Atogepant for preventing migraine [ID5090]

STA Report

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All authors read and commented on draft versions of the EAG report.

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List of Abbreviations

3+ TF	Patients in whom ≥3 prior preventive treatments have failed
A&E	Accident and emergency
AE	Adverse event
BASH	British Association for the Study of Headache
BNF	British National Formulary
BoNT/A	Botulinum toxin type A
BSC	Best supportive care
CCE	Cost-comparison evaluation
CFB	Change from baseline
CGRP	Calcitonin gene-related peptide
CI	Confidence interval
CM	Chronic migraine
CQ	Clarification question
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company submission
CSR	Clinical study report
CYP3A4	Cytochrome P450 3A4
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	External Assessment Group
eDiary	Electronic diary
EM	Episodic migraine
Epti	Eptinezumab
EQ-5D	European Quality of Life 5 Dimensions
EQ-5D-3L	European Quality of Life 5 Dimensions 3 Level Version
Ere	Erenumab
FE	Fixed effect
Fre	Fremanezumab
Gal	Galcanezumab
GP	General practitioner
HCRU	Healthcare resource use
HIT-6	Headache impact test-6
HR	Hazard ratio
HRG	Healthcare resource group
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ITT	Intent-to-treat
IWRS	Interactive Web Response System

IV	Intravenous
LS	Least squares
LSMD	Least squares mean difference
mAb	Monoclonal antibody
MAIC	Matching-adjusted indirect comparison
MAR	Missing-at-random
MD	Mean difference
MHD	Monthly headache day
mITT	Modified intent-to-treat
MMD	Monthly migraine days
MMRM	Mixed Model for Repeated Measures
MSQ	Migraine-specific quality of life questionnaire
MSQ-EF	Migraine specific quality of life emotional function subdomain
MSQ-RFP	Migraine specific quality of life role function-preventive subdomain
MSQ-RFR	Migraine specific quality of life role function-restrictive subdomain
MUD	Medication use day
N/A	Not applicable
NCT	National Clinical Trial
NHB	Net health benefit
NHS	National Health Service
NHWS	National Health and Wellness Survey
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
OATP	Organic anion transporting polypeptide
OR	Odds ratio
PAS	Patient access scheme
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PSSRU	Personal social services research unit
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RE	Random effect
Rim	Rimegepant
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of Product Characteristics

STA	Single technology appraisal
TA	Technology appraisal
TE	Treatment effect
TEAE	Treatment-emergent adverse event
TF	Treatment failure
Tx	Treatment
UK	United Kingdom
WTP	Willingness-to-pay

1 Executive summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Section 1.3 explains the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1. Summary of key issues

Issue	Summary of issue	Report sections
1	Exclusion of BoNT/A, rimegepant and eptinezumab as comparators in this STA	2.2.1, 2.3.3, 3.4.5, 4.2.3.3
2	NMAs within the overall migraine population vs 3+ TF subgroup for MMD-related outcomes in EM	3.4.1, 3.4.3, 4.2.6.4
3	Company preference for results from RE unadjusted NMAs for all outcomes in EM and CM	3.4.1, 3.4.3, 4.2.6.4
4	Uncertainty concerning the efficacy of atogepant vs comparators due to a lack of direct evidence and limitations of the NMAs	3.4.4
5	Uncertainty in the justification for the presence of monitoring costs	4.2.10.4
6	Inadequate source for injection related disutility	4.2.7.1
7	Incorrect calculation of long-term discontinuation	4.2.6.4

Abbreviations: 3+ TF, patients in whom ≥3 prior oral preventive treatments have failed; BoNT/A, botulinum toxin type A; CM, chronic migraine; EAG, External Assessment Group; EM, episodic migraine; MMD, monthly migraine days; NMA, network meta-analysis; RE, random effects; STA, single technology appraisal.

1.2 Overview of key model outcomes

Overall, the technology is modelled to affect quality-adjusted life years (QALYs) by:

- Reducing the number of monthly migraine days (MMDs) – the monoclonal antibodies (mAbs) are similarly effective at reducing MMDs as atogepant and therefore atogepant results in similar QALYs to the mAbs.

Overall, the technology is modelled to affect costs by:

- Reducing the number of MMDs which reduces the number of healthcare costs (the difference between the mAbs reduction in MMDs and atogepant is not statistically significant;
- Negative discontinuation rules, a higher proportion of mAb patients discontinue before the assessment period though a higher proportion achieve the assessment goal of more than or equal to 50% reduction in MMDs and so stay on treatment;
- Its lower unit price compared to the mAbs;
- Being given as a tablet, rather than intravenously (incurring one-off training costs on how to self-administer treatment and ongoing administration costs for patients who cannot self-administer treatment).

