstrated benefit. The ECLIPSE study has been presented in preliminary form but has not yet been published. Key outcomes include pain freedom and low recurrence. Post-marketing safety data suggest rare possible adverse effects such as alopecia and Raynaud's phenomenon.

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	A systematic review of spontaneous reporting system data (Giacon M, Terrazzino S. Post-marketing safety of CGRP monoclonal antibodies and gepants: A systematic review of spontaneous reporting system data. Headache. 2026 Mar 15. doi: 10.1111/head.70081.) identified some suspect drug reactions of alopecia and Raynaud's phenomenon across both monoclonal antibodies and gepants.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	None known.
22. Are you aware of any new evidence for the comparator treatment since the publication of NICE technology appraisal guidance [TA919]?	Zhang M, Guo A, Wu J, et al. Rimegepant for the acute treatment of migraine: A phase 3, multicenter, open-label, long-term safety and effectiveness study in adults from China. *Cephalalgia*. 2026;45(10). Tepper SJ, Jenkins A, Henriksen C, et al. A comparison of the persistence of acute treatment with rimegepant versus oral triptans in patients with migraine: A retrospective analysis of US claims data. *Cephalalgia*. 2025;45(7). doi:10.1177/03331024251352849 Ashina M, McAllister P, Gaul C, et al. Rimegepant for acute treatment of migraine in triptan-unsuitable adults: A randomized, double-blind, placebo-controlled phase 4 trial. *Cephalalgia*. 2025;45(11). Ailani J, Pavlovic J, Pixton GC, Fullerton T. Rimegepant safety and patient-reported outcomes among triptan-naïve, triptan-using, and triptan-failure participants: Subgroup analysis of an open-label, multicenter study. *Cephalalgia*. 2025;45(7).
23. How do data on real-world experience compare with the trial data?	Real-world data broadly reflect the populations treated in clinical trials.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. 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	No specific equality issues have been identified.

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.	
25. Please comment on the clinical equivalence between atogepant and rimegepant (Link to TA919). • Do you anticipate them to be offered in a similar position of the treatment pathway? If not, where would they differ? • Do you consider them to be clinically equivalent? (for example, similar efficacy and safety for the	Atogepant and rimegepant are expected to occupy a similar position in the treatment pathway. They are not clinically equivalent but are closely related. Atogepant has shown greater effectiveness in chronic migraine prophylaxis, and differences in acute efficacy cannot be excluded.

intended population) If not, please explain why they might be different?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Rimegepant and atogepant are likely to occupy similar positions within the migraine treatment pathway; however, a broader review of headache services is warranted, including consideration of integrated clinics led by pharmacists, ACPs, or specialist nurses to improve care while managing cost pressures.

The effectiveness of atogepant as an acute treatment remains difficult to assess in the absence of published clinical trial data, and class effects should not be assumed.

Gepants represent a valuable option for patients with medication-overuse headache and may help reduce inappropriate opioid use, alongside interventions such as greater occipital nerve blocks.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Atogepant for treating migraine [ID6615]

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.

NICE National Institute for Health and Care Excellence

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **27 April 2026.** 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.

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	Debbie Shipley
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: ☐ I have not completed part 2 of the statement
6. What is your experience of living with migraine ?	

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?**	
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	
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**	
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	

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	
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.	
13. Are there any other issues that you would like the committee to consider?	

NICE National Institute for Health and Care Excellence

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Atogepant for treating migraine [ID6615]

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.

NICE National Institute for Health and Care Excellence

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **27 April 2026.** 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.

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	Oscar Harvey
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: ☐ I have not completed part 2 of the statement
6. What is your experience of living with migraine ?	

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?**	
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	
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**	
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	

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	
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.	
13. Are there any other issues that you would like the committee to consider?	

NICE National Institute for Health and Care Excellence

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

BMJ TAG

Atogepant for treating migraine [ID6615]

Cost-comparison Technology Appraisal

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 177942.

Title:	Atogepant for treating migraine [ID6615]
Produced by:	BMJ Technology Assessment Group (BMJ-TAG)
Authors:	Steve Edwards, Director of Health Technology Assessment, BMJ-TAG, London Melina Vasileiou, Clinical Evidence Analyst, BMJ-TAG, London Tracey Jhita, Health Economics Manager, BMJ-TAG, London Victoria Wakefield, Principal Clinical Evidence Analyst, BMJ-TAG, London Ben Burges, Senior Clinical Evidence Analyst, BMJ-TAG, London
Correspondence to:	Steve Edwards, BMJ-TAG, BMJ Group, 5th Floor, 90 Whitfield Street, London W1T 4EZ, UK.
Date completed:	09/04/2026
Source of funding:	This report was commissioned by the NIHR Evidence Synthesis Programme as project number 177942.
Declared competing interests of the authors	No competing interests were declared which affect the impartiality of this report. BMJ Technology Assessment Group (BMJ-TAG) and the editorial team of The BMJ work independently to one another. The views and opinions expressed in this report are those of the BMJ-TAG.
Acknowledgments:	The EAG would like to thank Dr Nicola Giffin (Consultant Neurologist, Royal United Hospital NHS Trust) and Dr Abhit Chadhuri (Consultant Neurologist, University Hospital Plymouth NHS Trust and Nuffield Health Glasgow Hospital) for providing clinical advice throughout the project and feedback on the clinical and health economic sections of the report.
Rider on responsibility for report:	The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.
Report reference:	Edwards SJ, Vasileiou M, Jhita T, Wakefield V, Burgess B. Atogepant for treating migraine: A Cost-comparison Technology Appraisal. BMJ Technology Assessment Group, 2026.

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
Melina Vasileiou	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, background and clinical results sections
Victoria Wakefield	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and assisted with drafting the clinical results sections
Ben Burgess	Validation of the company's analyses; conduct of the EAG's additional analyses; assisted with drafting the clinical results sections
Tracey Jhita	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 background and economic sections

All authors read and commented on draft versions of the EAG report.

Checklist for submission

Item	Complete
All guidance notes highlighted in yellow from the template have been deleted or edited as necessary with highlighting removed from edited text unless AIC or CIC marking required.	Yes
All data from the CS have been validated	Yes
All calculations have been validated	Yes
All tables and figures are referenced in text	Yes
The table and figure references are sequential (use ctrl and A then F9 to update all fields in the document)	Yes
CiC markup: • all commercial in confidence numbers are highlighted in **********	Yes
Abbreviations have been added to every table in the report (including abbreviations in table caption)	Yes
Abbreviations have been compiled in a list in the front of the report	Yes
Abbreviations defined at the beginning of every major section	Yes
New page for the start of every major section (i.e. 1, 2, 3, 4, etc.)	
Spell check complete	Yes
Search and remove all double spaces (i.e.extra blank spaces) in the text using Ctrl f	Yes
All tables are formatted to BMJ style	Yes
First two pages of report have been completed.	Yes
All in-text citations are superscript	Yes
Generate bibliography	Yes
Manually format reference list	Yes
Copy edit and manually format automatically generated table of contents	Yes
All comments and track changes have been removed	Yes
Final version has been checked for formatting inconsistencies - section, figure, table headings shouldn't be "stranded" on the page before (i.e. ctrl+rtn to have a hard page break to stop this happening)	Yes
Ensure file name of version sent to NICE contains ID, drug/condition, document description and confidentiality marker.	Yes
Project number in header of email to NICE project team contacts and esptar@nihr.ac.uk	Yes

Table of Contents

List of Tables

List of Figures

List of Abbreviations

AEs	Adverse events
AI	Artificial intelligence
BMI	Body mass index
CfB	Change from baseline
CGRP	Calcitonin gene-related peptide
CI	Confidence interval
CrI	Credible interval
CSR	Clinical study report
DIC	Deviance information criterion
DSU	Decision Support Unit
EAG	External Assessment Group
ECG	Electrocardiogram
EQ-5D-5L	EuroQol 5-Dimension 5-Level
FE	Fixed effect
GLMM	Generalised linear mixed effects model
GP	General practitioner
HRQoL	Health-related quality of life
ICBs	Integrated Care Boards
ITT	Intention-to-treat
LS	Least squares
MBS	Most bothersome symptom
MCID	Minimum clinically important difference
MCMC	Monte Carlo Markov chains
MHRA	Medicines and Healthcare products Regulatory Agency
MMD	Monthly migraine days
MMRM	Mixed model for repeated measures
MQoLQ	Migraine Quality of Life Questionnaire
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NIM	Non-inferiority margin
NMA	Network meta-analysis
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
PAS	Patient Access Scheme
PSS	Personal Social Services
QD	Once daily
RCT	Randomised controlled trial
RE	Random effects

RoB	Risk of bias
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TSD	Technical Support Document
UK	United Kingdom
ULN	Upper limit of normal
USA	United States of America
VAS	Visual analogue scale
VP	Vague prior

1 Executive summary

A cost-comparison analysis was developed by the company to assess atogepant compared with rimegepant for the acute treatment of migraine with or without aura in adults who have either tried at least two triptans that did not work well enough or have contraindications or intolerance to triptans and have tried non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol without an adequate response.

To be considered for a cost-comparison technology appraisal, the National Institute for Health and Care Excellence (NICE) requires the intervention under review to be clinically similar to one treatment that NICE has previously recommended in technology appraisal guidance for the same indication. Rimegepant has previously been recommended by NICE as an option for the acute treatment of migraine with or without aura in adults, only if for previous migraines at least 2 triptans were tried and they did not work well enough or triptans were contraindicated or not tolerated, and NSAIDs and paracetamol were tried but did not work well enough (TA919).

Generally, the External Assessment Group (EAG) considers that, based on the clinical and cost-effectiveness evidence presented by the company, it is likely that atogepant and rimegepant are clinically similar for the treatment of acute migraine. Therefore, all else being equal, the EAG considers that atogepant is likely to be cost-saving compared with rimegepant, primarily due to its lower acquisition cost per tablet.

The EAG believes none of the issues discussed below would preclude a cost-comparison appraisal from being appropriate, but highlights them as limitations or factors for the committee to be aware of:

- the EAG considers the population included in the company's submission to be appropriate and consistent with previous NICE appraisals; however, the evidence is primarily based on patients with episodic migraine and may not fully represent all patients seen in routine clinical practice, such as those with chronic migraine, medication overuse, or greater prior treatment experience, who may have different treatment responses;
- the company's use of a random effects model with informative priors did not materially affect the results of the network meta-analyses (NMAs); however the company's justification for using informative priors based on concerns regarding sparse data may not fully apply, given the number of trials available to inform the network;

- the company's conclusion of clinical equivalence between atogepant and rimegepant is not supported by formal equivalence or non-inferiority analyses; the absence of statistically significant differences in the NMA indicates a lack of evidence of difference rather than evidence of clinical equivalence, which would require pre-specified margins and appropriate statistical methods and the EAG's additional analyses further highlight the uncertainty in the relative effectiveness estimates, introducing uncertainty in the assumption of comparable clinical effectiveness underpinning the cost-comparison approach. However, taking a pragmatic view of all the available evidence, including similarities in mechanism of action, administration method and clinical positioning, the EAG considers the treatments are likely to have broadly similar effectiveness.

The EAG notes that the 28-tablet pack of atogepant is substantially less expensive per tablet than the 2- and 7-tablet packs used in the company's base case. The company and the EAG's clinical experts expect atogepant to be prescribed in the same way as rimegepant, occurring in both primary and secondary care. Hospital and community prescribing may dispense from the most cost-effective pack size or prescribe smaller packs, thus the EAG recommends the committee consider potential cost savings as a range:
**********.

2 Background

Migraine is a neurological disorder characterised by recurrent attacks of moderate to severe headache lasting 4 to 72 hours, often accompanied by nausea, light and sound sensitivity and functional impairment.[1] Globally, migraine affects roughly 14% of people (about 1 in 7) and is among the leading causes of disability worldwide.[2]

Migraine exists on a spectrum from episodic migraine (<15 headache days/month) to chronic migraine, defined as headaches occurring 15 or more days/month for >3 months, with migraine features on ≥8 days/month.[3] Chronic migraine is associated with higher disability and healthcare utilisation compared with episodic forms.[3]

In the United Kingdom (UK), migraine affects an estimated 10 million people aged 15–69, making it one of the most prevalent neurological conditions.[4] People with migraine make frequent use of healthcare services, including general practitioner (GP) visits and emergency care, contributing significantly to NHS workload and costs. Annual NHS spending on migraine treatments and related headache care has been estimated at around £150 million.[5] Beyond direct costs, migraine has a considerable impact on productivity: work absence and reduced effectiveness while working contribute to tens of millions of lost workdays annually in the UK.[6] Estimates suggest over 40 million work or education days lost each year due to migraine with economic losses of billions to the UK economy.[7]

Section 1.3 of the company submission (CS) summarises the disease, including its epidemiology, diagnosis, disease and economic burden and current clinical pathway in the UK. Based on the information provided, and discussion with clinical experts, the External Assessment Group (EAG) considers that this information accurately reflects clinical practice.

The focus of this cost-comparison appraisal is atogepant as an acute treatment of migraine on a subset of its anticipated marketing authorisation, that is aligned with the population for which rimegepant is recommended for the treatment of migraine (NICE TA919).[8] Specifically, for the acute treatment of migraine in adults who have either:

- Tried at least two triptans and they did not work well enough, or
- Have contraindications or intolerance to triptans, and have tried non-steroidal non-inflammatory drugs (NSAID) and paracetamol without adequate response.

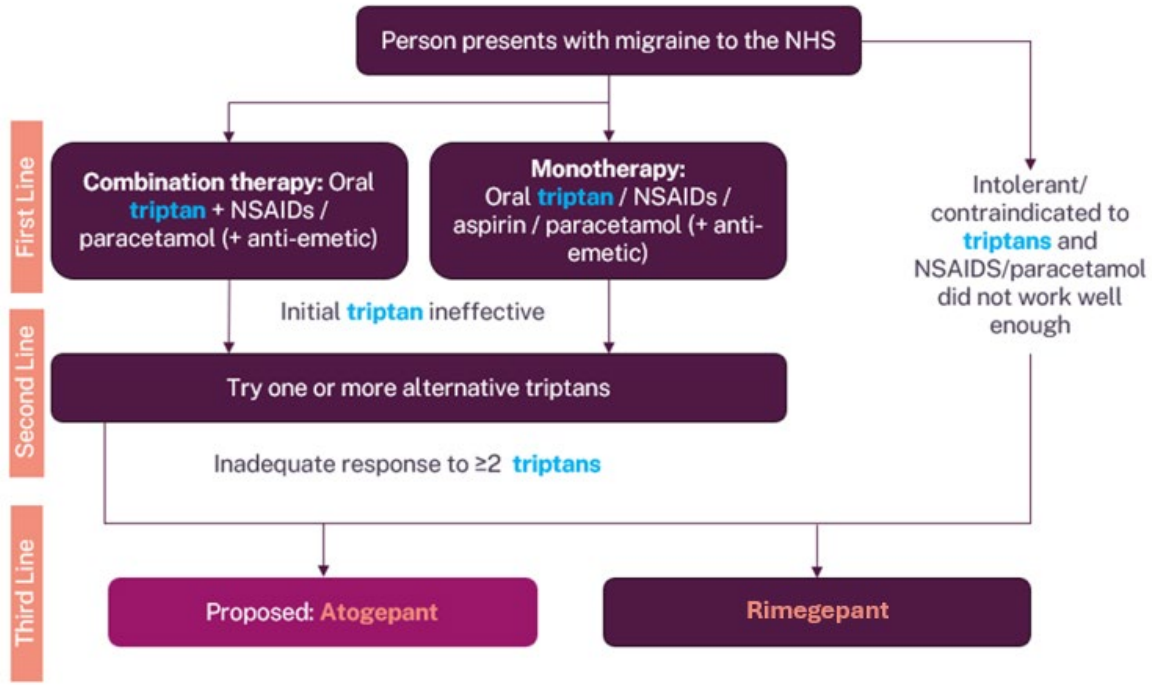
Atogepant is an orally administered calcitonin gene-related peptide (CGRP) receptor antagonist, approved for the preventive treatment of episodic and chronic migraine (TA973).[9] It acts by blocking CGRP receptors, stops the transmission of this neurotransmitter, which is elevated during migraine attacks, causing increased pain sensitivity and inflammation. Atogepant is an oral tablet taken as needed with a maximum recommended dose of 60 mg per day.[10]

The current treatment pathway for the acute treatment of migraine in the UK (including the proposed place for atogepant) was presented in the CS and is reproduced in Figure 1 below. The company intends for atogepant to be positioned alongside rimegepant in the third line of therapy after previous options have been exhausted.

Feedback from the EAG clinical experts suggested the company's pathway is partly consistent with UK practice; however, they noted that in routine care, many patients would typically undergo further optimisation of acute therapies before escalation to a gepant. This includes use of non-oral triptan formulations (e.g. subcutaneous or intranasal), particularly where oral triptans are ineffective due to delayed administration or vomiting, as well as trial of alternative triptans. Experts also noted that combination therapy (triptan plus NSAID with or without an anti-emetic) is generally more effective than triptan monotherapy and would be expected to be optimised in practice. EAG clinical experts indicated that these nuances are not fully captured in the company's pathway or in TA919, which focuses on the number of prior triptan trials rather than the manner of optimisation. As such, the treatment pathway presented may be simplified compared to clinical practice. Experts also noted that treatment pathways may vary by region and prescribing setting, with rimegepant available in primary care in some areas, whereas access to atogepant may be more restricted and typically initiated in secondary care.

Therefore, the EAG considers that the company's decision problem may represent a more treatment-experienced group than the broader population addressed by the company, and the implications of excluding further optimisation of acute therapies used in practice should be considered when interpreting the appropriateness of rimegepant as the only comparator.

Figure 1. The current treatment pathway for migraine in the UK and the proposed place for atogepant (reproduced from Figure 2 in the CS)



Abbreviations: NSAID, non-steroidal anti-inflammatory drug.

3 Critique of the decision problem in the company's submission

The company provided a summary of the final decision problem issued by the National Institute for Health and Care Excellence (NICE), together with the rationale for any deviation from it, in Section 1.1 of the company submission (CS). The CS covers only a subpopulation of those included in the anticipated marketing authorisations for atogepant. Atogepant is expected to be authorised for the acute treatment of migraine with or without aura in adults. The cost comparison only focuses on people in this group who have either tried at least two triptans that did not work well enough or have contraindications or intolerance to triptans and have tried non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol without an adequate response. The population matches that recommended for rimegepant in TA919.[8] The External Assessment Group (EAG) therefore considers this an appropriate subgroup of the population on which to base the cost-comparison for atogepant. A summary of the final scope issued by NICE, the decision problem addressed in the CS and the EAG's critique of this is provided in Table 1.