The modelling assumptions that have the greatest effect on the ICER are:

- Unit drug cost;
- Response;
- Long-term discontinuation.

1.3 Summary of the EAG's key issues

Table 2. Issue 1: Exclusion of BoNT/A, rimegepant and eptinezumab as comparators in this STA

Report section	2.2.1, 2.3.3, 3.4.5
Description of issue and why the EAG has identified it as important	In the CS, the company states that BoNT/A (CM only), rimegepant (EM only) and eptinezumab (EM and CM) are not relevant comparators for atogepant in the 3+ TF subgroup outlined in the decision problem. The company has provided NMA results for BoNT/A and included it in the economic model as a scenario, but the same was not done for rimegepant or eptinezumab. Given that the NICE recommendations for all three of these treatments is the same as that outlined for atogepant (albeit specific to CM and EM populations, respectively, for BoNT/A and rimegepant), the EAG considers it important that these treatments are also explored as comparators.[1-3] Furthermore, feedback from the EAG's clinical experts supports the inclusion of BoNT/A and rimegepant as comparators in the relevant populations, although there was less concern about eptinezumab being included as they considered it to be more resource intensive.
What alternative approach has the EAG suggested?	The EAG considers it important that these three comparators are included in this appraisal and considered as comparators during the decision-making process. The consideration of BoNT/A as a comparator in CM has already been facilitated by the company given NMA results have been provided and a scenario performed in the economic model. For rimegepant and eptinezumab, in response to CQ A1, the company reiterated its rationale for not including these two treatments as comparators and did not update NMAs or the economic model. The EAG has, therefore, updated the NMAs to include data for these treatments in the NMAs and included them as comparators in the economic model.
What is the expected effect on the cost-effectiveness estimates?	The inclusion of these treatments will not impact the pairwise cost-effectiveness estimates of treatments that the company already considers to be relevant comparators for this appraisal vs atogepant 60 mg (erenumab, galcanezumab and fremanezumab) but the results of the fully incremental analysis may change. ICERs for these additional treatments are included in Sections 6.2 and 6.3.
What additional evidence or analyses might help to resolve this key issue?	The EAG considers that the EAG-updated NMAs and economic model allow consideration of the clinical and cost-effectiveness of atogepant vs these additional comparators. Further clinical expert input may be useful to determine whether consideration of these treatments as comparators is important.

Abbreviations: 3+ TF, patients in whom ≥3 prior preventive treatments have failed; BoNT/A, botulinum toxin type A; CM, chronic migraine; CQ, clarification question; CS, company submission; EAG, External Assessment Group; EM, episodic migraine; ICER, incremental cost-effectiveness ratio; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; STA, single technology appraisal.

Table 3. Issue 2: NMAs within the overall migraine population vs 3+ TF subgroup for MMD-related outcomes in EM