Table 1. Summary of decision problem as outlined in the company submission

	Final scope issued by NICE	Decision problem addressed in the submission	EAG comment
Population	Adults with migraine (with or without aura)	Acute treatment of migraine with or without aura in adults who have either: Tried at least two triptans and they did not work well enough, or Have contraindications or intolerance to triptans, and have tried NSAIDs and paracetamol without adequate response	The population addressed in the submission is narrower than the original NICE scope. However, it matches that recommended for rimegepant in TA919 and so the EAG considers this appropriate. However, the EAG's clinical experts noted that in routine UK practice, further optimisation of acute therapies (combining a triptan with a NSAID and anti-emetic and considering non-oral preparations) may occur before initiation of a gepant, meaning that patients treated in practice may be more treatment-experienced

			than implied by the company.
Intervention	Atogepant	Atogepant (60mg) as needed, once daily	N/A – in line with final scope.
Comparator(s)	• Rimegepant • Paracetamol, with or without an anti-emetic • An NSAID (such as aspirin, ibuprofen, diclofenac or naproxen), with or without an anti-emetic • An oral or non-oral triptan (such as sumatriptan, zolmitriptan, rizatriptan, almotriptan or eletriptan), with or without an anti-emetic • Paracetamol with an oral or non-oral triptan, with or without an anti-emetic • An NSAID with a triptan, with or without an anti-emetic • Best supportive care	Rimegepant (75 mg) as needed once daily	Given the company's positioning of atogepant in the same population as rimegepant, where options used in earlier lines of treatment, including triptans and other analgesics, have been exhausted, the EAG considers the company's focus on rimegepant as the sole comparator appropriate. However, clinical experts indicated that further optimisation of acute therapies (e.g. trial of alternative triptans, use of non-oral formulations where needed, and combination therapy including a triptan, NSAID and anti-emetic) may occur in routine practice before a gepant.
Outcomes	The outcome measures to be considered include: • Reduction in headache pain (including freedom from pain) • Speed of onset • Freedom from most bothersome symptom • Reduction in nausea and vomiting • Reduction in hypersensitivity (e.g. light, sound, smell) • Regain of normal functioning • Prevention of recurrence • Use of rescue medication • Adverse effects of treatment • Health-related quality of life.	• Pain freedom • Pain relief • Sustained pain relief • Sustained pain freedom • Freedom from most bothersome symptom • Use of rescue medication • Ability to function normally • Absence of photophobia, phonophobia and nausea • Adverse effects • Health-related quality of life	Based on advice from clinical experts, the EAG considers that the outcomes presented in the CS and included in the company's network meta-analyses are clinically relevant to the decision problem and address the NICE final scope.

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. As the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out. 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 Personal Social Services perspective. The availability and cost of biosimilar and generic products should be taken into account.	• A cost-comparison analysis has been conducted in Microsoft Excel to estimate the incremental costs of atogepant versus rimegepant. • The time horizon for assessing costs was set to 2 years, which is sufficiently long to capture the majority of costs associated with the use of atogepant. • Costs were considered from an NHS and PSS perspective.	Appropriate.
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • Subgroups defined by migraine severity • People currently having treatment for the prevention of migraine • People for whom triptans do not work well enough, are contraindicated or not tolerated • Subgroups defined by the number of previous treatments • People with or who are at risk of	This submission will focus on the acute treatment of patients with migraine who have had at least two prior triptans and they did not work well enough, or triptans were contraindicated or not tolerated. This is in line with the final recommended population for rimegepant.	Considering the narrower decision problem population, the company limited subgroup analyses to those pre-specified in ECLIPSE (baseline migraine severity and preventive migraine medication use). Clinical expert opinion suggested limited effect modification for acute response based on subgroups. However, although not pre-specified in the

	medication overuse and developing associated symptoms including medication-overuse headache • Subgroups defined by severity or number of headache days per month		ECLIPSE trial, exploration of aura status and age may have provided additional reassurance regarding generalisability.

Abbreviations: CS, company submission; EAG, External Assessment Group; NICE, National Institute for Health and Care Excellence; NSAIDs, non-steroidal anti-inflammatory drugs; PSS, Personal Social Services.

3.1 Population

Alignment to NICE final scope and population in England

The NICE final scope focuses on all adults with migraine (with or without aura). The company chose to focus on a subpopulation of this group, representing a narrower population than the anticipated marketing authorisation (MA). It is intended for use for the acute treatment of migraine with or without aura in adults who have either:

- Tried at least two triptans that did not work well enough, or;
- Have contraindications or intolerance to triptans & have had NSAID and paracetamol without adequate response.

This is in line with the population included in NICE TA919 for rimegepant.[8] The EAG's clinical experts broadly agreed with the company's choice to focus on this subpopulation, given the choice to present a cost comparison against rimegepant. However, they noted that this population may not fully reflect the wider group of patients seen in clinical practice, because many patients would be expected to try optimised triptan strategies (including non-oral triptans and triptan + NSAID with/without antiemetic combinations) before escalation to a gepant. Therefore, based on clinical expert feedback, the EAG notes the company's population may be narrower than expected in clinical practice in England, but considers the company's choice to align with TA919 appropriate.

The EAG's clinical experts considered the population of the ECLIPSE trial broadly represented the population of interest, noting that the trial included patients aged up to 75 years, which is a broader upper age limit than often seen in other trials. However, the exclusion of patients with high acute medication use (≥10 days per month), and the restriction to episodic migraine (<15 headache days per month), may limit representation of patients with chronic migraine or medication overuse headache, who are often seen in routine practice. These patients may be less likely to respond to

treatment, and uncertainty remains regarding the extent to which gepants contribute to medication overuse headache when used frequently.

In summary, the EAG considers the data presented within the CS to be broadly representative of patients with migraine who would be eligible to receive atogepant in England. The population aligns with the population for which rimegepant is recommended (TA919), and it is therefore an appropriate focus for this cost comparison.[8] However, based on clinical expert feedback, the ECLIPSE trial population may not capture patients seen in routine practice who have chronic migraine or high acute medication use, and who may have undergone further optimisation of triptan strategies before escalation to a gepant. These populations are often the most challenging to treat in clinical practice and it is uncertain whether the ECLIPSE data are generalisable to them.

3.2 Intervention

The intervention matched the NICE final scope. Atogepant (brand name Aquipta®) does not currently have a marketing authorisation, for the acute treatment of migraine with or without aura in adults in the UK, but this is expected in April 2026. The expected indication is for the acute treatment of migraine with or without aura in adults.

Atogepant is administered as an oral tablet, with the maximum dose per day being 60mg, on an as-needed basis. The EAG's clinical experts considered the method of administration and dose in the company submission and the ECLIPSE trial to be reflective of standard treatment.

3.3 Comparators

Given the company's positioning of atogepant for the acute treatment of the population described above (patients with migraine who have received prior treatment with ≥2 triptans that did not work well enough, or who have contraindications or intolerance to triptans and who have tried NSAIDs and paracetamol without adequate response), which aligns with the positioning used in NICE TA919 for rimegepant, the EAG considers the company's choice to present a cost-comparison against rimegepant as the sole comparator appropriate. The EAG notes that the similar mechanism of action of atogepant and rimegepant and a similar mode of administration also justify the company's position of atogepant in the treatment pathway.

However, the EAG notes that rimegepant is available as an orally disintegrating tablet/wafer, whereas atogepant is available as an oral tablet. In the experience of the EAG's clinical experts, orodispersible formulations may be easier for patients to take during migraine attacks, particularly

when nausea is present, and may therefore be preferred by some patients for acute treatment. They may also be quicker to act.

The EAG notes that clinical expert feedback indicated that, in routine UK practice, further optimisation of acute therapies would often occur prior to initiating a gepant, including use of non-oral triptan formulations (e.g. subcutaneous or intranasal) and combination therapy (triptan plus NSAID with or without anti-emetic). As such, the population in clinical practice may represent a more treatment-experienced subgroup than reflected in the CS. In addition, treatment pathways may vary by region and prescribing setting, with access to gepants differing across Integrated Care Boards (ICBs) and between acute and preventive indications. These factors may influence the positioning of gepants in practice and should be considered when interpreting the appropriateness of rimegepant as the sole comparator.

3.4 Outcomes

The outcomes in the CS broadly match those in the NICE final scope, including measures of pain relief, pain freedom, sustained pain freedom, adverse events and health-related-quality-of-life. In particular, the following outcomes reported in the ECLIPSE trial captured those specified in the decision problem: pain freedom at two hours (primary outcome), absence of most bothersome symptom (MBS), pain relief and sustained pain freedom, use of rescue medication, ability to function normally, health-related quality of life endpoints including the EuroQol 5-Dimension 5-Level (EQ-5D-5L), patients satisfaction with medication, migraine quality of life questionnaire, among other scales and adverse event monitoring. The EAG focuses its critique on the primary outcome from ECLIPSE, pain freedom at 2 hours and the key secondary outcome, pain relief at 2 hours, which informed the company's economic model.

As there was no direct head-to-head data for the comparison of atogepant with rimegepant, the company conducted network meta-analyses (NMAs) to assess the relative efficacy and safety of the two treatments. The outcomes of interest in the company's NMAs were:

- pain-freedom at 2 hours,
- absence of MBS,
- pain relief at 2 hours,
- sustained pain relief from 2 to 24 hours,
- sustained pain relief from 2 to 48 hours,
- use of rescue medication within 24 hours,

- ability to function normally at two hours,
- sustained pain freedom from 2 to 24 hours,
- sustained pain freedom from 2 to 48 hours, and
- any adverse event.

The EAG notes that health-related quality of life was not used in the company's NMAs. EAG clinical experts indicated that generic quality of life measures such as the EQ-5D-5L are not routinely used in clinical practice for migraine. Instead, disease impact is typically assessed through clinical discussion with patients, including questions about the number of migraine and headache days per month (often assessed using simple migraine diaries) and the extent to which attacks limit function. Nevertheless, the quality-of-life measures included in the ECLIPSE trial were consistent with those commonly used in migraine trials.

Overall, based on advice from clinical experts, the EAG considers that the outcomes presented in the CS and included in the company's NMAs are clinically relevant to the decision problem and address the NICE final scope.

3.5 Subgroups

The NICE final scope specified several potential subgroups of interest, including migraine severity, number of prior treatments, and risk of medication overuse. The company limited the decision problem to patients with ≥2 prior triptans that did not work well enough or not tolerated and therefore did not consider separate subgroup analyses beyond those pre-specified in ECLIPSE (baseline migraine severity and preventative medication use).

Clinical expert feedback suggested that most of the subgroup factors listed in the final scope would not be expected to materially modify response to acute gepants. However, patients with greater prior treatment failures or higher migraine severity may have reduced response to acute treatment overall. Aura status and potentially age may represent clinically relevant subgroups that could have been explored; however, substantial effect modification is not expected. In addition, subgroup analyses by number of previous treatments or number of headache days per month were not pre-specified and not conducted, and data on patients at risk of medication overuse headache were not collected. Although the EAG noted major effect modification is not anticipated, exploring these subgroups may have provided additional reassurance regarding generalisability.

4 Summary of the EAG's critique of clinical effectiveness evidence submitted

4.1 Critique of the methods review

The company conducted a systematic literature review (SLR) to identify randomised controlled trials (RCTs) that compared the efficacy and safety of atogepant and relevant comparators for the acute treatment of migraine. The External Assessment Group (EAG) considers the SLR methods used by the company to be reasonable, although it notes that the SLR was conducted from a global perspective and the reasons for the final exclusion of studies relevant to this cost comparison are not clearly detailed. Table 2 contains the EAG's assessment of the company's methods used for the SLR, with full details reported in Appendix B of the company submission (CS).

Table 2. 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	CS Appendix B, Section B.1.1	**Appropriate** The following databases were searched: • MEDLINE (via PubMed); • Embase (via Elsevier); • Cochrane Central Register of Controlled Trials (CENTRAL); • Cochrane Database of Systematic Reviews; • MEDLINE In-process (via PubMed); • Epistemonikos. In addition, relevant conference proceedings, HTA websites, clinical trial registries/regulatory sites and bibliographies of accepted full-text articles (including SLRs) were reviewed to obtain further relevant references.
Search strategies	CS Appendix B, Section B.1.1.1	**Appropriate** The search strategies used were appropriate for the decision problem and included the relevant population, intervention, comparator and study designs. The database searches were conducted on 4 August 2025. The main trial in the CS for atogepant (ECLIPSE) was identified retrospectively, and additional publications for it were provided by the company.

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods
Inclusion criteria	CS Appendix B, Section B.1.2.1	**Broader than the NICE final scope and study size restriction** The inclusion criteria for the SLR were broader than those specified in the NICE final scope and decision problem, which the company reported was due to the SLR being conducted for a global perspective. The relevance of the inclusion criteria for the final inclusion of studies in the company's network meta-analyses is discussed further in Section 4. The EAG notes that the inclusion criteria restricted studies to those published in English and those with a sample size of ≥50 patients and ≥25 patients per arm, but the EAG does not consider these criteria likely to have impacted on the resulting inclusion of studies relevant to atogepant.
Screening	CS Appendix B, Section B.1.2.2	**Appropriate** Abstract and full-text screening was completed by two independent investigators, with discrepancies resolved by a third reviewer.
Data extraction	CS Appendix B, Section B.1.2.3	**Appears reasonable although the use of artificial intelligence (AI) to support data extraction represents an atypical approach** Information from the full articles was extracted through the use of AI data queries in the Grok 4 tool11 (except for confidential or paywalled studies which were extracted manually by an investigator). The extracted data were independently validated for completeness and accuracy by an investigator, and any discrepancies were resolved and reviewed by a second investigator, as needed.
Tool for quality assessment of included study or studies	CS Appendix B, Section B.3 and C.3; CS, Section B.3.5	**Some concerns** Study quality was assessed using the Cochrane risk of bias tool. However, explanations for the quality judgement for each domain were not provided and the 'other bias' domain was not included in the company's quality assessment results summary tables. The EAG also notes that the Cochrane risk of bias tool used by the company was replaced in 2019 by the revised Cochrane risk-of-bias tool for randomised trials (RoB 2) although the updated version of the tool does not appear to have been used for the company's quality assessments.

Abbreviations: AI, artificial intelligence; CS, company submission; EAG, External Assessment Group; NICE, National Institute for Health and Care Excellence; SLR, systematic literature review

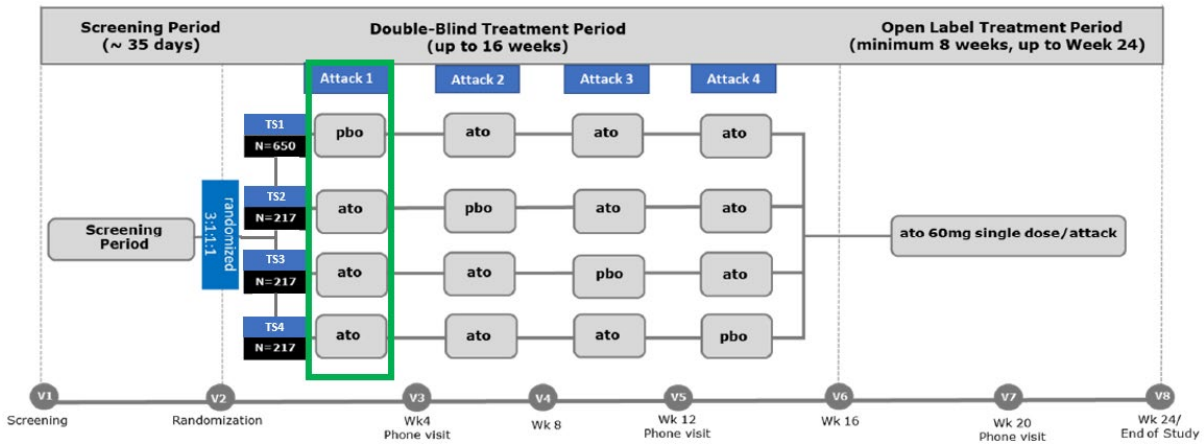
The SLR identified 4,074 records (after deduplication) in the search conducted in August 2025. A total of 279 full-text articles were screened and 169 of these articles (relating to 160 unique studies) met the global SLR inclusion criteria, with 1 study identified as relevant to atogepant. The included study with atogepant as the primary intervention was the Phase 3 ECLIPSE study, with data published at the European Headache Congress (EHC) 2025 and additional data available from the clinical study report.[11, 12] In addition, a further 7 of the remaining 159 studies were included in the company's indirect treatment comparisons (ITCs) and are discussed further in Section 4.4.1. The reasons for exclusion of the 152 remaining studies were not clearly detailed in the CS or it's appendices but a list of the titles of these studies is provided in the company's full list of included studies in the CS Appendix B.1.4.

4.2 Critique of trials of the technology of interest

4.2.1 ECLIPSE trial

The company's systematic literature review (SLR) identified one study that evaluated the efficacy of atogepant for adult patients with migraine, with or without aura, that was relevant to the decision problem. The ECLIPSE study (NCT06241313) was a Phase 3, randomised, double-blind, placebo-controlled, multiple-attack study with an open-label extension to evaluate the efficacy, safety, tolerability, and the consistency of effect of atogepant for the acute treatment of migraine in patients with a history of migraine (with or without aura).[11, 12] This 24-week trial consisted of two phases: an initial double-blind phase (up to 16 weeks) and a subsequent open-label phase (up to Week 24). Eligible patients were randomised (3:1:1:1) into four treatment sequence groups. During the double-blind phase, within 16 weeks, each patient treated one qualifying migraine with placebo and three with atogepant. Upon completion of these four treatments, they entered the OL phase, where all subsequent qualifying migraine attacks were treated with OL atogepant until the study concluded at Week 24. The study design of the ECLIPSE trial is displayed in Figure 2 below.

Figure 2. Study design of ECLIPSE trial (reproduced from CS, Figure 3)



Footnotes: The green box indicates the time period captured by the data presented within this submission; all key primary and secondary endpoints refer to data collected in Attack 1.

The key information for the trial is summarised in Table 3 below.

The External Assessment Group's (EAG's) critique of the design, conduct and analysis of the ECLIPSE trial is presented in Table 4 below. In line with the company's assessment, presented in the company submission (CS) section 3.5, the EAG considers ECLIPSE to be a high-quality trial at low risk of bias for the primary and key secondary outcomes. Overall, the EAG considers the eligibility criteria appropriate for the positioned population, although the restriction to episodic migraine and lower

acute medication use may modestly limit generalisability to patients with chronic migraine or medication overuse headache seen in clinical practice. Nevertheless, the EAG's clinical experts noted that the limited representation of patients with chronic migraine in acute treatment trials is not unique to this study but reflects a broader pattern in the evidence base. Furthermore, the NICE appraisal of rimegepant (TA919) did not distinguish between chronic and episodic migraine in its recommendations, despite the acute clinical evidence being derived primarily from patients with episodic migraine.[8] Therefore, while a restriction to episodic migraine may slightly limit generalisability, it is consistent with what is typically seen in acute migraine trials.