Report section	3.4.1, 3.4.3
Description of issue and why the EAG has identified it as important	For EM, the company has a preference for NMAs of MMD-related outcomes performed within the 3+ TF subgroup of ELEVATE given this trial was stratified for this factor at randomisation. However, the EAG notes that the comparator trials that provide 3+ TF subgroup data for EM (CONQUER, FOCUS and LIBERTY) were not stratified for this factor at randomisation (and baseline characteristics for this subgroup are not well reported), meaning bias for this analysis could be increased compared to the overall migraine population analyses in EM. Furthermore, the company prefers the RE unadjusted versions of these NMAs, which the EAG disagrees with given there does not appear to be sufficient data to inform between-study heterogeneity and uncertainty may be exacerbated unnecessarily. The company uses a lack of stratification for 3+ TF in the PROGRESS trial as a reason not to prefer analyses within the 3+ TF subgroup for MMD-related outcomes in CM, which the EAG accepts. Given this preference within the CM population, the potentially increased bias for the 3+ TF EM analyses, scarceness of the data in this specific subgroup (only one study for each comparison and smaller sample sizes included) and feedback from the EAG's clinical experts that there are no concerning differences between the 3+ TF and overall population of ELEVATE in terms of baseline characteristics, the EAG prefers the NMAs within the overall migraine population for EM, as well as CM, are used to inform the economic model. Given the results of these analyses differ at least slightly compared to the company's preferred analyses, this has the potential to alter cost-effectiveness outputs from the economic model. The EAG agrees with the company's preference for analyses in the overall migraine population for all other analyses, including all outcomes in CM and HRQoL, discontinuation and TEAE outcomes in EM. While it notes that using the overall migraine population for NMAs may reduce the applicability of these analyses to the population outlined in the decision problem (3+ TF), it acknowledges that data for discontinuation, TEAEs and HRQoL are particularly scarce for this subgroup and considers the analyses for MMD-related outcomes to be more robust in the overall migraine population.
What alternative approach has the EAG suggested?	For MMD-related efficacy outcomes in EM, the EAG has a preference for the overall migraine population analyses rather than the 3+ TF subgroup preferred by the company. The results of these are presented as the EAG's preferred NMAs within Section 3.4.3.1 Furthermore, the EAG considers the RE unadjusted NMAs for this 3+ TF subgroup in EM to be inappropriate given there appears to be insufficient data to inform between-study heterogeneity in these analyses and that a FE analysis would be more appropriate should the results in this subgroup be favoured.
What is the expected effect on the cost-effectiveness estimates?	In the CS, the use of the overall migraine population NMA data was explored as scenario 7a. This scenario was associated with [redacted] in NHB vs galcanezumab, erenumab and 225 and 675 mg fremanezumab, most notable for the comparison vs galcanezumab (Table 56 below). In terms of ICERs, when this preference was incorporated in addition to the EAG's other preferred changes to NMAs used in the model (see Key Issue 3 described in Table 4 below), it had a positive impact on atogepant results, with erenumab and galcanezumab remaining [redacted] and other comparators included by the company (fremanezumab 225 mg and 675 mg) also now [redacted] (see Table 60).

What additional evidence or analyses might help to resolve this key issue?	The EAG does not consider that any further evidence is required.

Abbreviations: 3+ TF, patients in whom ≥3 prior preventive treatments have failed; CM, chronic migraine; CS, company submission; EAG, External Assessment Group; EM, episodic migraine; FE, fixed effects; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; MMD, monthly migraine days; NHB, net health benefit; NMA, network meta-analysis; RE, random effects; STA, single technology appraisal; TEAE, treatment-emergent adverse events.

Table 4. Issue 3: Company preference for results from RE unadjusted NMAs for all outcomes in EM and CM

Report section	3.4.1, 3.4.3
Description of issue and why the EAG has identified it as important	The company has a preference for RE unadjusted NMAs for all outcomes in EM and CM populations, explaining that this is because there is reason to believe that heterogeneity exists amongst studies (meaning RE analyses are appropriate) and that RE analyses adjusted for baseline risk (placebo response) across studies do not lead to a substantially improved model fit. While the EAG agrees with RE analyses in most cases (the exception being when the 3+ TF subgroup results in EM are used by the company, although the EAG does not have a preference for 3+ TF analyses as described in Table 3), on review of model fit and impact on between-study heterogeneity, the EAG has a preference for alternative analyses for many outcomes. In most (but not all) cases this is a preference for RE adjusted rather than RE unadjusted analyses given the between-study heterogeneity estimated within the network is reduced with adjustment. Given the results of these analyses differ at least slightly compared to the company's preferred analyses, this has the potential to alter cost-effectiveness outputs from the economic model. EAG preferences that differ to the company's preferences are outlined below: • RE adjusted analyses for all MMD-related outcomes in EM (and within the overall migraine population rather than 3+ TF as already discussed in Table 3); • RE adjusted analyses for CFB in MMDs and ≥50% MMD reduction outcomes in CM; • FE unadjusted analysis for ≥30% MMD reduction in CM, given there appears to be insufficient data to inform between-study heterogeneity in the RE analysis (and adjusted analyses would not converge); • RE adjusted analysis for discontinuation in EM. The EAG notes that analyses adjusting for baseline risk (placebo response) were not performed for HRQoL or TEAE outcomes and the company and EAG has a preference for RE over FE analyses. While a lack of analyses with adjustment for these outcomes may be a limitation, the EAG notes that none of these analyses are used to inform the economic model.
What alternative approach has the EAG suggested?	Outcomes for which the EAG's preferred NMA models differ to the company's preferred models are outlined in the previous row.
What is the expected effect on the cost-effectiveness estimates?	The impact of the EAG's preferences in terms of NMAs used in the economic model on ICERs is demonstrated in Table 60 and Table 61. For EM, the EAG notes that this is the combined effect of changes to preferred NMA models as well as a preference for the analysis in the overall migraine population (see Key Issue 2 in Table 3 above). For EM, these changes had a positive impact on atogepant results, with erenumab and galcanezumab remaining [redacted] and other comparators included by the company (fremanezumab 225 mg and 675 mg) also now [redacted] (see Table 60). Similar was observed for CM; results for all comparators other than erenumab were [redacted] when these preferences were incorporated.