Table 3. Clinical effectiveness study of the technology of interest

	ECLIPSE (NCT06241313)
Role in this evaluation	Used as a key source of clinical effectiveness evidence. Included in the CS as a direct comparison with placebo and in the indirect treatment comparisons to help inform the company's comparisons between atogepant and rimegepant.
Study type	Phase III, randomised, double-blind, placebo-controlled, multiple-attack trial.
Patient group	Adults aged 18 to 75 years with a history of migraine (with or without aura) according to the ICHD-3 for ≥12 months, and with a history of 2 to 8 migraine attacks of moderate to severe headache pain in each of the three months prior to screening per investigator judgement.
Subgroups	Pre-planned subgroups: • Region (Europe, China, Japan or other), • Current use of prophylactic concomitant medication for migraine (yes or no), • Previous response to and use of triptans (triptan unsuitable, triptan experienced, or triptan naïve).
Exclusion criteria	Key exclusion criteria. Patients with: • Difficulty in distinguishing migraine headache from tension-type or other headaches, • History of an average of 15 or more headache days per month in the six months prior to Visit one/Screening/a current diagnosis of chronic migraine as defined by ICHD-3, • Current diagnosis of new persistent daily headache, trigeminal autonomic cephalalgia (e.g., cluster headache), and painful cranial neuropathy as defined by ICHD-3, • Hospital/emergency room treatment required for migraine attacks on three or more occasions within six months prior to Visit one/Screening, • ECG with clinically significant abnormalities, • QTcF > 450 msec for males or QTcF > 470 msec for females • Hypertension (sitting systolic blood pressure > 160 mm Hg or sitting diastolic blood pressure > 100 mm Hg at Visit one/Screening or Visit two/Randomisation), • Clinically significant abnormalities or laboratory values meeting any of the following criteria,

	ECLIPSE (NCT06241313)
	• ALT or AST > 1 × ULN, • Total bilirubin > 1 × ULN (except for subjects with a diagnosis of Gilbert's disease), • Serum albumin < 2.8 g/dL [4.06 µmol/L], • Presence of chronic, non-headache pain condition requiring daily pain medication, • History of hypersensitivity or clinically significant adverse reaction to a CGRP receptor antagonist, • Taken medication for acute treatment of headache (including acetaminophen, NSAIDs, triptans, ditans, ergotamine, opioids, gepants, or combination analgesics) 10 or more days per month in any of the 3 months prior to Visit 2/Randomisation, • Exposure to any gepant within 30 days prior to Visit 2/Randomisation, • Exposure to injectable monoclonal antibodies blocking the CGRP pathway within 6 months prior to Visit 2/Randomisation.
Intervention	Atogepant 60 mg (oral) tablets taken for the acute treatment of four qualifying migraine attacks during the double-blind treatment period (up to 16 weeks), after which subjects treated qualifying migraine attacks with atogepant 60 mg during the open-label treatment period until the end of the study at Week 24.
Comparator	Placebo
Duration	The total study duration consisted of a 35-day screening period, followed by up to 16 weeks of double-blind treatment, and then an open-label treatment phase lasting a minimum of 8 weeks and up to 24 weeks.
Location	147 sites including Belgium, Czechia, Germany, Hungary, Italy, Poland, Portugal, Slovakia, Spain, Sweden, United Kingdom (11 sites), Japan, China, Korea, and Taiwan

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CGRP, calcitonin gene-related peptide; ECG, electrocardiogram; ICHD, International Classification of Headache Disorders; MBS, most bothersome symptom; QTcF, corrected QT interval; NSAID, non-steroidal anti-inflammatory drug; ULN: upper limit of normal.

Table 4. EAG's summary of the design, conduct and analysis of the ECLIPSE trial

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Randomisation	Section 3.3.1 CS	**Appropriate** Patients were randomised in a 3:1:1:1 ratio to one of four treatment sequence groups, in which each patients received a placebo to treat one qualifying migraine attack and atogepant (administered as a 60 mg oral tablet as a single dose/attack) to treat three qualifying migraine attacks during the double-blind treatment period (phase one) within 16 weeks after randomisation. Randomisation was stratified by region (Europe, China, Japan, Other), use of and response to triptans (triptan unsuitable, triptan experiences and triptan naïve) and current use of prophylactic concomitant medication for migraine (yes/no).

Concealment of treatment allocation	Section 3.3.1 CS; Section 6.4, ECLIPSE Protocol	**Appropriate, with unclear method of sequence generation** Randomisation was conducted centrally via an IRT system, with all participants assigned a unique identification number at Visit 1/Screening. However, the EAG notes that the method used to generate the random sequence (e.g. block size, stratification, random number generator) was not explicitly described. Thus, sequence generation remains unclear. Nevertheless, allocation concealment appears adequate.
Eligibility criteria	CS Table 5; Company response to clarification questions	**Appropriate but restricted to episodic migraine and lower acute medication use** The EAG's clinical experts agreed that the inclusions and exclusion criteria for ECLIPSE were broadly appropriate and reflective of patients in clinical practice. However, they noted the trial included patients up to 75 years, which is broader compared to other acute migraine trials (often including patients up to 65 years). Clinical experts also noted the eligibility criteria restricted the trial population to patients with episodic migraine (<15 headache days per month), hence excluding patients with chronic migraine (≥15 headache days per month), who are typically more difficult to treat, and may have a lower response to treatment. However, the company noted that in NICE TA919, all relevant clinical trials were in individuals with episodic migraine (experiencing two to eight migraine attacks per month) and results were deemed generalisable to patients with chronic migraine.[8] In addition, clinical experts noted that attack frequency alone does not determine migraine classification, as a single migraine attack may last up to 72 hours. Thus, patients classified as having episodic migraine may still experience substantial functional impairment. Clinical experts noted the exclusion of patients using acute headache medication on ≥10 days per month (in any of the 3 months prior to Visit2/randomisation), may limit representation of patients with medication overuse headache, a population frequently seen in clinical practice. While this criterion is clinically reasonable, it may narrow the trial population relative to patients in clinical practice who have high acute medication use and potentially greater disease burden. In response to clarification questions, the company stated that this exclusion criterion is not expected to impact the relevance of the trial population to the anticipated population, noting that clinical experts consulted by the company did not consider this criterion to meaningfully impact generalisability. The EAG notes that while the exclusion of patients with high acute medication use may reduce representation of individuals with medication overuse headache, it is unlikely to influence the internal validity of the trial. The permitted and disallowed concomitant medication were considered by clinical experts to be appropriate and to reflect clinical practice. However, patients receiving anti-CGRP monoclonal antibodies (mAb) were excluded. Clinical experts noted that although combination use of gepants and monoclonal antibodies may occur in practice, evidence on combined efficacy is limited. Thus, exclusion of mAb-treated patients may reduce generalisability to a subset of specialist patients, although this is unlikely to affect internal validity.

Blinding	Section 3.3.1 in CS; Section 9.2 ECLIPSE Clinical study report	**Appropriate** ECLIPSE was a randomised, double-blind, placebo controlled trial, where atogepant and matching placebo tablets were identical in appearance. Participants and study physicians assessing and managing the treatments were blinded to the treatment allocation for each attack, during the double-blind treatment period (up to 16 weeks). After treating four qualifying migraine attacks, patients entered an open label treatment period that continued until the end of the study at Week 24, where they treated qualifying migraine attacks with OL atogepant.
Baseline characteristics	Section 3.3.3 in CS; Company response to clarification Table 14; CS Table; Appendices, Table 36	**Appropriate** The EAG's clinical experts considered the baseline characteristics of participants in the ECLIPSE trial to be broadly reflective of patients with episodic migraine seen in clinical practice in England who would be eligible for acute treatment with atogepant. Some differences were noted in mean BMI, which experts noted was slightly lower than might be expected in clinical practice in England. They emphasised that increased BMI is associated with more chronic migraine and this difference is clinically meaningful and could potentially influence treatment response, although the direction and magnitude of any impact on the treatment effect remain uncertain. The proportion of patients experiencing vomiting [redacted] was also considered lower than anticipated relative to clinical practice. Clinical experts noted that aura was not extensively characterised, which is common in acute migraine trials, and was not considered likely to influence the interpretation of the treatment effect. The EAG noted that the baseline characteristics of the ITT population and the mITT population used in the company's efficacy analyses were well balanced between arms, with only small numerical differences [redacted] occasionally noted across characteristics.
Dropouts	ECLIPSE Clinical study report, Section 11.1.2.2 and Table 14.1__1.3.1	**Appropriate** Participants with missing efficacy assessments at a specific time point during the double-blind period were classified as treatment failures (non-responders), for pain freedom, pain relief, absence of 1 symptom or ability to function normally at a specific time point for any attacks, consistent with a non-responder imputation approach. Three sensitivity analyses were conducted to assess robustness. Patients who did not treat 4 qualifying migraine attacks during the double-blind period (up to 16 weeks) were to be discontinued from the study at Visit 6 (week 16). During the double-blind period [redacted] subjects ([redacted] of the ITT population) discontinued, primarily due to failure to treat four qualifying migraine attacks [redacted] Discontinuation rates were similar across treatment sequences, and very few discontinuations were due to adverse events. During the open-label period, [redacted] discontinued, primarily due to withdrawal by subject [redacted] with no study discontinuations due to adverse events. Attrition was largely protocol-driven rather than treatment-related with similar rates across treatment sequences; therefore, the EAG

		considers the risk of attrition bias to be low and unlikely to impact results.
Statistical analysis		
Sample size and power	CS Table 8;	**Appropriate** The study planned enrolment of approximately 650 randomised subjects per treatment group, providing at least 90% power to detect treatment difference between atogepant and placebo for the primary efficacy endpoint (pain freedom at two hours), assuming a difference of 7.5% between atogepant and placebo, at a two-sided 0.05 significance level. A fixed sequence procedure was used to control the Type I error rate for multiple comparisons. The power calculation is appropriate for demonstrating superiority for the primary endpoint. The primary analysis for atogepant vs placebo forming the focus of this submission was conducted on the mITT population ([redacted] vs [redacted]), which is slightly smaller than planned enrolment and may slightly reduce precision.
Analysis for estimate of effect	CS, Section 3.3.1 and Table 8	**Appropriate** The treatment effect for the primary endpoint (pain freedom at 2 hours) was estimated using a generalised linear mixed effects model (GLMM) in the mITT population. Although participants were randomised to treatment sequences (3:1:1:1), the first qualifying attack was analysed for the primary and key secondary endpoints in a 1:1 placebo vs atogepant allocation on that attack. Treatment effects were expressed as odds ratios with 95% confidence intervals. Key secondary endpoints were analysed using the same approach.
Handling of missing data	ECLIPSE Statistical analysis, Section 9.2	**Appropriate, although analyses relying on observed cases assume missing at random** For binary responder endpoints (e.g. pain freedom at 2 hours, pain relief, absence of one symptom) during the double-blind period, participants who did not provide the required assessment were classified as treatment failures (non-responder imputation). For other efficacy endpoints, including those evaluated during the open-label period, continuous endpoints as well as ePRO endpoints evaluated during the double blind period, mixed effects models (MMRM/GLMM) were applied using observed data without formal imputation of missing values.
Outcome assessment	CS, Section 3.3.1 and 3.4 (Table 7)	**Appropriate** Clinical expert feedback indicated that the clinical outcomes used in ECLIPSE (e.g. pain freedom and pain relief at 2 hours) are generally aligned with how acute migraine treatments are assessed in practice. However, health-related-quality-of-life instruments such as EQ-5D-5L and MQoLQ are not routinely used in NHS clinical practice. In routine care, clinicians more commonly assess treatment effectiveness through patient-reported headache frequency (e.g. monthly headache days), functional impact, and sometimes use of tools such as the HIT-6 questionnaire.

		Clinical experts noted that pain freedom at 2 hours is considered more clinically meaningful than pain relief alone, although for the latter, improvement in associated migraine symptoms such as nausea (and aura where relevant) is also important when evaluating response. The following data sets were used: **mITT population:** Consisted of all randomised subjects who received at least 1 dose of study drug during the double-blind treatment period, recorded a baseline migraine headache severity measurement, and had at least 1 post dose migraine headache severity or migraine-associated symptom measurement at or before the 48-hour timepoint based on headache eDiary for any attack during the double-blind period; was used for the analysis of the primary endpoints. **safety population:** Consisted of all subjects who received at least 1 dose of study drug during the double-blind treatment period; was used for the analysis of adverse events

Abbreviations: BMI, body mass index; CGRP, Calcitonin Gene-Related Peptide; CS, company submission; EAG, External Assessment Group; EQ-5D-5L,EuroQol 5-Dimension 5-Leve; GLMM, Generalised linear mixed effects model; ITT, intention-to-treat; mAb, monoclonal antibody; mITT, modified intention-to-treat; MMRM, Mixed model for repeated measures; MQoLQ, Migraine-Specific Quality of Life Questionnaire; NICE, National Institute for Health and Care Excellence; NSAIDs, non-steroidal anti-inflammatory drugs;.

4.2.1.1 Additional clarification on concomitant and prior medication use

The EAG sought clarification regarding rescue medication use, current use of concomitant prophylactic medication and prior exposure to any gepants (mITT population). In response to clarification questions, the company provided the requested information. The EAG notes that the types of rescue medication were similar between treatment arms, with a higher proportion of use in the placebo arm. The most commonly used rescue medications (NSAIDs) were consistent with UK clinical practice as per input from the EAG's clinical experts. Although EAG clinical expert opinion indicated uncertainty regarding whether concomitant prophylactic treatment would be expected to influence response to acute therapy, the EAG notes that current use of prophylactic concomitant medication was balanced between treatment arms and subgroup analyses were explored and did not suggest modification of the treatment effect (see section 4.3.2). Prior exposure to a gepant (most commonly rimegepant) was low overall and broadly comparable between arms, with only a very small difference between groups (**** , with prior exposure to a gepant being slightly higher in the placebo arm compared to atogepant. Thus, the EAG did not identify any concerns related to the use of rescue medication, prophylactic medication or prior exposure to a gepant.

4.3 Clinical effectiveness results

Results of the ECLIPSE trial are presented in sections 3.6, 3.7 and 3.8 of the CS. The results most relevant to the scope of the cost comparison are presented below.

4.3.1 Individual trial results

4.3.1.1 Pain freedom at 2 hours

The company identified pain freedom at 2 hours as the gold standard endpoint for the acute treatment of migraine. EAG clinical experts agreed that pain freedom was more clinically meaningful than pain relief alone, noting that the latter should ideally be accompanied by improvement in associated migraine symptoms and/or aura, which may be more difficult to measure consistently in clinical practice.

In the ECLIPSE trial (mITT population), 24.3% of patients receiving atogepant achieved pain freedom at 2 hours compared with 13.1% receiving placebo (Table 5). This corresponded to an odds ratio (OR) of 2.36 (95% CI: 1.76 to 3.15; p<0.0001), reflecting a substantial relative improvement in pain freedom compared to placebo.

Table 5. Pain freedom at two hours after the double-blind dose for the first attack (mITT population; reproduced from Table 11, CS)

	Atogepant (N=605)[a] n/N1 (%)[b]	Placebo (N=618)[a] n/N1 (%)[b]	OR (95%CI) vs Placebo[c]	P-value
Pain freedom at 2 hours	[redacted]	[redacted]	[redacted]	[redacted]

Footnote: [a]N= number of subjects in the mITT population; [b]n=Number of responders/N1=number of patients who received the treatment for the specified attack and had baseline headache severity for that attack. Missing data were imputed as non-responder; [c]The odds ratios between group treatment differences for the primary endpoint are derived from the GLMM methods. The total mITT population includes 1223 patients; the mITT efficacy attack 1 population includes [redacted] patients.

Abbreviations: CI, confidence interval; CS, company submission; GLMM, generalised linear mixed effects model; mITT, modified intent to treat.

4.3.1.2 Secondary endpoints

Results of the key secondary outcomes (Table 6) were consistent with the primary endpoint, with statistically significant differences favouring atogepant over placebo across all outcomes assessed (p≤0.0001).

The EAG notes that atogepant was associated with higher odds of:

- Freedom from most bothersome symptom (MBS) at 2 hours;
- Pain relief at 2 hours;
- Sustained pain relief from 2 to 24 hours; and
- Ability to function normally at 2 hours.

The EAG notes that pain relief at 2 hours was also used by the company in the economic model to define response to treatment, with response probabilities informed by the ECLIPSE trial. Further details are discussed in the economic evaluation sections (Section 5). The sustained pain relief from 2 to 24 hours indicates maintenance of the treatment effect over a 24-hour period following the treated attack. The EAG also notes that use of rescue medication within 24 hours was significantly lower with atogepant compared with placebo.

Overall, these findings demonstrate consistent treatment effects across symptom relief, functional outcomes and need for rescue medication, supporting the robustness of the primary endpoint.

Table 6. Analysis results for the key secondary efficacy outcomes (mITT population; reproduced from Table 12, CS)

	Atogepant (N=605) [a] n/N1 (%) [b, c]	Placebo (N=618)[a] n/N1 (%) [b, c]	OR (95%CI) vs Placebo [d]	P-value [e]
MBS free at 2 hours	[redacted]	[redacted]	[redacted]	[redacted]
Pain relief at 2 hours	[redacted]	[redacted]	[redacted]	[redacted]
Sustained pain relief 2 to 24 hours	[redacted]	[redacted]	[redacted]	[redacted]
Rescue medication use within 24 hours	[redacted]	[redacted]	[redacted]	[redacted]
Ability to function normally at 2 hours	[redacted]	[redacted]	[redacted]	[redacted]

Footnote: [a]N= number of subjects in the mITT population; [b]n=Number of responders/N1=number of patients who received the treatment for the specified attack and had baseline headache severity for that attack; [c]The point estimate for all key secondary endpoints is responder rate; [d] The odds ratios between group treatment differences for the primary and all key secondary endpoints are derived from the GLMM methods; [e] Adjusted p-value use fixed-sequence procedure to control the overall type I error rate for multiple comparisons. The total mITT population includes 1223 patients; the mITT efficacy attack 1 population includes [redacted] patients.

Abbreviations: CI, confidence interval; CS, company submission; GLMM, generalised linear mixed effects model; mITT, modified intent to treat.

Other secondary outcomes were also reported from the ECLIPSE trial (Section 3.6.3 in the CS). The EAG notes that the majority (7 of the 11 other endpoints) showed statistically significant differences favouring atogepant over placebo, with results generally consistent with the primary and key

secondary endpoints. However, the study was not powered to detect treatment differences for these outcomes and so the results should be considered supportive and interpreted with caution.

4.3.1.3 Health-related quality of life

Health-related quality of life (HRQoL) was assessed using several patient-reported outcome measures in the ECLIPSE trial. The European Quality of Life-5 Dimension 5 level (EQ-5D-5L) was the measure used to inform the economic model and is therefore the focus of this section. Results are summarised in Table 7 below.

At 24 hours after the double-blind dose, participants treated with atogepant showed a statistically significantly greater improvement from baseline in EQ-5D-5L compared with placebo ([redacted]). Improvements were also observed in EQ-5D VAS scores, with a greater increase from baseline in the atogepant group compared with placebo ([redacted]). The EAG notes results indicate improved self-reported quality of life at 24 hours following treatment.

Table 7. Change from baseline in EQ-5D-5L scores at 24 hours after the double-blind dose (mITT population; reproduced from CS, Table 14)

Descriptive statistics					Model-based results (N=[redacted])[a,b]				
					Within-group change from baseline		Between-groups difference (compared with placebo)		
Treatment	N_OBS[c]	Baseline mean (SD)	Postbaseline mean (SD)	Unadjusted mean CfB (SD)	LS mean (SE)	95% CI	LS Mean (SE)	95% CI	Nominal p-value
EQ-5D-5L descriptive system index score									
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Atogepant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ VAS score									
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Atogepant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnote: [a] MMRM analysis includes treatment group, attack, treatment group-by-attack interaction, region (Europe, China, Japan, and other), historical triptan-response stratum (Triptan Unsuitable, Triptan Experienced, or Triptan Naïve), use of medication for migraine prevention (yes/no) and baseline headache severity (moderate or severe) for the attack. The EQ-5D-5L baseline score and baseline-by-attack interaction will also be included in the model. Unstructured covariance structure is used. The model includes only observed data. No imputation used; [b]Number of unique subjects contributing to the model estimates; [c] Number of subjects with observed measurements at both baseline and post-baseline.

Abbreviations: CI, confidence interval; CfB, change from baseline; CS, company submission; EQ-5D-5L, European Quality of Life-5 Dimensional-5 Level; LS, least square; mITT, modified intention to treat; MMRM, mixed model for repeated measures; OBS, observed; SD, standard deviation; SE, standard error; VAS, visual analogue scale.