What additional evidence or analyses might help to resolve this key issue?	The EAG does not consider that any additional evidence regarding MMD-related outcomes is required. It notes that a lack of baseline-adjusted analyses for HRQoL outcomes and TEAEs may be a limitation but does not consider this to be a priority given these outcomes are not used to inform the economic model.

Abbreviations: 3+ TF, patients in whom ≥3 prior preventive treatments have failed; CFB, change from baseline; CM, chronic migraine; EAG, External Assessment Group; EM, episodic migraine; FE, fixed effects; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; MMD, monthly migraine days; NMA, network meta-analysis; RE, random effects; TEAE, treatment-emergent adverse events.

Table 5. Issue 4: Uncertainty concerning the efficacy of atogepant vs comparators due to a lack of direct evidence and limitations of the NMAs

Report section	3.4.4
Description of issue and why the EAG has identified it as important	The EAG notes that there is no direct evidence available for atogepant vs any of the comparators included in this appraisal, and clinical effectiveness estimates used in the economic model are from indirect comparisons. The company highlights various factors that differ across studies included in the NMAs, particularly overall migraine population analyses, which the EAG has discussed and added to in Section 3.4.4. This includes differences in terms of study population and concomitant treatments received, outcome definitions and time-points, methods of analysis and differences in placebo response. The EAG considers these differences to be unavoidable given data that can be used for comparator studies depends on what methods have been used in those trials and what has been published. Where appropriate, the EAG has a preference for analyses that have adjusted for baseline risk (placebo response), which should reduce some uncertainty related to this aspect. Furthermore, the use of RE analyses over FE analyses in most cases should capture some of this remaining uncertainty, although the EAG notes that this does not completely resolve concerns about any heterogeneity that may remain unaccounted for. Differences between studies, such as clinical and methodological heterogeneity, that may not be completely accounted for even in the EAG's preferred NMAs may reduce the certainty with which conclusions about the relative effect of atogepant vs comparators can be made (and the resulting cost-effectiveness estimates).
What alternative approach has the EAG suggested?	The EAG considers the remaining heterogeneity between studies to be an unresolvable limitation of the data available for comparator studies given data analysed for comparator studies is reliant on data that has been published.
What is the expected effect on the cost-effectiveness estimates?	Any potential impact on the cost-effectiveness estimates is unclear.
What additional evidence or analyses might help to resolve this key issue?	The EAG considers these to be unresolvable limitations of the data available for comparator studies.

Abbreviations: 3+ TF, patients in whom ≥3 prior preventive treatments have failed; EAG, External Assessment Group; FE, fixed effects; NMA, network meta-analysis; RE, random effects.

Table 6. Issue 5: Potential double counting of monitoring costs

Report section	4.2.10
Description of issue and why the EAG has identified it as important	Healthcare specialist costs are already incorporated into the model under the umbrella of healthcare resource use, which applies these costs by patient MMD. There is no reason to believe these costs excluded monitoring. The company suggests prescription/monitoring costs will be lower for atogepant since prescriptions/monitoring can be provided 50:50 by specialists/GP to atogepant patients as opposed to 100% specialists with mAb/BoNT/A. The EAG is uncertain if this would be possible since in order to apply for a confidential PAS a treatment cannot be regularly prescribed in primary care and part of the company's case for lower monitoring costs is an expectation of different prescribing behaviour/ Furthermore, rimegepant, another oral treatment for prevention of migraine did not include any difference in monitoring costs, versus mAbs, in the final model base case accepted by committee.
What alternative approach has the EAG suggested?	Remove monitoring costs.
What is the expected effect on the cost-effectiveness estimates?	This is expected to make atogepant less cost effective compared to all relevant comparators.
What additional evidence or analyses might help to resolve this key issue?	The EAG would require evidence showing the treatment can continue to be prescribed in secondary care, in order to meet the PAS restrictions, whilst receiving an alternate form of monitoring.

Abbreviations: BoNT/A, botulinum toxin type A; EAG, External Assessment Group; GP, general practitioner; mAbs, monoclonal antibodies; MMD, monthly migraine days. PAS, patient access scheme.

Table 7. Issue 6: The source for injection related utility is inadequate

Report section	4.2.7.1
Description of issue and why the EAG has identified it as important	The company used a UK study which performed a time trade-off task to derive injection related disutility. The value for SC injections (mAb administration was not statistically significant. Furthermore, the utility values are not based on EQ-5D. The EAG believes this disqualifies it from being used in the model.
What alternative approach has the EAG suggested?	Remove injection related disutility.
What is the expected effect on the cost-effectiveness estimates?	This is expected to make atogepant less cost effective compared to all relevant comparators aside from rimegepant.
What additional evidence or analyses might help to resolve this key issue?	The EAG would require evidence from a source that used UK data, EQ-5D utility and showed a statistically significant difference in utility.

Abbreviations: EAG, External Assessment Group; mAb, monoclonal antibody; SC, subcutaneous.

Table 8. Issue 7: Long term discontinuation appears to have been incorrectly calculated

Report section	4.2.6.4
Description of issue and why the EAG has identified it as important	The company's calculation appears to be based on an assumption that the total number of patients who discontinue in a study will have discontinued by the mean time to discontinuation. This will significantly over-estimate long-term discontinuation.
What alternative approach has the EAG suggested?	Use long-term discontinuation from TA659 (0.44%).
What is the expected effect on the cost-effectiveness estimates?	This should improve the cost-effectiveness of whichever treatment is the most effective, since a lower long-term discontinuation will provide a bigger benefit to whichever treatment has the most patients remaining on treatment, after the assessment phase.
What additional evidence or analyses might help to resolve this key issue?	The EAG would require further explanation of the rationale/justification behind the calculation method.

Abbreviations: EAG, External Assessment Group; TA, technology appraisal.

1.4 Other key issues

The EAG also had a number of other issues with the company's modelling assumptions, these are summarised in Table 9.

Table 9. Other key issues

Item	Section
In the EM arm the minimum MMD restriction of 1 does not appear justified. The EAG preference is for this restriction to be 0.	4.2.6.4
Some of the acute medications listed appear to not have used the cheapest price from BNF/eMIT available for the given dose/pack size.	4.2.10.4

Abbreviations: BNF, British National Formulary; EAG, External Assessment Group; EM, episodic migraine; eMIT, electronic market information tool; MMD, monthly migraine day.

1.5 Summary of EAG's preferred assumptions and resulting ICER

Table 10 summarises the EAG's preferred assumptions for the prevention model and the cumulative impact these assumptions have on the ICER. All ICERs in Table 10 are south-west or south-east quadrant ICERs aside from rimegepant (rimegepant is cheaper and less effective than the comparators). Based on willingness-to-pay (WTP) thresholds of £20,000 or £30,000 per QALY, atogepant could be considered cost-effective compared to each mAb as the EAG's preferred base case ICERs are above these WTP thresholds. Botulinum toxin (BoNT/A) is more cost-effective than

atogepant at £20,000 and £30,000 (chronic migraine only) and rimegepant is more cost-effective at a WTP threshold of £20,000 (episodic migraine only).

Table 10. Summary of EAG's preferred model assumptions and cumulative results (Episodic migraine)

Preferred assumption	Cumulative ICER (£/QALY) Atogepant vs comparator					
	Epti	Rim	Ere	Gal	Fre	Fre
Company base case	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Removal of monitoring costs. Section 4.2.10.4	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Removal of injection related disutility. Section 4.2.7.1	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Alternate long-term discontinuation source (0.44%). Section 4.2.6.3	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
MMD limit set to 0 Section 4.2.6.4	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Updated acute medication costs Section 4.2.10.4	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Updates to the NMA - Using mITT population for EM, addition of rimegepant and eptinezumab, alternate use of RE/FE and adjusted/unadjusted where justified Section 4.2.6.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*SW quadrant ICER (atogepant is cheaper and less effective than the comparator)

Abbreviations: EAG, External Assessment Group; EM, episodic migraine; Ept, eptinezumab; Ere, erenumab; FE, fixed effects; Fre, fremanezumab; Gal, galcanezumab; ICER, incremental cost-effectiveness ratio; mAb, monoclonal antibody; mITT, modified intention to treat; MMD, monthly migraine day; NA, not applicable; NMA, network meta-analysis; QALY, quality adjusted life year; RE, random effects; Rim, rimegepant.