Additional HRQoL measures reported in the ECLIPSE trial included the Patient Satisfaction with Study Medication (PSSM) and the Migraine Quality of Life questionnaire (MQoLQ). The EAG notes results across these measures were consistent with the EQ-5D-5L findings, with participants treated with

atogepant reporting higher medication satisfaction at 2 and 24 hours after the double-blind dose and improvements across MQoLQ domains, including work functioning, social functioning, energy/vitality, feelings and concerns, and migraine symptoms compared with placebo. Results on additional measures of the cognitive function scale and patient global impression of change were also in line with other HRQoL measures, suggesting improved response rates with atogepant compared to placebo.

Overall, apart from improvements in pain outcomes, ECLIPSE trial results suggest that atogepant is associated with (short-term) improvements in HRQoL and functioning at 24 hours compared with placebo. Findings from additional patient-reported outcome measures were consistent with the EQ-5D-5L results, providing supportive evidence of a benefit of atogepant.

4.3.2 Subgroup analyses

In the CS, it is reported that subgroup analyses were planned in the ECLIPSE trial population, for the primary endpoint (pain freedom at 2 hours), for the following factors:

- Region (Europe, China, Japan, or other);
- Current use of prophylactic concomitant medication for migraine (yes or no);
- Previous response to and use of triptans (triptan unsuitable, triptan experienced, or triptan naïve).

The CS reports that treatment with atogepant was associated with higher response rates compared with placebo across subgroups. The EAG notes treatment effect for the subgroup of patients relevant to the company's decision problem (≥2 triptans and they did not work well enough, or triptans were contraindicated or not tolerated) showed similarly positive results to the mITT population, with a primary endpoint OR versus placebo of [redacted]. The EAG notes that while the results of the mITT and the subgroup of patients matching the company's decision problem were broadly consistent, the subgroup analysis demonstrated a numerically higher benefit for atogepant compared to placebo, although the wider confidence intervals reflect a higher uncertainty associated with this effect estimate.

Th EAG requested additional clarification from the company to better understand whether treatment effect of atogepant vs placebo was consistent across pre-specified subgroups and assess potential heterogeneity of the treatment effect in the mITT population used in the company's analysis of clinical effectiveness, for the primary endpoint (pain freedom at 2 hours) but also for key secondary endpoints of pain relief at 2 hours and sustained pain freedom from 2 to 24 hours. In

response to clarification questions, the company provided forest plots for the pre-specified subgroup analyses from the ECLIPSE trial for the mITT population.

The EAG notes that for pain freedom at 2 hours, treatment effects consistently favoured atogepant over placebo across the majority of subgroups assessed. Odds ratios were ********** in the Europe, China and Japan region subgroups, in the triptan-unsuitable and triptan-experienced subgroups and regardless of preventive migraine medication use. In some subgroups (e.g. 'other' region and triptan naïve) confidence intervals **********, however, point estimates remained consistent in direction with the overall mITT population. In addition, the EAG notes that wide confidence intervals reflected uncertainty likely associated with small subgroup sizes.

Overall, the EAG noted the subgroup analyses for pain freedom at 2 hours do not suggest a clinically meaningful effect modification by region, prior to triptan use, or concomitant preventive medication use. The EAG notes this was in line with the EAG's clinical expert feedback and that current analyses were not powered to detect differences between subgroups. Subgroup analyses for key secondary endpoints were also provided and were generally consistent in direction with the primary endpoint.

In response to clarification questions, the company also provided subgroup analyses results by region ('Europe' versus 'China, Japan and other') for all efficacy outcomes explored. The EAG notes that overall, the direction of effect is consistent, with results favouring atogepant over placebo across subgroups, with overlapping confidence intervals. An exception was freedom from MBS at 2 hours, which was ********** in the European subgroup but not in the China, Japan and other subgroup.

4.3.3 Adverse effects

The EAG notes that for the first migraine attack, the incidence of treatment-emergent adverse events (TEAEs) was similar between atogepant and placebo groups. Severe and serious TEAEs were rare (<0.5%), with no clear differences between groups. No deaths were reported and the number of people with adverse events leading to discontinuation was very low (<0.5%). These are summarised in Table 8 below.

Table 8. Overview of adverse events for the first migraine attack during the double-blind period (Safety Population; reproduced from CS, Table 23)

Event, n (%)	Placebo (N=624)	Atogepant (N=607)
TEAE	84 (13.5)	76 (12.5)

TEAE related to study treatment	20 (3.2)	25 (4.1)
Severe TEAE	1 (0.2)	0
Serious TEAE	1 (0.2)	0
TEAE leading to discontinuation of study treatment	1 (0.2)	1 (0.2)
TEAE leading to death	0	0
All death	0	0
Reported within 48 hours following administration of study drug		
48-hour TEAE	34 (5.4)	34 (5.6)
48-hour TEAE related to study treatment	16 (2.6)	24 (4.0)
Severe 48-hour TEAE	1 (0.2)	0
Serious 48-hour TEAE	0	0
48-hour TEAE leading to discontinuation of study treatment	1 (0.2)	0
48-hour TEAE leading to death	0	0
Abbreviations: CS, company submission; TEAE, treatment-emergent adverse event.		

Over the entire double-blind period, across migraine attacks, TEAEs were more frequent in the atogepant group compared to placebo. However, during this period, participants were treated with atogepant for three migraine attacks, whereas the received placebo for only one attack. Severe, serious adverse events and TEAEs leading to discontinuation were rare (<1%), and no deaths occurred. These are summarised in Table 9. The CS reports that during the entire double-blind period, the AEs reported in ≥2% of all subjects were nasopharyngitis (4.6%) and upper respiratory tract infection (2.3%).

Table 9. Overview of adverse events for all migraine attacks during the double-blind period (Safety Population; reproduced from ECLIPSE Clinical Study Report; Table 14.3__1.2)

Event, n (%)	Placebo (N=1177)	Atogepant (N=1195)	Total (N=1232)
TEAE 1	[redacted]	[redacted]	397 (32.2)
TEAE related to study treatment	[redacted]	[redacted]	85 (6.9)
Severe TEAE	[redacted]	[redacted]	4 (0.3)
Serious TEAE	[redacted]	[redacted]	7 (0.6)
TEAE 1 leading to discontinuation of study treatment	[redacted]	[redacted]	9 (0.7)
TEAE 1 leading to death	[redacted]	[redacted]	[redacted]
All deaths	[redacted]	[redacted]	[redacted]
Reported within 48 hours following administration of study drug			
48-hour TEAE	[redacted]	[redacted]	145 (11.8)
48-hour TEAE related to study treatment	[redacted]	[redacted]	64 (5.2)
Severe 48-hour TEAE 1	[redacted]	[redacted]	1 (<0.1)
Serious 48-hour TEAE 1	[redacted]	[redacted]	1 (<0.1)

48-hour TEAE 1 leading to discontinuation of study treatment	[redacted]	[redacted]	[redacted]
48-hour TEAE 1 leading to death	[redacted]	[redacted]	[redacted]

Abbreviations: TEAE, treatment-emergent adverse event.

The Summary of Product Characteristics (SmPC) for atogepant reports that, when atogepant was used daily for prophylaxis, the most commonly reported adverse reactions were nausea (7%), constipation (7%) and fatigue/somnolence (5%), with the majority of these cases being mild and none being serious.

For acute treatment, gastrointestinal disorders were reported as the most common adverse reaction. Specifically, nausea was the only adverse reaction reported in [redacted] of atogepant treated patients [redacted] with a reasonable possibility of being related to treatment. Discontinuation due to adverse events was rare [redacted] This was in line with the experience of the EAG's clinical experts, who emphasised that atogepant is most commonly associated with constipation in the context of preventative treatment, but this is not likely to be an issue in acute treatment. However, related gastrointestinal problems may still occur that may manifest as nausea, which is also a common feature of migraine.

In addition, clinical experts highlighted that there may be an increased risk of cardiovascular events associated with gepants; however, the magnitude of this risk is likely to be low.[13] Finally, the SmPC reports that there is limited data on the use of atogepant in pregnant women and atogepant is not recommended during pregnancy.

4.4 Critique of the indirect treatment comparison

In the absence of direct head-to-head evidence comparing atogepant and rimegepant, the company conducted network meta-analyses (NMAs) to estimate their relative efficacy and safety for the acute treatment of migraine.

The analyses were informed by a systematic literature review (SLR) that identified randomised controlled trials with relevant efficacy, safety and tolerability data for existing and upcoming acute treatments of migraine. Eligible studies included adult populations with migraine, treated with atogepant 60mg, rimegepant 75mg or placebo. Outcomes of interest included key efficacy endpoints commonly reported in acute migraine trials (e.g. pain freedom and pain relief at 2 hours) as well as safety outcomes. Full inclusion criteria for studies included in the NMAs are summarised in Table 10 below.

Table 10. Inclusion criteria for studies in the NMA (reproduced from CS, Table 19)

Category	Inclusion Criteria
Population	Adults (18 years and older) with a migraine diagnosis (with or without aura)
Treatment(s) of interest	Atogepant 60 mg Rimegepant 75 mg Placebo
Outcomes of interest	**Efficacy outcomes** • Pain freedom at 2 hours • Absence of the most bothersome symptom at 2 hours • Pain relief at 2 hours • Sustained pain relief at 2-24 hours • Sustained pain relief at 2-48 hours • Rescue medication use within 24 hours • Ability to function normally at 2 hours • Sustained pain freedom at 2-24 hours • Sustained pain freedom at 2-48 hours **Safety outcomes:** • Any AEs

Abbreviations: AE: adverse event; CS, company submission; NMA: network meta-analysis.

4.4.1 Critique of trials identified and included in the indirect treatment comparison

As discussed in Section 4.1, the company's SLR identified 160 studies and eight of these were identified as relevant for inclusion in the NMAs for the overall population, as they included treatment with either atogepant or rimegepant. The eight included studies consist of the ECLIPSE RCT of atogepant versus placebo[11] and seven RCTs of rimegepant versus placebo. All eight RCTs were multi-centre trials, with two of the studies being international multi-centre trials, four were conducted in the USA, one conducted in centres in China and South Korea and the remaining study was conducted solely in Japan. The EAG notes that all of the rimegepant RCTs were single-attack migraine trials, whereas the ECLIPSE trial of atogepant was a multi-attack trial, although only results from the first attack were used in the NMAs.

A summary of the eight studies included in the company's NMAs is presented in Table 11 below.

Table 11. Overview of studies included in the NMAs (reproduced from Table 20 of the company submission)

Study	Author and Year	Treatments	Phase	Study setting	Blinding	Number of attacks
ECLIPSE	AbbVie (data on file) 2025[11]	Atogepant 60 mg QD Placebo	Phase 3	Multi-centre international	Double-blind	Multiple attacks[a]
BHV3000-302	Lipton 2019[14]	Rimegepant 75 mg QD Placebo	Phase 3	Multi-centre USA	Double-blind	Single attack
Marcus 2014	Marcus 2014[15]	Rimegepant 75 mg QD Placebo	Phase 2	Multi-centre USA	Double-blind	Single attack
BHV3000-301	Lipton 2024[16]	Rimegepant 75 mg QD Placebo	Phase 3	Multi-centre USA	Double-blind	Single attack
BHV3000-310	Yu 2023[17]	Rimegepant 75 mg QD Placebo	Phase 3	Multi-centre China/South Korea	Double-blind	Single attack
BHV3000-303	Croop 2019[18]	Rimegepant 75 mg QD Placebo	Phase 3	Multi-centre USA	Double-blind	Single attack
BHV3000-313	Ikeda 2025[19]	Rimegepant 75 mg QD Placebo	Phase 3	Multi-centre Japan	Double-blind	Single attack
BHV3000-406	Ashina 2025[20]	Rimegepant 75 mg QD Placebo	Phase 4	Multi-centre international	Double-blind	Single attack

Footnotes: [a] Primary efficacy analyses in ECLIPSE were conducted using data for the first attack only.
Abbreviations: mITT, modified intention to treat; N/A, not applicable; NMA, network meta-analysis; QD, once daily.

As discussed in Section 4.2.1, the EAG considers ECLIPSE to be a high-quality trial at low risk of bias for the primary and key secondary outcomes. The company reported that they conducted quality assessments for the seven rimegepant studies included in the NMAs using the Cochrane tool for assessing the risk of bias (RoB).[21] The company considered all eight of the RCTs included in the NMAs to be low risk of bias across all domains, although the EAG notes that no rating was given for the domain 'other bias' (Table 15 of the company submission appendices). The EAG also notes that an updated version of the Cochrane RoB tool was published in 2019,[22] which the company could have used. Due to time constraints, the EAG was unable to fully validate all of the company's risk of bias assessments, but the EAG is not aware of any major issues affecting the robustness of any of the included trials. The EAG notes that the company also conducted an NMA feasibility assessment to assess the suitability of conducting NMAs using the included trials. The company's feasibility assessment included consideration of potential heterogeneity between the included studies with respect to patient characteristics, study design, interventions, and outcomes. In summary, the company considered the studies included in the NMA to be broadly comparable, with limited heterogeneity between trials. The company also reported that an advisory board of five UK clinical experts specialising in headache and neurology did not consider there to be any meaningful differences between the studies included in the NMA.[23]

The population criteria for inclusion in the SLR required patients to be adults and have a migraine diagnosis, with or without aura. In response to clarification questions the company highlighted that all the rimegepant trials included in the NMA were restricted to patients with EM (company response to clarification question A16b). The EAG notes that the ECLIPSE trial also comprised of only patients with EM (Section 3.1).

The company provided a summary of baseline characteristics of patients (e.g. age, sex, race and body mass index [BMI]) across the studies included in the NMA in figures in the company submission appendix C.1 with numerical data also provided in response to clarification questions. The EAG notes that baseline characteristics were broadly comparable across the studies, although there were some variations between the studies; for example, the proportion of females in the studies ranged from 77% to 93% and some baseline characteristics, such as BMI were not reported in all studies.

The EAG also notes that two of the included rimegepant studies (BHV3000-313[19] and BHV3000-310[17]) were conducted exclusively in east Asian populations, with all of the other included trials in the NMA conducted in the USA or multinational populations. The company reported that they had conducted a targeted literature review to assess whether any differences in baseline characteristics, such as ethnicity, could be considered as potential treatment effect modifiers (TEMs) in the acute treatment of migraine and no conclusive evidence of TEMs was identified. In addition, the company stated that their clinical experts also considered the baseline characteristics of the included studies were broadly similar, and their clinical experts did not consider that there would be any relevant TEMs.[23] In response to clarification questions, the company also conducted sensitivity analyses excluding the two studies conducted exclusively in east Asian populations and the results of these are discussed in Section 4.4.3.1 below.

4.4.2 Critique of the methods used for the indirect treatment comparison

The company's NMAs comparing atogepant with rimegepant were conducted using the modified intention-to-treat (mITT) population, consistent with TA919. For all included NMA trials, the primary endpoint was measured based on the response to the first migraine attack treated with the acute medication, ensuring equivalent time points across all trials.

The outcomes of interest in the company's NMAs were:

- Efficacy outcomes:
    - Pain freedom at 2 hours;
    - Absence of the most bothersome symptom at 2 hours;

    - Pain relief at 2 hours;
    - Sustained pain relief at 2-24 hours;
    - Sustained pain relief at 2-48 hours;
    - Rescue medication use within 24 hours;
    - Ability to function normally at 2 hours;
    - Sustained pain freedom at 2-24 hours;
    - Sustained pain freedom at 2-48 hours.
- Safety outcomes:
    - Any AEs.

The company highlighted that the outcomes were well defined across the more recent trials, although exact definitions appeared to differ slightly across trials. Data on all outcomes of interest were available for all but two studies (Marcus 2014[14] and BHV3000-310[16]).[15, 17] However, based on the outcome assessment the company conducted, no trials were excluded from the NMAs for not reporting data for any of the endpoints of interest or due to the definitions of their endpoints. However, the EAG notes that variation in outcome definitions across trials may introduce a degree of heterogeneity and could affect comparability of effect estimates across trials included in the network.

The EAG notes that all analyses reported by the company were conducted using a Bayesian hierarchical generalised linear model approach, with model estimates generated using Monte Carlo Markov chains (MCMC). The EAG notes that both fixed-effect (FE) and random-effects (RE) NMAs were conducted, with both informative priors (IP) and vague priors (VP), where sufficient data were available for any theoretical estimation of between-trial heterogeneity. Model fit and complexity were assessed using the deviance information criterion (DIC) and total residual deviance, with comparisons used to inform the selection of the preferred model. Details of the company's NMA methods are presented in Section 3.9.3.5 of the CS and Appendix C.

In response to clarification questions, the company provided the necessary files to re-run the company's analyses and the EAG conducted independent validation of the company's NMA using OpenBUGS. Due to time constraints, the EAG validated a sample of the company's analyses for all outcomes, focusing on the RE IP model results, as this was the company's preferred model. The EAG was able to reproduce the results reported in the company submission with only negligible numerical differences occasionally identified. Moreover, in response to clarification questions, the company provided additional model diagnostics, model convergence and results plots, including Gelman-Rubin diagrams, trace plots, leverage plots and rank plots. The EAG reviewed these and did not identify any apparent issues with model convergence or model fit.

The company reports the FE and RE models showed similar fit across outcomes of interest, with differences between models being small (<3 points or between 3 and 5 points), except for sustained pain relief from 2 to 24 hours. The company reports that the RE model was selected for the main analysis because it provided a better statistical fit to the data. The EAG notes, the choice RE model only resulted in modest improvement in fit. This suggests limited evidence of any substantial between study heterogeneity across the network. However, the company also reported that evidence of heterogeneity varied across outcomes and did not meaningfully impact model conclusions. To manage the natural variation in the study data without overly increasing the uncertainty range, a specific version of the RE model (with an "informative prior") was chosen by the company. The model fit comparisons of FE and RE models are presented in Table 12 below.

Table 12. Model fit statistics (reproduced from CS, Table 21)

Outcome	Model	DIC	Residual Deviance	SD
Pain freedom at two hours	FE	[redacted]	[redacted]	[redacted]
	RE (IP)	[redacted]	[redacted]	[redacted]
	RE (VP)	[redacted]	[redacted]	[redacted]
Absence of MBS at two hours	FE	[redacted]	[redacted]	[redacted]
	RE (IP)	[redacted]	[redacted]	[redacted]
	RE (VP)	[redacted]	[redacted]	[redacted]
Pain relief at two hours	FE	[redacted]	[redacted]	[redacted]
	RE (IP)	[redacted]	[redacted]	[redacted]
	RE (VP)	[redacted]	[redacted]	[redacted]
Sustained pain relief from 2 to 24 hours	FE	[redacted]	[redacted]	[redacted]
	RE (IP)	[redacted]	[redacted]	[redacted]
	RE (VP)	[redacted]	[redacted]	[redacted]
Sustained pain relief from 2 to 48 hours	FE	[redacted]	[redacted]	[redacted]
	RE (IP)	[redacted]	[redacted]	[redacted]
Use of rescue medication within 24 hours	FE	[redacted]	[redacted]	[redacted]
	RE (IP)	[redacted]	[redacted]	[redacted]
Ability to function normally at two hours	FE	[redacted]	[redacted]	[redacted]
	RE (IP)	[redacted]	[redacted]	[redacted]
Sustained pain freedom from 2 to 24 hours	FE	[redacted]	[redacted]	[redacted]
	RE (IP)	[redacted]	[redacted]	[redacted]
	RE (VP)	[redacted]	[redacted]	[redacted]
Sustained pain freedom from 2 to 48 hours	FE	[redacted]	[redacted]	[redacted]
	RE (IP)	[redacted]	[redacted]	[redacted]
Any AE	FE	[redacted]	[redacted]	[redacted]
	RE (IP)	[redacted]	[redacted]	[redacted]

[redacted]

The EAG requested further clarification from the company on the rationale for preferring RE models with IP over RE models with VP, particularly given the apparent similarity in the model fit compared with VP. In response to clarification, the company stated that the RE model with IP was selected as the preferred approach, as it allowed for the incorporation of external evidence to estimate between-study heterogeneity while avoiding unrealistically wide credible intervals that may arise when vague priors are used in sparse networks. The company specified that IP were used to improve the estimation of between study variance and to increase the reliability of the model in situations where data is limited.