Table 11. Summary of EAG's preferred model assumptions and cumulative results (Chronic migraine)

Preferred assumption	Cumulative ICER (£/QALY) Atogepant vs comparator					
	Epti	Bot	Ere	Gal	Fre	Fre
Company base case	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Removal of monitoring costs. Section 4.2.10.4	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Removal of injection related disutility. Section 4.2.7.1	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternate long-term discontinuation source (0.44%). Section 4.2.6.3	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated acute medication costs Section 4.2.10.4	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Updates to the NMA - Using mITT population for EM, addition of rimegepant and eptinezumab, alternate use of RE/FE and adjusted/unadjusted where justified Section 4.2.6.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*SW quadrant ICER

Abbreviations: Bot, botulinum toxin type A; EAG, External Assessment Group; EM, episodic migraine; Epti, eptinezumab; Ere, erenumab; FE, fixed effects; Fre, fremanezumab; Gal, galcanezumab; ICER, incremental cost-effectiveness ratio; mAb, monoclonal antibody; mITT, modified intention to treat; MMD, monthly migraine day; NA, not applicable; NMA, network meta-analysis; QALY, quality adjusted life year; RE, random effects; Rim, rimegepant.

2 Introduction and background

2.1 Introduction

Herein is a critique of the evidence submitted to the Single Technology Appraisal (STA) in support of the clinical and cost-effectiveness of atogepant (Aquipta™; AbbVie) for the prevention of migraine in adults who have ≥4 migraine days per month, as covered by the UK marketing authorisation for this treatment.[4] As noted in Section 2.2.1, the indication assessed in this STA is narrower than the marketing authorisation as it is specific to those in whom ≥3 prior oral preventive drug treatments have failed (3+ TF). This includes episodic migraine (EM) and chronic migraine (CM), which are defined as <15 headache days per month and ≥15 headache days per month with ≥8 days qualifying as migraine, respectively, by the International Headache Society.[5-7]

2.2 Background

Within Section B.1 of the company submission (CS), the company provides an overview of:

- atogepant, including its mechanism of action, indications, dose and method of administration (Section B.1.2 of the CS);
- migraine, including diagnosis and classification, clinical presentation, epidemiology, disease burden, and current treatment options (Section B.1.3 of the CS).

In this section, the External Assessment Group (EAG) focuses mostly on areas that were commented on by the EAG's clinical experts. The clinical experts largely agree with the company's statements in Section B.1 of the CS; however, they consider botulinum toxin (BoNT/A) to be a relevant treatment in CM, noting that waiting lists can also be an issue for the monoclonal antibody (mAb) treatments erenumab, fremanezumab and galcanezumab, not just for BoNT/A. They also note that there are other factors that may impact the decision between mAbs and BoNT/A in CM, such as patient preference (for example, willingness to travel to have BoNT/A treatment), and contraindications and side effects of mAbs which may mean that BoNT/A is the treatment of choice (see Key Issue 1 in Table 2).

The company suggests that as an oral treatment, atogepant may be more likely to be prescribed and/or monitored by secondary care general neurologists and in primary care. Its base case includes initiation for atogepant by either a headache specialist or general neurologist (50:50), with follow-up conducted in primary care by GPs. A scenario with prescribing by GPs is included in Section 5.1.4 (given there may be potential for this in the future). One of the EAG's clinical experts noted that, in

their opinion, it would be reasonable for it to be prescribed in secondary headache clinics by a neurologist who is a specialist in headache or by general practitioners (GPs) with a specialist interest in headache, but the second expert explained that this may not be realistic at least initially, although it may be a possibility over time. They note that the recently recommended rimegepant (also an oral treatment) requires initiation in secondary care or headache clinics and that general neurology services may struggle to follow-up patients after 12 weeks to assess response even if they did prescribe atogepant, meaning this may need to be done in tertiary care by a headache specialist.

2.2.1 Position of atogepant in the UK treatment pathway

A summary of the treatment pathway described by the company is presented in Figure 1 below, which includes division into EM and CM once three oral preventive treatments (drugs that are not migraine-specific) have failed, which is the population of relevance to this appraisal; the EAG's clinical experts consider this to be an accurate representation of the current pathway for migraine prevention in UK clinical practice. However, they note that in their respective centres mAbs are currently only used for CM patients and that EM services are not yet established.