The EAG notes that the choice of prior did not meaningfully influence the overall NMA results/estimated treatment effects, with odds ratios remaining broadly consistent across models using informative and vague priors. Differences between models were primarily observed in the width of the credible intervals. Nevertheless, NICE Decision Support Unit (DSU) Technical Support Document 3 (TSD3) highlights that posterior estimates of between-trial heterogeneity in Bayesian random-effects meta-analyses is likely to be extremely sensitive to the choice of prior, particularly when data are sparse.[24] However, the EAG notes that in the current CCE, the network included eight trials in total, with seven trials informing rimegepant. Therefore, the available trial data may have been sufficient to appropriately inform the estimation of between-trial heterogeneity without the need to rely on informative priors.

Overall, while the EAG notes that the choice of prior did not meaningfully influence the treatment effects, the justification for preferring IPs based on concerns regarding sparse data may be less directly applicable in this case.

The EAG also examined the handling of missing outcome data across trials included in the NMA. In most studies (7 out of 8), missing data were handled using non-responder imputation with patients with missing data treated as treatment failures. However, one study (Marcus 2014) used the Last Observation Carried Forward (LOCF) approach.[15] As highlighted by the company in response to clarification questions, LOCF is a less conservative method of handling missing data and may result in higher estimated response rates compared to a non-responder or treatment failure imputation. Although the proportion of missing data in Marcus 2014 was reported to be modest and similar across treatment arms, the use of different imputation approaches across trials may introduce some heterogeneity in the network. Nevertheless, the EAG notes that given that only one study used LOCF

and the proportion of missing data was not high, the potential impact of that on the NMA results is limited.

4.4.3 Results of the indirect treatment comparison

The results of the company's NMAs are presented in section 3.9.5.2 of the CS and section C.4 of the Appendices document. Relative treatment effects were estimated for all treatments included in the NMAs. Both FE and RE models were explored using IP and VP, with the company identifying the RE model with IP as the preferred model (as discussed in Section 4.4.2 above). The evaluation of this section focuses on the comparison between atogepant and rimegepant based on the company's preferred model.

Across the majority of efficacy and safety outcomes, the NMA results suggested no statistically significant differences between atogepant and rimegepant, with odds ratios (ORs) generally close to 1 and confidence intervals crossing the null. . Treatment rank plot results provided with the company's response to clarification questions, were consistent with this, with rimegepant having approximately a *** probability of being ranked most effective for the primary outcome of pain freedom at 2 hours, indicating no clear ranking difference between treatments. The only outcome for which there was a statistically significant difference was use of rescue medication, where treatment with atogepant was associated with a reduced risk of requiring rescue medication during a migraine attack compared with rimegepant. Results are presented in Table 13 below.

The EAG notes that the range of rescue medications permitted in the ECLIPSE trial was broader than those permitted in the rimegepant trials. In particular, based on the company's response to clarification questions, ECLIPSE allowed the use of triptan, ditans, ergot derivatives and opioids, whereas trials informing rimegepant mostly restricted rescue medication to simple analgesics and antiemetics, with triptans permitted only under limited circumstances in some (two out of seven) trials. The company clarified that the criteria for allowing rescue medication were otherwise similar across trials, with rescue medication permitted from 2 hours post-dose and any use before this time point considered treatment failure. Nevertheless, the EAG notes that differences in the availability of rescue medication across trials may influence the likelihood of rescue medication use and, therefore, may affect the comparability of this outcome across studies included in the NMA. As the use of rescue medication is influenced both by treatment response and trial protocol, results should be interpreted with caution.

Table 13. Summary of efficacy and safety outcomes from the NMA (RE model with IP; reproduced from CS, Table 22)

	Atogepant vs. rimegepant OR (95% CrI)
Pain freedom at two hours (primary endpoint)	**********
Absence of MBS at two hours	**********
Pain relief at two hours	**********
Sustained pain relief from 2 to 24 hours	**********
Sustained pain relief from 2 to 48 hours	**********
Use of rescue medication within 24 hours	**********
Ability to function normally at two hours	**********
Sustained pain freedom from 2 to 24 hours	**********
Sustained pain freedom from 2 to 48 hours	**********
Any AE	**********

Abbreviations: AE, adverse event; CrI, credible interval; MBS, most bothersome symptom of migraine; NMA, network meta-analysis; OR, odds ratio.

In response to clarification questions, the company clarified that the definition of 'any AE' corresponds to 'treatment-emergent adverse event' and includes all adverse events regardless of intensity (mild, moderate, or severe), whether they are serious or nonserious AEs and whether or not they are potentially related to treatment. The EAG also requested that the company provide an NMA for treatment-related adverse events, which was subsequently presented. Based on the results of the RE model with IP, there was no statistically significant difference for atogepant compared with rimegepant (**********).

In light of the critique on the choice of priors (see Section 4.4.2) the EAG notes that the choice of prior did not impact the ORs, which were similar between the two models and only impacted the uncertainty around the effect estimate as reflected by the wider 95% credible intervals in the results of the RE model with VP. For example, for the primary efficacy endpoint, pain freedom at 2 hours, NMA results using a VP showed no statistically significant difference between atogepant and rimegepant (**********). Similarly, results for pain relief at 2 hours, which was used to inform the economic model, the NMA results using a VP were in line with results using IP (**********).

The EAG notes that in the CS, the company did not perform formal statistical equivalence or non-inferiority testing to support claims of clinical equivalence between atogepant and rimegepant. In response to clarification questions, the company stated that conclusions of clinical equivalence were primarily based on the observed results of the NMA, which demonstrated no statistically significant differences between atogepant and rimegepant across the primary and all but one of the secondary outcomes evaluated. The company noted that this interpretation was supported by clinical expert

opinion, indicating that treatments demonstrate comparable efficacy and safety profiles. The company also stated that this approach is consistent with precedent in cost-comparison technology appraisals (as identified by Lee *et al.* 2024).[25]

However, the EAG does not agree that the absence of statistically significant differences between treatments provides robust evidence of clinical equivalence. EAG clinical expert input also highlighted potential inter-patient variability in response and tolerability, with some patients responding better to one treatment than the other. However, the statistical analyses presented in the NMA are appropriate for assessing whether a statistically significant difference exists between treatments, but they are not designed to demonstrate equivalence or non-inferiority. Importantly, a non-significant result should not be interpreted as evidence that treatments are clinically equivalent.[26] The EAG notes that, instead, formal statistical methods are required to demonstrate equivalence or non-inferiority between interventions.[26] Importantly, clinical equivalence or non-inferiority is a fundamental assumption of the NICE cost-comparison pathway and, as noted by multiple EAGs, methods (such as the use of minimum clinically important differences [MCIDs] or non-inferiority margins [NIMs]) exist to allow companies to robustly demonstrate that an intervention is statistically equivalent, or non-inferior, to a comparator (Burgess *et al.* 2025; Downs *et al.* 2025.; Lee *at al*. 2025).[27-29] These typically involve pre-specified equivalence margins or non-inferiority margins based on clinically meaningful differences and allow investigators to determine whether the true treatment effect lies within an acceptable range of difference between interventions.[26]

In the absence of formal equivalence or non-inferiority testing, the evidence presented by the company cannot be considered sufficient to demonstrate that atogepant and rimegepant are clinically equivalent and support the company's conclusions. Therefore, the EAG considers that the results of the NMA indicate a lack of evidence for a statistically significant difference between treatments rather than evidence of clinical equivalence, and do not, on their own, establish whether treatments can be considered equivalent (see Section 4.5 for further discussion of this uncertainty).

4.4.3.1 Sensitivity analysis excluding east Asian studies

The EAG noted that two studies included in the meta-analyses (BHV3000-313[16] and BHV3000-310[18])[17, 19] were conducted exclusively in east Asian populations, whereas other rimegepant trials included USA or multinational populations and the ECLIPSE trial included a non-USA, multinational population. Although the company considered populations across trials included in the NMAs to be comparable and did not consider ethnicity to be a treatment effect modifier, the EAG's clinical

experts noted that factors such as BMI and concomitant medication or rescue medication use may differ across countries and may reflect differences in disease severity and treatment (e.g. increased BMI being associated with more chronic migraine); however there is limited evidence to suggest that these factors directly modify treatment response. Therefore, the EAG requested that the company conduct sensitivity analyses excluding studies conducted exclusively in east Asian populations.

Following the company's response to clarification questions, the EAG notes that the exclusion of these studies resulted in wider credible intervals, indicating slightly reduced precision. However, point estimates and overall conclusions remained consistent with the company's primary analysis. The results of the sensitivity analyses are presented in the company's response to clarification questions.

4.5 Additional work on clinical effectiveness undertaken by the EAG

As previously described, the company assumed that atogepant is equivalent to rimegepant due to 95% credible intervals overlapping zero ((indicating no statistically significant differences) across outcomes (except for use of rescue medication within 24 hours). However, as previously noted (Section 4.4.3), the EAG does not consider this to be an appropriate approach to infer equivalence between two treatments.[26-29] Therefore, the EAG performed additional analyses to assess whether atogepant can be considered statistically non-inferior to rimegepant.

Typically, non-inferiority is assessed by assessing whether 95% credible intervals surrounding a point estimate overlap a non-inferiority margin (NIM). Often, a NIM is aligned with the value for a minimum clinically important difference (MCID), thus ensuring that assessments of non-inferiority are also clinically meaningful/relevant.[30] However, the company has not presented any NIMs or MCIDs and the EAG has not been able to identify any established or validated NIMs or MCIDs from the available literature, for the primary outcome of pain freedom at 2 hours and the key secondary outcome of pain relief at 2 hours.

As such, the EAG utilised a method previously presented at ISPOR 2025 to perform assessments of non-inferiority. This approach uses the posterior draws from an NMA to estimate the hypothetical NIM required for there to be a 90% probability that atogepant is non-inferior to rimegepant. Accordingly, the magnitude of the hypothetical NIM, including whether it is clinically plausible, can provide information as to whether it is likely that atogepant can be considered non-inferior to rimegepant. Ultimately, this analysis is only recommended in situations where a NIM, or MCID, is not available.

The EAG used study-level outcome data provided by the company in response to clarification questions (number of events and total participants per arm) and derived treatment effect estimates (odds ratios and associated measures of uncertainty) for the outcomes of pain freedom at 2 hours and pain relief at 2 hours, to inform the EAG's additional analyses.

The EAG then performed NMAs using random-effects models with both vague and informative priors, in line with the methods and values set out by the company in the submission and subsequent clarification responses. Overall, the EAG performed the following four NMAs:

- Random-effects NMA with vague priors for pain freedom at two hours;
- Random-effects NMA with informative priors for pain freedom at two hours;
- Random-effects NMA with vague priors for pain relief at two hours; and
- Random-effects NMA with informative priors for pain relief at two hours.

The results of each NMA are shown in Table 14 below.

Table 14. Point estimates for the comparison of atogepant to rimegepant for the NMAs performed by the EAG.

	Atogepant vs rimegepant OR (95% CrI)	
	RE model with VP	RE model with IP
Pain freedom at two hours (primary endpoint)	**********	**********
Pain relief at two hours	**********	**********

Abbreviations: CrI, credible interval; IP, informative prior; OR, odds ratio; RE, random effects; VP, vague prior.

Based on the results presented above, the EAG notes there was broad alignment between the point estimates obtained by the EAG and those reported by the company, although there were some differences in the upper 95% credible intervals (CrI) for the vague priors NMA for pain relief at two hours (company's upper 95%CrI: ****) and the informative priors NMA for pain freedom at two hours (company's upper 95%CrI: ****).

Based on the Bayesian NMA results, for each outcome and model, the EAG was able to calculate the probability that atogepant was more effective than rimegepant. These probabilities are shown in Table 15 below. Accordingly, for pain freedom at two hours, there was a ********** that atogepant was more effective than rimegepant. In contrast, for pain relief at two hours, there was a ********** that atogepant was more effective than rimegepant.

Table 15. Probability of atogepant being more effective than rimegepant (based on Bayesian NMA results)

	Probability that atogepant is more effective than rimegepant	
	RE model with VP	RE model with IP
Pain freedom at two hours (primary endpoint)	*****	*****
Pain relief at two hours	*****	*****

Abbreviations: CrI, credible interval; IP, informative prior; OR, odds ratio; RE, random effects; VP, vague prior.

The required hypothetical NIMs, for a 90% probability that atogepant is non-inferior to rimegepant, are shown in Table 16. For the outcome of pain freedom at two hours, the required hypothetical NIMs are **** and **** in the vague and informative prior models, respectively (i.e., the odds of a patient being pain free at two hours are **** higher in the rimegepant group compared to the atogepant group). Likewise, for the outcome of pain relief at two hours, the required hypothetical NIMs are **** and **** in the vague and informative prior models, respectively (i.e., the odds of a patient experiencing pain relief at two hours are **** higher in the rimegepant group compared to the atogepant group). The EAG notes that for both outcomes, the hypothetical NIMs required for there to be a 90% probability that atogepant is non-inferior to rimegepant are high. Given the magnitude of these hypothetical NIMs, the EAG is unclear whether hypothetical thresholds would be considered clinically plausible given the absence of any MCIDs for these endpoints.

Table 16. Hypothetical NIMs required for atogepant to be non-inferior to rimegepant

	Hypothetical NIM for a 90% probability of atogepant being non-inferiority to rimegepant	
	RE model with VP	RE model with IP
Pain freedom at two hours (primary endpoint)	****	****
Pain relief at two hours	****	****

Abbreviations: CrI, credible interval; IP, informative prior; OR, odds ratio; RE, random effects; VP, vague prior.

Overall, the EAG notes that the absence of statistically significant differences in the NMA suggests no clear difference in effectiveness between atogepant and rimegepant. However, in the absence of formal equivalence or non-inferiority analyses, these findings should not be interpreted as evidence of clinical equivalence. While the EAG does not identify evidence suggesting meaningful differences between treatments, there remains insufficient evidence to robustly demonstrate clinical equivalence. The EAG's additional analyses do not materially change the overall conclusions of the NMA but highlight the degree of uncertainty in the available evidence.

4.6 Conclusions of the clinical effectiveness section

The company has submitted evidence in support of the clinical similarity of atogepant to rimegepant for the acute treatment of migraine with or without aura in adults who have either tried at least two triptans that did not work well enough or have contraindications or intolerance to triptans and have tried non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol without an adequate response. The EAG notes that atogepant has a similar mechanism of action to rimegepant and both drugs are administered orally, with rimegepant available as an orally disintegrating tablet/wafer and atogepant as an oral tablet. The EAG considers rimegepant to be an appropriate comparator for consideration in the relative clinical efficacy and safety of atogepant.

The EAG notes that the company's chosen population represents a narrower subgroup than the full anticipated marketing authorisation and the NICE final scope but aligns with the population for which rimegepant is recommended (TA919) and is therefore appropriate for the purposes of this cost comparison. The company presented clinical evidence for atogepant in adult patients with migraine from the ECLIPSE trial, which compared the efficacy and safety of atogepant with placebo. The EAG considers ECLIPSE to be a high-quality RCT, which included the relevant population, intervention and outcomes to match the NICE final scope and address the decision problem.

The EAG's clinical experts considered that the population in ECLIPSE was broadly consistent with patients in clinical practice in England who would be eligible for acute treatment with atogepant. They noted that the trial included patients aged up to 75 years, which is a broader upper age limit than often seen in trials. Baseline characteristics were generally reflective of clinical practice, although some differences were noted, including a slightly lower BMI, which EAG clinical experts advised may influence treatment response. However, the trial's restriction to patients with lower acute medication use and episodic migraine, although consistent with the evidence used to inform the previous NICE technology appraisal for rimegepant (TA919), may limit representation of patients with chronic migraine and medication overuse headache who are often seen in clinical practice and may be less likely to respond to treatment. Therefore, while appropriate for decision-making in the context of a cost-comparison, some uncertainty regarding generalisability to the broader clinical population remains.

The company presented evidence for outcomes including pain freedom at 2 hours (primary outcome), pain relief at 2 hours (key secondary outcome used in the economic model), sustained pain relief, sustained pain freedom, freedom from most bothersome symptom (MBS), use of rescue medication, ability to function normally, adverse effects and health-related quality of life. The EAG

considers that ECLIPSE provides evidence of a substantial relative improvement in pain freedom at 2 hours from atogepant compared to placebo and statistically significant differences favouring atogepant in terms of freedom from MBS, pain relief at 2 hours, sustained pain relief from 2 to 24 hours, rescue medication use, ability to function normally and health-related quality of life. The ECLIPSE trial provided evidence of a similar incidence of treatment-emergent adverse events (TEAEs) between treatments during the first attack, while severe and serious TEAEs or TEAEs leading to discontinuation were rare.

No trials have been conducted that report a direct comparison of atogepant and rimegepant. The company therefore performed network meta-analyses (NMAs) to estimate the relative efficacy and safety for the acute treatment of migraine for this comparison. Outcomes of interest included key efficacy endpoints commonly reported in acute migraine trials (e.g. pain freedom and pain relief at 2 hours) as well as safety outcomes. The company conducted NMAs using a Bayesian hierarchical generalised linear modelling framework, exploring both fixed-effects and random-effects models with analyses conducted using informative and vague priors. Eight RCTs were included in the network, comprising one trial of atogepant 60 mg versus placebo (ECLIPSE) and seven trials of rimegepant 75mg versus placebo. Across the majority of efficacy and safety outcomes, the NMA results demonstrated no statistically significant differences between atogepant and rimegepant, with effect estimates generally [redacted] and credible intervals crossing the line of no effect. The only outcome where a statistically significant difference was observed was the use of rescue medication, where atogepant was associated with a reduced risk compared to rimegepant.

The company reported that fixed-effects and random-effects models demonstrated similar model fit across outcomes. While residual deviance was improved with the random-effects model, overall differences in model fit were small. The company nevertheless selected random-effects models with informative priors as their preferred analysis approach. While the EAG notes that the choice of prior (informative vs vague prior) did not meaningfully influence the estimated treatment effects, NICE DSU Technical Support Document 3 highlights that posterior estimates of between-study heterogeneity can be sensitive to the choice of prior, particularly when data are sparse. However, in the present analysis, the network included 8 trials overall, with seven trials informing the comparison of rimegepant with placebo, suggesting that the available data may have been sufficient to estimate between-trial heterogeneity without relying on an informative prior.

The EAG notes that the company interpreted the absence of statistically significant differences in the NMA as evidence of comparable effectiveness between atogepant and rimegepant. However, the

EAG notes that no formal equivalence or non-inferiority analyses were conducted and that the absence of statistically significant differences indicates a lack of evidence of difference rather than evidence of clinical equivalence. Demonstrating equivalence would require pre-specified margins and appropriate statistical methods. In light of this, the EAG undertook additional analyses to explore the relative effectiveness of atogepant and rimegepant in the absence of formal equivalence or non-inferiority testing. These analyses demonstrated similar point estimates, wide 95% credible intervals crossing the line of no effect and approximately equal probabilities of treatment benefit, indicating substantial uncertainty and no clear difference in effectiveness between treatments. Overall, these findings introduce uncertainty in assuming comparable clinical effectiveness within the cost-comparison framework. However, taking a pragmatic view of all of the available evidence, including similarities in the mechanism of action, mode of administration and positioning in the clinical pathway, the EAG considers that the treatments are likely to have broadly similar effectiveness.

5 Summary of the EAG's critique of cost comparison evidence submitted

For the purposes of the cost-comparison analysis, the company has considered that the only difference in costs between atogepant and rimegepant (the comparator the company considers is the most relevant for the appraisal) is drug acquisition costs. Clinical similarity for the two drugs in the company's cost analysis is based on response to treatment, measured using the outcome of pain relief at 2 hours. In addition to the company's primary assumption of clinical similarity for atogepant and rimegepant, the other key assumptions that underpin the company's cost analysis are as follows:

- Atogepant and rimegepant are both oral drugs and thus do not incur administration costs.
- Healthcare resource use, including hospitalisations, accident and emergency (A&E) visits, GP visits and monitoring costs (assumed to be the cost of a visit with a specialist) is the same for atogepant and rimegepant, but the company has included these costs in their analysis for completeness. Details of healthcare resource use and monitoring costs included in the company's cost analysis are presented in Section 4.2.3 of the company submission (CS), but as there are no assumed cost differences between the two treatments, which the External Assessment Group (EAG) agrees with, they are not discussed further in the EAG report.
- Annual discontinuation of treatment (13.5%) is assumed to be the same between atogepant and rimegepant. Treatment discontinuation data are not available from ECLIPSE due to the trial design, and so data are based on the modified intention-to-treat (mITT) population from a 52-week open-label long-term safety study of rimegepant versus placebo (BHV3000-201).[31]
- The number of migraine attacks per month ([redacted]) is assumed to be the same for both drugs. The data are based on the baseline monthly migraine days from ECLIPSE ([redacted] days) and the assumption that a migraine attack lasts 48 hours.
- The safety profile of both drugs is comparable based on the indirect treatment comparison (ITC) presented in Section 4.4.
- There is no difference in mortality. Background mortality is based on age- and sex- adjusted general population life tables for England for 2021–2023.[32]

The company's cost analysis was not a simple costing study, instead it was a decision tree plus a Markov model with a two-year time horizon and is summarised in Appendix 10.1 of this report. However, as mentioned earlier, the key driver of the cost difference between atogepant and

rimegepant is the difference in the drug acquisition costs. As such, changes in any of the other assumptions in the model have no influence on the direction of the cost difference between atogepant and rimegepant, except to change the magnitude.

The proposed list price of atogepant for a 2- and 7-pack of 60 mg tablets is £25.78 and £90.23, respectively, resulting in a cost per tablet of £12.89. The dose of atogepant is 60 mg taken orally up to once daily, as needed.

The list price of rimegepant for a 2- and 8-pack of 75 mg oral dispersible tablets (ODT) is £28.80 and £103.20, respectively. The cost per rimegepant ODT is £12.90, which is 1 penny more expensive than atogepant. Over a two-year time horizon, atogepant results in cost savings of ***** compared with rimegepant (see Section 6.1). A pack of 28 x 60 mg tablets of atogepant is available, with a confirmed list price of £182.16, resulting in cost per tablet of £6.51, which is substantially less than the cost of rimegepant ODT. The company explored the confirmed list price of a 28-tablet pack of atogepant in scenario analyses, which resulted in cost-savings of ****** (see Section 6.1.1).

In the company's model, non-responders to gepant treatment incur the cost of a 2-pack of tablets, which assumes one tablet wastage. Responders incur the cost of one tablet, and thereafter for each migraine attack over the two-year time horizon only the cost of one tablet is applied. In their clarification response, the company explained that the ECLIPSE protocol specified one tablet per migraine attack.

No wastage is applied for responders to treatment as the company assumed that patients would keep spare tablets to use for their next migraine attack.

5.1 EAG critique

The EAG considers that, overall, the company's case for atogepant being cost-saving compared to rimegepant, under the assumption of clinical similarity, has been made. The EAG notes that the cost per tablet for the 28 tablet-pack size of atogepant is substantially less expensive than the proposed cost per tablet of the 2 tablet- and 7 tablet-pack size (used in the company's base case). The EAG's clinical expert advised that if a patient responds to treatment, then a number of tablets are prescribed rather than a whole pack. Additionally, the EAG's clinical experts confirmed that prescribing of rimegepant can be in either primary or secondary care as it has "green light" status in the formulary for primary care treatment, meaning initiation and prescribing of treatments with this status can be in all care settings.[33] The EAG's clinical experts considered that if atogepant is

recommended, it will likely have the same "green light" status as rimegepant. Therefore, hospital or community prescribing may take tablets from the least expensive pack size of a medicine to give to patients, or the smaller pack sizes may be prescribed.

During the clarification stage, the EAG requested, and the company provided, a scenario analysis where the cost per tablet of atogepant is based on the 28-tablet pack price (£6.51). The results of the scenario demonstrated that atogepant was associated with cost savings of ******* over a two-year time horizon. The EAG considers that because there is potential for a mix of prescribing to take place and with different pack prices for atogepant available, it is worthwhile to consider the cost savings as a range, from ********** to **********.

As described earlier, the company's cost analysis was not a simple cost model but instead was a decision tree with a long-term Markov Model. The company's model is aligned with that used for TA919 and only captures differences in drug acquisition and does not include any additional benefits for atogepant over rimegepant. To reassure the committee that the complex model produces a reliable estimate of cost savings for atogepant, the EAG requested the company provide a simple cost model. In their clarification response, the company supplied the requested analysis. The company's simplified analysis was based on the following assumptions:

- Two-year time horizon.
- 100% of patients are prescribed one 2-pack of gepant tablets for the first migraine attack.
- For each subsequent migraine attack, the cost of one gepant tablet is incurred.
- In ECLIPSE, the monthly migraine days at baseline were **** days. Assuming a migraine attack lasts for 48 hours, the number of migraine attacks per month was ***, resulting in **** attacks per year.

The simple costing approach resulted in estimated cost savings of ***** for atogepant compared to rimegepant over a two-year time horizon, compared with the company's base case estimate of an ***** saving. The key differences between the two approaches are: that the company's base case result factors in non-responders to treatment, and it considers discontinuation of gepant treatment over the time horizon of the analysis.

In the company's base case, it was assumed that patients would take one gepant tablet per migraine attack, as per the ECLIPSE protocol. Generally, the EAG's clinical experts agreed that it was

reasonable to assume one tablet per migraine attack. The EAG's clinical experts explained that if pain freedom was not achieved after the first dose, then there is limited benefit from a second dose on the second day of an attack. However, there may be some patients who would take a second dose on day 2 of a migraine attack. Nonetheless, the company did provide a scenario exploring an assumption where the cost of two tablets is incurred per migraine attack and resulted in cost savings of [redacted] for atogepant.

5.2 Summary statement

Under the assumption that atogepant and rimegepant are clinically similar and, all else being equal, the EAG considers that atogepant is likely to be cost-saving compared with rimegepant.

6 Company and EAG cost comparison results

6.1 Company base case results

Table 17 presents the company's deterministic base case results and show that over a two-year time horizon, compared to rimegepant, atogepant is associated with a cost saving of *****, based on the proposed list price of atogepant.

Table 17. Company's deterministic base case results

Interventions	Drug acquisition costs (£)	Healthcare resource use and monitoring costs (£)	Total Costs (£)	Incremental costs (£)
Rimegepant	*********	*******	*********	*
Atogepant	*********	*******	*********	******

6.1.1 Company's sensitivity and scenario analyses

The company undertook a series of scenario analyses to assess the impact of applying alternative assumptions to key model parameters including several analyses requested by the EAG at the clarification stage. These scenarios are presented in Table 18. Atogepant remained cost saving across all scenarios tested.

Table 18. Company scenario analysis

Scenario	Incremental costs
Base case	******
Time horizon – 10 years	******
Time horizon – 20 years	******
Atogepant pack usage: 65% 2-tablet pack, 25% 7-tablet pack, 10% 28-tablet pack. Rimegepant pack usage: 70% 2-tablet pack, 30% 8-tablet pack.	*******
3.5% discount applied to costs	******
Cost of one-time specialist visit at treatment initiation excluded	******
50% of all packs are wasted for responders discontinuing treatment after the first model cycle	******
General population mortality excluded	******
EAG requested scenarios	
Simple cost analysis – CQ B1	******
Two tablets assumed per migraine attack – CQ B3	******
Cost per tablet of atogepant based on list price of 28-tablet pack – CQ B4	********

Abbreviations: CQ, clarification question; EAG, External Assessment Group.

6.2 Additional economic analysis undertaken by the EAG

The EAG agreed with the company's approach to the cost analysis and is satisfied that any areas of uncertainty were explored in the company's scenario analysis and scenarios provided on request in their clarification response. As mentioned previously, there are different prices proposed for the 2- and 7-tablet pack sizes of atogepant compared the list price for the 28-tablet pack size and there is potential for a mix of prescribing to take place. Thus, the EAG prefers to consider the potential cost savings as a range, using the highest and lowest price per tablet of atogepant supplied by the company. As such, the range of cost savings estimated for atogepant is [redacted] compared to rimegepant.

7 Equalities and innovation

The company has not described any equalities or innovation considerations associated with atogepant in the company submission. Additionally, the External Assessment Group (EAG) is unaware of any equality or innovation considerations.

8 EAG commentary of the robustness of the evidence submitted by the company

Clinical

Generally the External Assessment Group (EAG) considers that, based on the available clinical evidence, atogepant and rimegepant are likely to have broadly similar effectiveness for the acute treatment of migraine. However, the evidence is based on indirect comparisons, and the absence of formal equivalence or non-inferiority testing introduces uncertainty over clinical equivalence. Despite this, taking a pragmatic view of all the available evidence, the EAG considers the assumption of comparable clinical effectiveness to be reasonable for decision-making within a cost-comparison framework.

Economic

Generally, the EAG considers that, based on the clinical and cost-effectiveness evidence presented by the company, it is likely that atogepant and rimegepant are clinically similar for the treatment of acute migraine. Therefore, all else being equal, the EAG considers that atogepant is likely to be cost-saving compared with rimegepant.

The EAG considers that because there is potential for a mix of prescribing to take place and with different pack prices for atogepant available, it is worthwhile to consider the cost savings as a range, from [redacted].

9 References

1. Wijeratne T, Oh J, Kim S, Yim Y, Seo Kim M, Shin J, et al. Global, regional, and national burden of headache disorders, 1990–2021, with forecasts to 2050: A Global Burden of Disease study 2021. *Cell Reports Medicine* 2025; **6**: 102348.
2. National Migraine C. Impact of migraine. 2026.
3. Katsarava Z, Buse D, Manack A, Lipton R. Defining the Differences Between Episodic Migraine and Chronic Migraine. *Current Pain and Headache Reports* 2011; **15**: 86-92.
4. Brain Research UK. Migraine, n.d. Available from: https://www.brainresearchuk.org.uk/neurological-conditions/migraine. Date accessed: Mar 2026.
5. England N. Improved NHS migraine care to save thousands of hospital stays, 2020. Available from: https://www.england.nhs.uk/2020/01/improved-nhs-migraine-care/. Date accessed: Mar 2026.
6. National Migraine C. Migraine at work: A national Migraine Centre factsheet, n.d. Available from: https://www.nationalmigrainecentre.org.uk/understanding-migraine/factsheets-and-resources/migraine-at-work/. Date accessed: Mar 2026.
7. National Migraine C. Migraine and work: The employment impact of migraine doesn't just affect the individual, n.d. Available from: https://www.nationalmigrainecentre.org.uk/corporate-wellbeing/migraine-and-work/. Date accessed: Mar 2026.
8. National Institute for Health and Care Excellence. Rimegepant for treating migraine (TA919). 2023. Available from: https://www.nice.org.uk/guidance/ta919. Date accessed: February 2026.
9. National Institute for H, Care E. Atogepant for preventing migraine (TA973). Available at: https://www.nice.org.uk/guidance/TA973. [Last accessed: 5 March 2026]. Date accessed.
10. Formulary BN. Atogepant, n.d. Available from: https://bnf.nice.org.uk/drugs/atogepant/. Date accessed: Mar 2026.
11. AbbVie Data on File [CONFIDENTIAL]. ECLIPSE Clinical Study Report, 2025.
12. Dycke AV, Brand-Schieber E, Ornello R, Lee MJ, Guo H, Luo L, et al., editors. Efficacy, Safety, and Tolerability of Atogepant for the Acute Treatment of Migraine: Results from the ECLIPSE Trial. 19th European Headache Congress (EHC); 2025; Lisbon, Portugal.
13. Lusk BJ, Wilson L, Moore C, Yarnell S, Kalapura C, Choudhury A, et al. Calcitonin Gene-Related Peptide Inhibitors and Cardiovascular Events in Patients With Migraine: A Retrospective, Observational, Cohort Study. *Neurology* 2026; **106**: e214479.
14. Lipton RB, Croop R, Stock EG, Stock DA, Morris BA, Frost M, et al. Rimegepant, an Oral Calcitonin Gene-Related Peptide Receptor Antagonist, for Migraine. *The New England journal of medicine* 2019; **381**: 142-9.
15. Marcus R, Goadsby PJ, Dodick D, Stock D, Manos G, Fischer TZ. BMS-927711 for the acute treatment of migraine: a double-blind, randomized, placebo controlled, dose-ranging trial. *Cephalalgia* 2014; **34**: 114-25.
16. Lipton RB, Thiry A, Morris BA, Croop R. Efficacy and Safety of Rimegepant 75 mg Oral Tablet, a CGRP Receptor Antagonist, for the Acute Treatment of Migraine: A Randomized, Double-Blind, Placebo-Controlled Trial. *J Pain Res* 2024; **17**: 2431-41.
17. Yu S, Kim BK, Guo A, Kim MH, Zhang M, Wang Z, et al. Safety and efficacy of rimegepant orally disintegrating tablet for the acute treatment of migraine in China and South Korea: a phase 3, double-blind, randomised, placebo-controlled trial. *Lancet neurol* 2023; **22**: 476-84.
18. Croop R, Goadsby PJ, Stock DA, Conway CM, Forshaw M, Stock EG, et al. Efficacy, safety, and tolerability of rimegepant orally disintegrating tablet for the acute treatment of migraine: a randomised, phase 3, double-blind, placebo-controlled trial. *The Lancet* 2019; **394**: 737-45.

19. Ikeda K, Matsumori Y, Kudo M, Ishikawa T, Hoshino Y, Yoshimatsu H, et al. Efficacy and safety of rimegepant for the acute treatment of migraine in Japan: A dose-ranging, double-blind, randomized controlled trial. *Headache* 2025.
20. Messoud Ashina et al., "A Phase 4 Randomized Double-blind Placebo-Controlled Study of Rimegepant for Acute Treatment of Migraine in Adults Unsuitable for Triptan Use," in Annual Metting of the American Headache Society, Minneapolis, 2025.
21. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**: d5928.
22. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *Bmj* 2019; **366**: l4898.
23. AbbVie Data on File [CONFIDENTIAL]. Atogepant in Migraine UK Advisory Board Meeting Report, 2025.
24. Dias S, Sutton A, Welton NJ, Ades AE. NICE DSU TECHNICAL SUPPORT DOCUMENT 3: HETEROGENEITY: SUBGROUPS, META-REGRESSION, BIAS AND BIAS-ADJUSTMENT, 2012. Available from: https://www.ncbi.nlm.nih.gov/books/NBK395886/pdf/Bookshelf_NBK395886.pdf. Date accessed: Mar 2026.
25. Lee D, Allen A, Lovell A, Abdelsabour A, Wilson E, Melendez-Torres GJ. How similar is similar enough? Assessment of indirect treatment comparisons to support similarity for NICE's cost comparison route, 2024. Available from: https://www.ispor.org/docs/default-source/euro2024/how-similar-is-similar-enough-cost-comparison-poster-ispor142603-pdf.pdf?sfvrsn=21e7eb7b_0. Date accessed: Mar 2026.
26. Lakens D, Scheel M, Isager P. Equivalence Testing for Psychological Research: A Tutorial. *Advances in Methods and Practices in Psychological Science* 2018; **1**: 259-69.
27. Burgess B, Ip S, Downes N, Walters A, Dadswell C, Edwards S. A Novel Framework to Assess Non-Inferiority in National Institute for Health and Care Excellence (NICE) Cost-Comparison Evaluations (CCEs) where Network Meta-Analyses (NMAs) Report Non-Statistically Significant Differences, 2025. Available from: https://www.ispor.org/docs/default-source/cti-meeting-21305-documents/239846eb-affa-4c6c-9fb3-045eaae22396.pdf?sfvrsn=75548d0e_0. Date accessed: Mar 2026.
28. Downes N, Walters A, Burgess B, IP S, Dadswell C, Edwards S. Evaluating Clinical Similarity: a Systematic Review of Methods Used Within National Institute for Health and Care Excellence (NICE) Cost-Comparison Evaluations (CCEs) When Relying on Statistically Non-Significant Differences from Indirect Treatment Comparisons (ITCs), 2025. Available from: https://www.ispor.org/docs/default-source/cti-meeting-21305-documents/e1d7a692-dfc6-4f68-82bd-fad285dcd087.pdf?sfvrsn=f8df2ff4_0. Date accessed: Mar 2026.
29. Lee D, Allen A, Lovell A, Abdelsabour A, Wilson E, Melendez-Torres GJ. How Similar Is Similar Enough? Assessment of Indirect Treatment Comparisons to Support Similarity for National Institute for Health and Care Excellence's Cost Comparison Route. *Value in Health* 2025; **28**: 1770-9.
30. Althunian TA, de Boer A, Groenwold RHH, Klungel OH. Defining the non-inferiority margin and analyzing non-inferiority: An overview: Methods used to choose the margin and analyze non-inferiority. *Br J Clin Pharmacol* 2017; **83**: 1636-42.
31. Johnston K, Powell LC, Popoff E, L'Italien GJ, Pawinski R, Ahern A, et al. Cost-effectiveness of rimegepant oral lyophilisate compared to best supportive care for the acute treatment of migraine in the UK. *Journal of medical economics* 2024; **27**: 627-43.
32. Office for National Statistics (ONS). National life tables: UK. 2025. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables Date accessed: February 2026.

33. NHS. The Traffic Light System and Classification of Medicines. 2026. Available from: https://remedy.bnssg.icb.nhs.uk/formulary-adult/bnssg-joint-formulary/the-traffic-light-system-and-classification-of-medicines/. Date accessed: 12/03/2026.

10 Appendices

10.1 Model structure summary

The company presented a decision tree plus Markov model (Figure 4 of the CS) to estimate the total costs of atogepant and rimegepant over a two-year time horizon. The model cycle length was assumed to be 48 hours (the assumed length of a migraine attack).