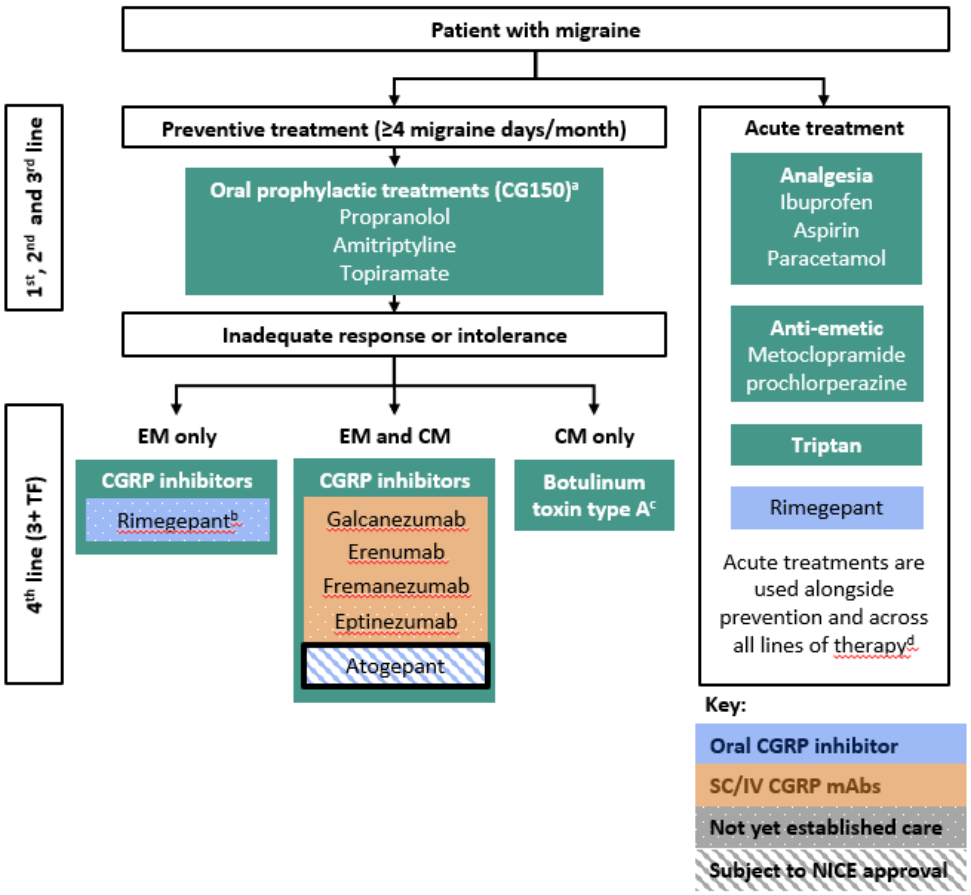
Current options recommended by the National Institute for Health and Care Excellence (NICE) for those in whom three oral preventives have failed (and who have ≥4 monthly migraine days [MMDs]) include three mAbs (erenumab, galcanezumab and fremanezumab; NICE TA682, TA659 and TA764, respectively) for EM and CM,[8-10] BoNT/A for CM only (NICE TA260; requires headaches on at least 15 days per month of which at least 8 days are with migraine),[1] and the more recently recommended eptinezumab (NICE TA871; EM and CM) and rimegepant (NICE TA906; EM only).[2, 3] All but one of these treatments are administered via injection; subcutaneous for mAbs, intramuscular for BoNT/A and intravenous for eptinezumab. Rimegepant is the exception because, as for atogepant, it is an oral treatment.

In this appraisal, the company has focused on the three mAbs as comparators for atogepant. BoNT/A has also been included in network meta-analyses (NMAs) and as a scenario in the economic model for CM. However, the company does not focus on this comparison as, based on feedback from clinical experts it consulted, it considers access to BoNT/A to be restricted, it requires dedicated in-clinic time (unlike atogepant) and that its use in the NHS is in decline. The company also excludes eptinezumab and rimegepant as comparators in this appraisal given they have only recently been recommended, with NICE recommendations not published at the time of scoping (the EAG notes that they were, however, listed in the final scope subject to NICE evaluation). It does not consider them to be part of established clinical practice yet and does not anticipate them becoming

established practice at the point of committee decision, citing low market share in the 3+TF group, which is further supported by clinical expert opinion elicited by the company. The EAG's clinical experts agreed that eptinezumab may not be important to this appraisal, given that it is a recent recommendation with very low use currently. One expert noted that it may be considered too resource intensive to use in preference to other treatments, meaning the frequency of its use may not change considerably in the near future. While they agreed that rimegepant is not currently used often, one clinical expert noted that there is potential for this to change in the near future and, should atogepant be recommended and oral options preferred for an individual patient, it is likely that clinicians would be making a decision between atogepant and rimegepant in EM. Therefore, it may be particularly important to compare atogepant with rimegepant in this appraisal. Feedback regarding BoNT/A was that it is still a relevant treatment in CM as there is a choice to be made between mAbs and BoNT/A in patients with CM that are eligible for either (as noted above under Section 2.2). Regarding eptinezumab and rimegepant, the EAG considers it important to explore the inclusion of these treatments as comparators in this appraisal given they are both recommended within the same population as outlined for atogepant (although rimegepant is only recommended for EM patients) and have the potential to be used as options alongside atogepant if it were to be recommended, acknowledging that eptinezumab may be less important based on feedback from one clinical expert discussed earlier.