Patients enter the model after experiencing a single migraine attack and receive gepant treatment. Response to treatment was defined as pain relief at 2 hours, aligned with the outcome of the economic model used in TA919.[8] Non-responders to treatment enter the Markov model in the "off treatment" health state, incur no further costs and remain there for the rest of the model time horizon or until death. Responders to treatment remain in the "on treatment" health state until they discontinue treatment and enter the "off treatment" health state or until death. Patients in the "on treatment" health state have a per cycle probability of a migraine attack. The probability of a migraine attack per cycle was estimated to be *** (calculated by dividing migraine attacks per month by the number of 48-hour periods in a month).

As mentioned in Section 5 the company included healthcare resource use (HCRU) and monitoring costs for atogepant and rimegepant for completeness, even though it was assumed there are no differences between the treatments. Monitoring costs were based on a single cost of a specialist visit applied to all patients in the first cycle of the model and no further monitoring was assumed. HCRU costs in the model cover hospitalisations, accident and emergency visits and GP visits. These costs are only applied in the "on treatment" health state and only for a proportion of patients that are in moderate/ severe pain at 24 hours (***%, derived from ECLIPSE). Further details of HCRU and monitoring costs are described in Section 4.2.3 of the company submission.

Single Technology Appraisal

Atogepant for treating migraine [ID6615]

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 **noon on 20 April 2026** 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 ********** should be highlighted in turquoise and all information submitted as '**********' in pink.

Factual Inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 13 of the EAG report states: '*The company's conclusion of clinical equivalence between atogepant and rimegepant is not supported by formal equivalence or non-inferiority analyses; the absence of statistically significant differences in the NMA indicates a lack of evidence of difference rather than evidence of clinical equivalence, which would require pre-specified margins and appropriate statistical methods and the EAG's additional analyses further highlight the uncertainty in the relative effectiveness estimates, introducing uncertainty in the assumption of comparable clinical effectiveness underpinning*	The wording here should be revised as follows: *'The company's conclusion of clinical* ~~***equivalence***~~ ***similarity*** *between atogepant and rimegepant is not supported by formal equivalence or non-inferiority analyses* ~~***the absence of statistically significant differences in the NMA indicates a lack of evidence of difference rather than evidence of clinical equivalence, which would require pre-specified margins and appropriate statistical methods and***~~ ***as such analyses would require pre-specified margins, which as noted, are not available.*** *The* ***uncertainty in the*** *EAG's additional analyses* ~~***further highlight uncertainty in the relative effectiveness estimates, introducing uncertainty in the assumption of comparable clinical effectiveness underpinning the cost-comparison approach***~~ ***supports***	The EAG's statements throughout the report focus on the absence of formal equivalence or non-inferiority analyses and state that, therefore, clinical equivalence based on the network meta-analyses (NMAs) between atogepant and rimegepant has not been demonstrated. This framing may not clearly distinguish between: 1) formal statistical equivalence or non-inferiority, which requires pre-specific margins and 2) the standard set out in NICE's cost-comparison guidance, which is that the new technology should provide similar or greater health benefits at similar or lower cost.[1] While the Company recognise that formal clinical equivalence based on the NMA was not demonstrated, as noted in the response to CQ A2, NICE methods only require that the technology has similar or greater	This is not a factual inaccuracy. The EAG notes, that in response to CQ A2, the company states that *'conclusions of clinical equivalence were primarily based on the observed results of the NMA, which demonstrate no statistically significant difference between atogepant and rimegepant…'* The EAG interprets 'clinical equivalence' in its standard methodological sense which requires formal equivalence or non-inferiority analyses. The original wording of the report reflects a methodological distinction between the absence of statistically significant differences and demonstration of clinical equivalence. Hence, the original wording, which does include the EAG's position that the treatments likely have similar effectiveness, has been retained.

the cost-comparison approach.'	***that these results are not robust enough for decision-making. However, it is important to note that NICE do not require formal clinical equivalence analyses for cost-comparison appraisals, rather evidence on the clinical or biological plausibility of similarities;[1] there is minimal uncertainty associated with the evidence of comparable clinical effectiveness presented in the submission****.'*	health benefits to support a cost-comparison appraisal. The NICE user guide for the cost-comparison template does not require companies to prove formal statistical equivalence. In this appraisal, conclusions of similarity in overall health benefits were primarily based on the observed results of the NMA, which demonstrated no statistically significant differences between atogepant and rimegepant across the primary and all but one of the secondary outcomes evaluated. This interpretation is further supported by the company and	

Page 48 of the EAG report states: '*In the absence of formal equivalence or non-inferiority testing, the evidence presented by the company cannot be considered sufficient to demonstrate that atogepant and rimegepant are clinically equivalent and support the company's conclusions.'*	The wording here should be revised as follows: *'In the absence of formal equivalence or non-inferiority testing, the evidence presented by the company cannot be considered sufficient to demonstrate* ***~~that atogepant and rimegepant are clinically equivalent and support the company's conclusions~~ clinical equivalence between atogepant and rimegepant in a strict statistical sense. However, formal equivalence testing is not required by NICE's cost-comparison guidance.'***	EAG clinical experts who determined the treatments to have comparable efficacy and safety profiles. As noted by the EAG, the lack of established non-inferiority margins (NIMs) or minimal clinically important differences (MCIDs) in the literature precludes a formal non-inferiority analysis robust enough to inform decision-making. The EAG also notes that the hypothetical NIMs required to achieve 90% probability of non-inferiority in their additional analysis are high, further underlining the lack of an agreed, clinically justified margin. Given this context, it would be more factually accurate for the report to distinguish clearly between the lack of formal equivalence/non-inferiority testing and the question of whether the available evidence supports similar health benefits. The NMA and the EAG's additional analyses do not show statistically significant or clearly clinically important differences	As above, this is not a factual inaccuracy. The original wording has been retained.
Page 49 of the EAG report states: *'As previously described, the company assumed that atogepant is equivalent to rimegepant due to 95% credible intervals overlapping zero (indicating no statistically*	This statement should be amended as follows: *'As previously described, the company assumed that atogepant* ***~~is equivalent to~~ and*** *rimegepant* ***are similar*** *due to 95% credible intervals overlapping zero (indicating no statistically significant differences) across outcomes*		As above, this is not a factual inaccuracy. In the company submission, the term 'equivalence' has been used stating that the NMA demonstrates equivalence in outcomes between atogepant and rimegepant, based on a lack of statistically significant

significant differences) across outcomes (except for use of rescue medication within 24 hours).'	*(except for use of rescue medication within 24 hours).'*	between atogepant and rimegepant. The current wording in the EAG report implies uncertainty in the evidence supporting clinical similarity, therefore the Company's suggested revisions to the text make it clear that the uncertainty lies in the formal testing of clinical equivalence, which is not a requirement in NICE's cost-comparison guidance.	differences. The EAG wording reflects this position.
Page 14 of the EAG report states: *'Migraine exists on a spectrum from episodic migraine (<15 headache days/month) to chronic migraine, defined as headaches occurring 15 or more days/month for >3 months, with migraine features on ≥8 days/month.'*	This should be revised to more clearly reflect the definition of chronic migraine as follows: *'Migraine exists on a spectrum from episodic migraine (<15 headache days/month) to chronic migraine, defined as headaches occurring 15 or more days/month for >3* ***consecutive*** *months, with migraine features on ≥8 days/month.'*	The current wording omits the key requirement that chronic migraine criteria are met for a *consecutive* 3-month period. Adding "consecutive" ensures that the description aligns more closely with standard diagnostic criteria, thereby improving clinical accuracy of the report and preventing misinterpretation of chronic migraine status.	Thank you. This has been amended.

Page 15 of the EAG report states: '*Atogepant is an oral tablet with a maximum recommended dose of 60 mg per day*.'	This statement should be revised to describe the administration of atogepant for acute treatment of migraine as follows: '*Atogepant is an oral tablet* ***taken as needed*** *with a maximum recommended dose of 60 mg per day*.'	The current wording does not accurately reflect the dosage description provided in Table 2 of the Company Submission. Revising the statement aligns the EAG report with the Company's wording, and the Summary of Product Characteristics for atogepant.	
Page 57 of the EAG report states: '*The dose of atogepant is 60 mg taken orally up to once daily, as needed.'*	This statement should be revised to describe the administration of atogepant for acute treatment of migraine as follows: '***~~The dose of~~*** *Atogepant is* ***~~60 mg~~*** *taken orally* ***~~up to once daily,~~*** *as needed,* ***up to a maximum recommended dose of 60 mg per day***.'		This is not a factual inaccuracy. No change required.
Page 15 of the EAG report states: '*Clinical expert feedback suggested the company's pathway is partly consistent with UK practice'*	Please revise this statement as follows: ''***~~Clinical expert~~*** *Feedback* ***from the EAG's clinical experts*** *suggested the company's pathway is partly consistent with UK practice'*	As currently worded, it is unclear whether this statement refers to clinical experts consulted by the Company or by the EAG. This is important because, as noted in Section 1.3.3 of the Company Submission, clinical experts consulted by the Company agreed that the treatment pathway presented is in line with UK clinical practice.[2] As this	Thank you. This has been amended.

		statement reflects the views of clinical experts consulted independently by the EAG, this should be clearly stated to avoid ambiguity.	
Page 15 of the EAG report states: *'Experts also noted that treatment pathways may vary by region and prescribing setting, with rimegepant availability in primary care in some areas, whereas atogepant is currently only available in secondary care for migraine prevention.'*	This statement should be revised as follows: *'Experts also noted that treatment pathways may vary by region and prescribing setting;* ***~~with rimegepant availability in primary care in some areas, whereas atogepant is currently only available in secondary care for migraine prevention~~ both rimegepant and atogepant are available in primary care for migraine prevention in some areas and rimegepant is also available in some areas in primary care for acute treatment of migraine.'***	Atogepant is available in primary care for migraine prevention, as primary care initiation, primary care initiation following specialist recommendation, as well as primary care continuation following specialist initiation. As discussed in response to CQ B6, here is an example of each category from relevant local formularies; primary care initiation (Black Country), primary care initiation following specialist recommendation (Greater Manchester) and primary care continuation following specialist initiation (e.g. North East and North Cumbria).	Thank you. Amended, partially in line with the suggested wording to reflect that access to atogepant may vary by region and prescribing pathway rather than being limited to secondary care only.
Page 19–20 of the EAG report states: '*However, exploration of aura status and age may have provided additional*	This statement should be revised to ensure it is clear that exploration of subgroups stratified by aura status and age were not pre-specified subgroups in the ECLIPSE trial, as follows:	The current wording could be interpreted as implying that subgroup analyses by aura status and age could have been presented by the Company. In the ECLIPSE trial, these were not pre-specified subgroups, and	Thank you. This sentence has been revised to state that these subgroups were not pre-specified.

reassurance regarding generalisability.'	'***Although*** *exploration of aura status and age may have provided additional reassurance regarding generalisability,* ***subgroup analyses stratified by aura status and age were not pre-specified in the ECLIPSE trial.'***	such analyses could not be provided within the Company Submission. Revising the statement to make this explicit improves clarity about the available evidence and avoids overstating the feasibility of additional subgroup exploration.	
Page 21 of the EAG report states: '*Atogepant (brand name Aquipta®) does not currently have a marketing authorisation in the UK, but this is expected* in April 2026.'	This statement should be revised as follows: '*Atogepant (brand name Aquipta®) does not currently have a marketing authorisation* ***~~in the UK, but this is expected in April 2026.~~*** **for** the acute treatment of migraine with or without aura in adults in the UK, but this is expected in April 2026.'	As noted in Table 2 of the Company Submission, atogepant is already indicated for prophylaxis of migraine in adults who have at least 4 migraine days per month.[3] Therefore, clarification is needed that atogepant currently has marketing authorisation in the UK in this indication, and that the marketing authorisation for the acute treatment of migraine with or without aura in adults is anticipated in April 2026.	Thank you. This has been amended.
Page 22 of the EAG report states: *'As there was no direct head-to-head data for the comparison of atogepant with rimegepant, the company conducted network meta-analyses*	This statement should be revised as follows: *'As there was no direct head-to-head data for the comparison of atogepant with rimegepant, the company conducted network meta-analyses (NMAs) to assess the*	The proposed change clarifies that the NMAs were conducted to estimate relative, rather than absolute, efficacy and safety between atogepant and rimegepant.	Thank you. This has been amended.

(NMAs) to assess the efficacy and safety of the two treatments.'	***relative** efficacy and safety of the two treatments.'*		
Page 25 of the EAG report states: *'A total of 270 full-text articles were screened… . The reasons for exclusion of the 153 remaining studies were not clearly detailed in the CS.'*	This should be revised as follows: *'A total of **279** full-text articles were screened… . The reasons for exclusion of the **152** remaining studies were not clearly detailed in the CS.'*	The current number of full-text articles screened and studies excluded in the Company Submission is reported inaccurately in the EAG report and should be updated. Correct values are reported in Company Submission Appendix B.1.3 and Company Submission Section 3.1 and 3.9.	Thank you. This has been amended.
Page 34, Table 6 of the EAG report contains the incorrect footnote labelled [c] and footnote notations [d] and [e], with no further explanation in the footnote. It also states that Table 6 is reproduced from Table 11 in the Company Submission.	Please could these footnotes be added: '*[a] N= number of subjects in the mITT population; [b] n=Number of responders/N1=number of participants in that group;* ; ***[c] ~~The odds ratios between group treatment differences for the primary endpoint are derived from the GLMM methods.~~ The point estimate for all key secondary endpoints is responder rate; [d] The odds ratios between group treatment differences for the primary and all key secondary endpoints are derived from the GLMM methods;***	The footnotes in this table are incomplete and may overlook important caveats relating to the data. Adding the missing footnote explanations will ensure the table is self-contained, transparent, and interpretable. Additionally the referenced table from the Company Submission was reported inaccurately and should be updated.	Thank you. These have been amended.

	[e] ***Adjusted p-value use fixed-sequence procedure to control the overall type I error rate for multiple comparisons.*** *The total mITT population includes 1223 patients; the mITT efficacy attack 1 population includes* **** *patients*.' Additionally, please could the table title be updated to reflect that Table 6 has been reproduced from **Table 12** of the Company Submission.		
Page 38, Table 9 of the EAG report states that the n (%) of patients in the atogepant arm of the safety population for all migraine attacks during the double-blind period who experienced TEAE 1 is *********.	This should be updated to ********** as per Table 14.3_1.2 in the ECLIPSE CSR.[4]	The n (%) of patients in the atogepant arm safety population for all migraine attacks during the double-blind period who experienced a TEAE in the ECLIPSE trial was reported inaccurately and should be updated.	Thank you. This has been amended.
Page 39 of the EAG report states: *'Specifically, nausea was the adverse reaction that most commonly led to discontinuation for acute treatment* ******.'	This statement should be removed.	The current statement is incorrect; nausea was not the adverse reaction that most commonly led to discontinuation of acute treatment, and the cited value of **** refers to the incidence of nausea as a TEAE unrelated to discontinuations. As	Thank you. The original wording has been amended in line with the clinical study report to clarify that nausea was the only adverse event reported in *** of atogepant-treated patients and discontinuations due to adverse events were ******

		reported in the ECLIPSE CSR (pages 3005–3006), there were no discontinuations due to adverse events after the first migraine attack and the proportion discontinuing due to nausea over the entire double-blind period was ***** overall.[4] This statement should therefore be removed to avoid misrepresenting the safety profile of atogepant.	
Page 51 of the EAG report states: *'… there were some differences in the upper 95% credible intervals (Crl) for the vague priors NMA for pain relief at two hours (company's upper 95%Crl: ****) and the informative priors NMA for pain freedom at two hours (company's upper 95%Crl: ****).'*	This statement should be revised as follows: *'… there were some differences in the upper 95% credible intervals (Crl) for the vague priors NMA for pain relief at two hours (company's upper 95%Crl: ****) and the informative priors NMA for pain freedom at two hours (company's upper 95%Crl: ****).'*	The upper 95% CrI for the NMA with informative priors for pain freedom at 2 hours was reported inaccurately and should be updated.	Thank you. This has been amended.
Page 53 of the EAG report states: '*Baseline characteristics were generally reflective of*	The EAG should clarify the source of the statement that BMI could influence treatment response within the report.	It is important to capture the source of this assumption to ensure it can be accurately interpreted.	Thank you. The text has been revised to state that BMI was informed by EAG clinical expert opinion.

clinical practice, although some differences were noted, including a slightly lower BMI, a factor that could influence treatment response.'		As confirmed by UK clinical experts at an advisory board (previously detailed in the Company Submission), no treatment effect modifiers were identified for the acute treatment of migraine.[2] Furthermore, the inclusion criteria, baseline migraine severity and outcome definitions were highly comparable across all identified rimegepant studies, which again was confirmed by clinical and health economic experts consulted by the Company.	
Page 54 of the EAG report states: '*The company reported that fixed-effects and random-effects models demonstrated similar model fit across outcomes, suggesting only modest improvement in fit when using random-effects models. The company nevertheless selected random-effects models with informative priors as their*	This statement should be revised as follows: *'The Company reported that fixed-effects and random-effects models demonstrated similar model fit across outcomes~~, suggesting only modest improvement in fit when using random-effects models~~* ***however, residual deviance was notably improved using a random-effects model indicating better statistical fit. As such,*** *the company* ***~~nevertheless~~*** *selected random-effects models with*	The current wording does not fully reflect the Company's rationale for model selection within the NMA, as detailed in Section 3.9.5.1 of the Company Submission. In particular, it understates the improvement in model fit (residual deviance) observed with random-effects models. Revising the text to note that residual deviance was notably improved with the random-effects model clarifies that the choice was supported by better statistical fit, rather	Thank you. Partially amended. The text has been revised to acknowledge the residual difference was improved with the random effects model. However, the original wording was not factually inaccurate and reflected that the overall differences in model fit were small, as reported in the Company submission.

preferred analysis approach.'	*informative priors as their preferred analysis approach'*	than being made despite similar overall fit.	
Page 60, Table 17 of the EAG report states that the Company base case total costs are: • Rimegepant: £******** • Atogepant: £********	These values should be revised to report the correct Company base case total costs for atogepant and rimegepant as reported in Table 34 of the Company Submission: • Rimegepant: £******** • Atogepant: £********	The Company base case total costs were reported inaccurately and should be updated.	Thank you for highlighting the error. This has been corrected in the EAG report.

Typographical Errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 10 of the EAG report states: '*LS :east squares'*	This should be revised as follows: '*LS* ***Least*** *squares'*	Typographical error.	Thank you. This has been amended.
Page 18 of the EAG report states: *'However, clinical experts indicated that further optimisation of acute therapies (e.g. trial of alternative triptans, use of non-oral formulations where needed, and combination therapy including a triptan, NSAI and anti-emetic) may occur in routine practice before a gepant.'*	This should be revised as follows: *'However, clinical experts indicated that further optimisation of acute therapies (e.g. trial of alternative triptans, use of non-oral formulations where needed, and combination therapy including a triptan,* ***NSAID*** *and anti-emetic) may occur in routine practice before a gepant.'*	Typographical error.	Thank you. This has been amended.

Page 48 of the EAG report states: *'The company also stated that this approach is consistent with precedent in co-comparison technology appraisals (as identified by Lee et al. 2024).'*	This should be revised as follows: *'The company also stated that this approach is consistent with precedent in **cost-**comparison technology appraisals (as identified by Lee et al. 2024).'*	Typographical error.	Thank you. This has been amended.
Page 22 of the EAG report states the following as one bullet point in the list of the outcomes of interest in the Company's NMAs: • '*sustained pain relief from 2 to 48 hours,* *use of rescue medication within 24 hours'*	This should be revised to be two separate bullet points to make it clear these are two separate outcomes of interest, as with the other listed outcomes of interest as follows: • '*sustained pain relief from 2 to 48 hours* • *use of rescue medication within 24 hours'*	Formatting error.	Thank you. This has been amended.
Page 28 of the EAG report states: '*Table 4. EAG's summary of the design, conduct and analysis of the ECIPSE trial'*	This should be revised as follows: '*Table 4. EAG's summary of the design, conduct and analysis of the **ECLIPSE** trial'*	Typographical error.	Thank you. This has been amended.
Page 30 of the EAG report states: *'The proportion of patients experiencing vomiting [redacted] was also considered lower than anticipated relative to clinical practice.'*	This statement should be revised to reflect that the proportion of patients experiencing vomiting was [redacted] in the atogepant arm specifically, or [redacted] overall, for example: *'The proportion of patients experiencing vomiting **in the atogepant arm** [redacted] was also considered lower than anticipated relative to clinical practice.'*	Typographical error.	Thank you. This has been amended.

Page 31 of the EAG report states: *'The primary analysis for atogepant vs placebo forming the focus of this submission was conducted on the mITT population ([redacted] vs [redacted]), which is lightly smaller than planned enrolment and may slightly reduce precision.'*	This should be revised as follows: *'The primary analysis for atogepant vs placebo forming the focus of this submission was conducted on the mITT population ([redacted] vs [redacted]), which is **slightly** smaller than planned enrolment and may slightly reduce precision.'*	Typographical error.	Thank you. This has been amended.
Page 35 of the EAG report states: *'Improvements were also observed in EQ-5D VAS scores, with a greater increase from baseline in the atogepant group compared with placebo ([redacted]).'*	This should be revised as follows: '*Improvements were also observed in EQ-5D VAS scores, with a greater increase from baseline in the atogepant group compared with placebo ([redacted]).'*	Typographical error.	Thank you. This has been amended.
Page 43 of the EAG report states: '*The EAG was able to reproduce the results reported in the company submission with only negligible numerical differences occasionally*.'	This statement should be revised for clarity as follows: '*The EAG was able to reproduce the results reported in the company submission with only negligible numerical differences occasionally **identified***.'	Typographical error.	Thank you. This has been amended.
Page 49 of the EAG report states: '*In response to clarification questions, the EAG notes that the exclusion of these studies resulted in wider credible intervals, indicating slightly reduced precision.'*	This statement should be amended for clarity: '~~***In response to clarification questions***~~ ***Following the Company's response to*** *clarification questions, the EAG notes that the exclusion of these studies resulted in wider credible intervals, indicating slightly reduced precision.'*	Typographical error.	Thank you. This has been amended.

Page 53 of the EAG report states: *'However, the trial's restriction to patients with lower acute medication use and episodic migraine, although consistent with the evidence used to inform previous NICE technology appraisal for rimegepant (TA919).'*	This statement should be revised as follows: *'However, the trial's restriction to patients with lower acute medication use and episodic migraine, although consistent with the evidence used to inform* ***the*** *previous NICE technology appraisal for rimegepant (TA919).'*	Typographical error.	Thank you. This has been amended.
Page 54 of the EAG report states: *'The ECLIPSE provided evidence of a similar incidence of treatment-emergent adverse events (TEAEs) between treatments during the first attack, while severe and serious TEAEs or TEAEs leading to discontinuation were rare.'*	This statement should be revised as follows: *'The ECLIPSE* ***trial*** *provided evidence of a similar incidence of treatment-emergent adverse events (TEAEs) between treatments during the first attack, while severe and serious TEAEs or TEAEs leading to discontinuation were rare.'*	Typographical error.	Thank you. This has been amended.
Page 56 of the EAG report states: *'Healthcare resource use, including hospitalisations, accident and emergency (A&E) visits, GP visits and monitoring costs (assumed to be the cost of a visit with a specialist) are the same for atogepant and rimegepant, but the company has included these costs in their analysis for completeness.'*	This statement should be revised as follows: *'Healthcare resource use, including hospitalisations, accident and emergency (A&E) visits, GP visits and monitoring costs (assumed to be the cost of a visit with a specialist)* **is** *the same for atogepant and rimegepant, but the company has included these costs in their analysis for completeness.'*	Typographical error.	Thank you for highlighting this error. The EAG report has been corrected.
Page 57 of the EAG report states: *'The EAG considers that, overall, the company's case for atogepant being cost-saving compared to rimegepant, under the assumption of clinical similarity.'*	This statement is unfinished, and should be revised to ensure clarity. Based on the statements made elsewhere in the report that '*atogepant is likely to be cost-saving compared with rimegepant*', an example of an appropriate amendment is as follows:	The current sentence is incomplete. As written, it lacks a clear conclusion (e.g. whether the EAG agrees or disagrees	Thank you for highlighting this error. The EAG report has

	'The EAG considers that, overall, the company's case for atogepant being cost-saving compared to rimegepant ***is appropriate****, under the assumption of clinical similarity.'*	with the Company's case). Elsewhere in the report, the EAG states that '*atogepant is likely to be cost-saving compared with rimegepant'*, indicating that the EAG considers the Company's case broadly appropriate. Completing the sentence as suggested or similar ensures consistency with statements made elsewhere in the report.	been corrected.
Page 57 of the EAG report states: *'The list price of rimegepant for a 2- and 8-pack of 75 mg oral dispersible tablets (ODT) is £28.80 and 103.20, respectively.'*	This statement should be revised to report the correct list price for a 2-pack of rimegepant as follows:	Typographical error.	Thank you for highlighting this error. The EAG report has been corrected.

	*'The list price of rimegepant for a 2- and 8-pack of 75 mg oral dispersible tablets (ODT) is £**25.80** and £103.20, respectively.'*		
Page 58 of the EAG report states: '*100% of patients are prescribed on 2-pack of gepant tablets for the first migraine attack.'*	This statement should be revised as follows: '100% of patients are prescribed **one** 2-pack of gepant tablets for the first migraine attack.'	Typographical error.	Thank you for highlighting this error. The EAG report has been corrected.

Highlighting issues

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Page 21 of the EAG report states the date of anticipated marketing authorisation for atogepant for the acute treatment of migraine with or without aura in adults.	The anticipated marketing authorisation date for atogepant to treat acute migraine is commercially confidential and therefore should be marked as confidential.	This should be amended to: '…*expected in* April 2026.'	Thank you. This has been amended.
Page 28 of the EAG report states: '[redacted]'	This information is published and therefore does not need to be marked as confidential.[5]	This should be amended to: *'Randomisation was conducted centrally via an IRT system, with all participants assigned a unique identification number at Visit 1/Screening. '*	Thank you. This has been amended.

Page 30 of the EAG report states the proportion of patients experiencing vomiting in the ECLIPSE trial that are unpublished without confidentiality highlighting.	Unpublished data from the ECLIPSE trial are not planned for publication and should be marked as confidential.	This should be amended to: *'The proportion of patients experiencing vomiting* [redacted] *was also considered lower than anticipated relative to clinical practice.'*	Thank you. This has been amended.
Page 30 of the EAG report states the numerical differences of baseline characteristics between arms in the ECLIPSE trial that are unpublished without CiC highlighting.	Unpublished data from the ECLIPSE trial are not planned for publication and should be marked as confidential.	This should be amended to: *'The EAG noted that the baseline characteristics of the ITT population and the mITT population used in the company's efficacy analyses were well balanced between arms, with only small numerical differences* [redacted] *occasionally noted across characteristics.'*	Thank you. This has been amended.
Page 30 of the EAG report states: '[redacted],	This information is published and stated in the Company Submission without marking and therefore does not need to be marked as confidential.[5]	This should be amended to: '*Participants with missing efficacy assessments at a specific time point during the double-blind period were classified as treatment failures (non-responders), for pain freedom, pain relief, absence of 1 symptom or ability to function*	Thank you. This has been amended.

consistent with a non-responder imputation approach. Three sensitivity analyses were conducted to assess robustness. [redacted]'		*normally at a specific time point for any attacks, consistent with a non-responder imputation approach. Three sensitivity analyses were conducted to assess robustness. Patients who did not treat 4 qualifying migraine attacks during the double-blind period (up to 16 weeks) were to be discontinued from the study at Visit 6 (week 16).'*	
Page 31 of the EAG report states: [redacted]	This information is published and stated in the Company Submission without marking and therefore does not need to be marked as confidential.[5]	This should be amended to: '*For binary responder endpoints (e.g. pain freedom at 2 hours, pain relief, absence of one symptom) during the double-blind period, participants who did not provide the required assessment were classified as treatment failures (non-responder imputation). For other efficacy endpoints, including those evaluated during the open-label period, continuous endpoints as well as ePRO endpoints evaluated during the double-blind period, mixed*	Thank you. This has been amended.

<table>
<tr>
<td>**********
**********.’</td>
<td></td>
<td>effects models (MMRM/GLMM) were applied using observed data without formal imputation of missing values.’</td>
<td></td>
</tr>
<tr>
<td>Page 33 of the EAG report states:
‘This corresponded to an odds ratio (OR) of
****
** reflecting a substantial relative improvement in pain freedom compared to placebo.’</td>
<td>This information is published and stated in the Company Submission and therefore does not need to be marked as confidential.[6]</td>
<td>This should be amended to:
‘This corresponded to an odds ratio (OR) of 2.36 (95% CI: 1.76 to 3.15; p<0.0001), reflecting a substantial relative improvement in pain freedom compared to placebo.’</td>
<td>Thank you. This has been amended.</td>
</tr>
<tr>
<td>Page 33, Table 5 of the EAG report states:
<table>
<tr><th></th><th>Atogepant (N=605)[a]
n/N1 (%)[b]</th><th>Placebo (N=618)[a]
n/N1 (%)[b]</th><th>OR (95% CI) vs Placebo[c]</th><th>P-value</th></tr>
<tr><td>Pain freedom at 2 hours</td><td>********
*******</td><td>******
******
</td><td>****
******
******
*</td><td>*****
**</td></tr>
</table>
</td>
<td>These values are published and presented in the Company Submission and therefore do not need to be marked as confidential.[6]</td>
<td>This should be amended to:
<table>
<tr><th></th><th>Atogepant (N=605)[a]
n/N1 (%)[b]</th><th>Placebo (N=618)[a]
n/N1 (%)[b]</th><th>OR (95% CI) vs Placebo[c]</th><th>P-value</th></tr>
<tr><td>Pain freedom at 2 hours</td><td>146/602 (24.3)</td><td>80/612 (13.1)</td><td>2.36 (1.76 to 3.15)</td><td><0.0001</td></tr>
</table>
</td>
<td>Thank you. This has been amended.</td>
</tr>
</table>

Page 34, Table 6 of the EAG report states:

	Atogepant (N=605) [a] n/N1 (%) [b, c]	Placebo (N=618)[a] n/N1 (%) [b, c]	OR (95% CI) vs Placebo [d]	P-value [e]
MBS free at 2 hours	[redacted]	[redacted]	[redacted]	[redacted]
Pain relief at 2 hours	[redacted]	[redacted]	[redacted]	[redacted]
Sustained pain relief 2 to 24 hours	[redacted]	[redacted]	[redacted]	[redacted]
Rescue medication use within	[redacted]	[redacted]	[redacted]	[redacted]

These values are published and presented in the Company Submission and therefore do not need to be marked as confidential.[6]

This should be amended to:

	Atogepant (N=605) [a] n/N1 (%) [b, c]	Placebo (N=618)[a] n/N1 (%) [b, c]	OR (95% CI) vs Placebo [d]	P-value [e]
MBS free at 2 hours	263/602 (43.7)	200/612 (32.7)	1.77 (1.41 to 2.24)	≤0.001
Pain relief at 2 hours	434/602 (72.1)	333/612 (54.4)	2.35 (1.85 to 2.98)	≤0.001
Sustained pain relief 2 to 24 hours	348/602 (57.8)	164/612 (26.8)	4.04 (3.18 to 5.15)	≤0.001
Rescue medication use within	91/602 (15.1)	327/613 (53.3)	0.14 (0.11 to 0.19)	≤0.001

Thank you. This has been amended.

24 hours Ability to function normally at 2 hours [redacted]	24 hours Ability to function normally at 2 hours 288/602 (47.8) 245/613 (40.0) 1.68 (1.29 to 2.18) ≤0.0001		
Page 37–38 of the EAG report states results of subgroup analyses from the ECLIPSE trial that are unpublished without CiC highlighting.	Unpublished data from the ECLIPSE trial are not planned for publication and should be marked as confidential.	This should be amended to: *'In some subgroups (e.g. 'other' region and triptan naïve) confidence intervals* [redacted] *however, point estimates remained consistent in direction with the overall mITT population. In addition, the EAG notes that wide confidence intervals reflected uncertainty likely associated with small subgroup sizes… An exception was freedom from MBS at 2 hours, which was* [redacted] *in the European subgroup but not in the China, Japan and other subgroup. '*	Thank you. This has been amended.

Page 38–39, Table 9 of the EAG report states:

Event, n (%)	Placebo (N=1177)	Atogepant (N=1195)	Total (N=1232)
TEAE 1	[redacted]	[redacted]	[redacted]
TEAE related to study treatment	[redacted]	[redacted]	[redacted]
Severe TEAE	[redacted]	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]	[redacted]
TEAE 1 leading to discontinuati	[redacted]	[redacted]	[redacted]

The data presented in this table for the total population are published and therefore do not need to be marked as confidential.[6]

This should be amended to:

Event, n (%)	Placebo (N=1177)	Atogepant (N=1195)	Total (N=1232)
TEAE 1	[redacted]	[redacted]	397 (32.2)
TEAE related to study treatment	[redacted]	[redacted]	85 (6.9)
Severe TEAE	[redacted]	[redacted]	4 (0.3)
Serious TEAE	[redacted]	[redacted]	7 (0.6)
TEAE 1 leading to discontinuation of study treatment	[redacted]	[redacted]	9 (0.7)
TEAE 1 leading to death	[redacted]	[redacted]	0
All deaths	[redacted]	[redacted]	0

Thank you. This has been amended.

on of study treatment			
TEAE 1 leading to death	*	*	*
All deaths	*	*	*
Reported within 48 hours following administration of study drug			
48-hour TEAE	****** **	******* **	****** ****
48-hour TEAE related to study treatment	****** **	******* *	****** **
Severe 48-hour TEAE 1	****** **	*	***** ***
Serious 48-hour TEAE 1	*	******* *	***** ***
48-hour TEAE 1 leading to discontinuation of study treatment	****** *	*******	******

Reported within 48 hours following administration of study drug			
48-hour TEAE	****** **	******* **	145 (11.8)
48-hour TEAE related to study treatment	****** **	******* *	64 (5.2)
Severe 48-hour TEAE 1	****** **	*	1 (<0.1)
Serious 48-hour TEAE 1	*	******* *	1 (<0.1)
48-hour TEAE 1 leading to discontinuation of study treatment	****** *	*******	6(0.5)
48-hour TEAE 1 leading to death	*	*	0

48-hour TEAE 1 leading to death	*	*	*
Page 39 of the EAG report states that: *The Summary of Product Characteristics (SmPC) for atogepant reports that, when atogepant was used daily for prophylaxis, the most commonly reported adverse reactions were [redacted], with the majority of these cases being mild and none being serious.*	These data are published in the SmPC for atogepant in the preventative indication and therefore do not need to be marked as confidential.[7]	This should be amended to: *The Summary of Product Characteristics (SmPC) for atogepant reports that, when atogepant was used daily for prophylaxis, the most commonly reported adverse reactions were nausea (7%), constipation (7%) and fatigue/somnolence (5%), with the majority of these cases being mild and none being serious.*	Thank you. This has been amended.
Page 46 of the EAG report states results from the NMA which are unpublished without CiC highlighting.	Results from the NMAs comparing atogepant and rimegepant are not planned for publication and are therefore confidential.	This should be amended to: '*Across the majority of efficacy and safety outcomes, the NMA results suggested no statistically significant differences between atogepant and rimegepant, with odds ratios (ORs) generally* [redacted] *and confidence intervals crossing the null… with rimegepant having approximately a* [redacted] *probability of being ranked most effective*	Thank you. This has been amended.

		for the primary outcome of pain freedom at 2 hours…'	
Page 51 of the EAG report states the results of the EAG's non-inferiority analyses without CiC highlighting.	Results of the EAG's non-inferiority analyses are derived from confidential NMA data that are not anticipated to be published and therefore should be marked as confidential.	These sections should be amended to: *'Accordingly, for pain freedom at two hours, there was a* [redacted] *probability that atogepant was more effective than rimegepant. In contrast, for pain relief at two hours, there was a* [redacted] *that atogepant was more effective than rimegepant'* And: *'For the outcome of pain freedom at two hours, the required hypothetical NIMs are* [redacted] *and* [redacted] *in the vague and informative prior models, respectively (i.e., the odds of a patient being pain free at two hours are ~**% higher in the rimegepant group compared to the atogepant group). Likewise, for the outcome of pain relief at two hours, the required hypothetical NIMs are* [redacted] *and* [redacted] *in the vague and*	Thank you. This has been amended.

		*informative prior models, respectively (i.e., the odds of a patient experiencing pain relief at two hours are ~**% higher in the rimegepant group compared to the atogepant group).'*	
Page 54 of the EAG report states results from the NMA which are unpublished without CiC highlighting.	Results from the NMAs comparing atogepant and rimegepant are not planned for publication and are therefore confidential.	This should be amended to: '*Across the majority of efficacy and safety outcomes, the NMA results demonstrated no statistically significant differences between atogepant and rimegepant, with effect estimates generally* ********** *and credible intervals crossing the line of no effect..'*	Thank you. This has been amended.

References

1. Johnston K, Harris L, Powell L, et al. Monthly migraine days, tablet utilization, and quality of life associated with Rimegepant - post hoc results from an open label safety study (BHV3000-201). J Headache Pain 2022;23:10.
2. AbbVie Data on File [CONFIDENTIAL]. Atogepant in Migraine UK Advisory Board Meeting Report, 2025.
3. Medicines and Healthcare products Regulatory Agency. Atogepant- Summary of product Characteristics. Available at: https://products.mhra.gov.uk/search/?search=atogepant&page=1 [Last accessed: August 2025].
4. AbbVie Data on File [CONFIDENTIAL]. ECLIPSE Clinical Study Report, 2025.
5. ClinicalTrials.gov. Study of Oral Atogepant Tablets to Assess Safety and Efficacy in Adult Participants With Migraine (ATO ACUTE) (NCT06241313). Available at: https://www.clinicaltrials.gov/study/NCT06241313 [Last accessed: October 2025].
6. Dycke AV, Brand-Schieber E, Ornello R, et al. Efficacy, Safety, and Tolerability of Atogepant for the Acute Treatment of Migraine: Results from the ECLIPSE Trial, In 19th European Headache Congress (EHC), Lisbon, Portugal, 2025.
7. Medicines and Healthcare products Regulatory Agency (MHRA). Atogepant- Summary of product Characteristics. Available at: https://mhraproducts4853.blob.core.windows.net/docs/d98e68718f3bc2e4af9da4af380b02d31b13de7d [Last accessed: October 2025].