Overall, the EAG considers that the positioning of atogepant as a treatment after at least three prior preventive oral treatments have failed is appropriate but that there may be additional comparators worth considering in the appraisal (see Key Issue 1 in Table 2), which the EAG has included as part of this report. Further discussion of the comparators that are currently not considered relevant by the company is provided in Section 2.3.

Figure 1. Anticipated clinical pathway of care for migraine patients (reproduced from Figure 3 of the CS)



Abbreviations: CGRP, calcitonin gene-related peptide; CM, chronic migraine; CS, company submission; EM, episodic migraine; IV, intravenous; NICE, National Institute for Health and Care Excellence; SC, subcutaneous; TF, treatment failures.

2.3 Critique of the company's definition of the decision problem

The company provided a summary of the final scope issued by NICE in Section B.1.1 of the CS, together with the rationale for any deviation from the final scope.[11] This is reproduced in Table 12 below with the EAG's critique included. Key differences between the decision problem addressed in the CS and the NICE final scope are discussed in greater detail in the sections that follow this table, but the EAG's main concern is around the complete exclusion of eptinezumab and rimegepant as comparators (see Key Issue 1 in Table 2). In addition, the EAG also considers BoNT/A to be a relevant comparator in CM, while the company does not (see Key Issue 1 in Table 2). Analyses including this comparator have, however, already been presented by the company as part of the CS.

Table 12. Summary of decision problem and differences relative to NICE final scope (adapted from Table 1 of the CS)

	Final scope issued by NICE[11]	Decision problem addressed in the submission	Rationale if different from the scope	EAG comment
Population	Adults with migraine who have 4 or more migraine days a month, in whom at least 3 preventive drug treatments have failed	As per the NICE final scope	The population is aligned to a subgroup of the UK marketing authorisation, the NICE-recommended population for the available CGRP mAbs, as well as the anticipated positioning of atogepant in UK clinical practice based on feedback from clinicians.[4, 8-10, 12] In addition, feedback from clinicians suggests that atogepant is suitable for use in patients for whom ≥3 prior preventive treatments have failed.[12]	The population covered in the CS is in line with the NICE final scope, although narrower than the marketing authorisation for atogepant.[4] It is also in line with NICE recommendations made for mAbs, botulinum toxin type A (CM only), eptinezumab and rimegepant (EM only). Clinical evidence from atogepant trials specific to the 3+ TF group is provided within the CS for EM and can be found in the CSR for CM. For efficacy outcomes in EM, NMAs within the 3+ TF group were presented in the CS but not for CM as the trial was not stratified by treatment history; these results were, however, provided as part of the CCE process for atogepant earlier in 2023. However, the EAG considers analyses in the overall populations for EM and CM, regardless of prior treatment history, to be more robust due to limited data availability for the 3+ TF subgroup and concerns about lack of trial stratification for treatment history.

				NMAs for other outcomes, including HRQoL, TEAEs and all-cause discontinuation, were not performed in the 3+ TF group due to a lack of data available for comparator treatments. These were instead performed in the overall EM and CM migraine populations, which the EAG considers to be reasonable. The EAG's clinical experts consider the 3+ TF and overall populations of the atogepant trials to be a reasonable reflection of the UK 3+ TF population, with no important differences in baseline characteristics between the 3+ TF and overall populations noted. They consider the exclusion of those with >4 prior treatments in the atogepant trials to be unfortunate but the potential impact of this on the results of the trial is unclear. See Section 2.3.1 below for further discussion.
Intervention	Atogepant	Atogepant (60 mg*); as per the NICE final scope	N/A	The intervention covered in the CS and atogepant clinical trials matches the NICE final scope, with the 60 mg dose of atogepant focused on. While the company highlight the availability of the 10 mg dose in the footnote of

				this table for specific patients, the EAG notes that evidence for the 10 mg dose of atogepant has not been included in the CS. The EAG is unsure whether the use of concomitant preventive treatments in some patients within the PROGRESS trial for CM is reflective of UK clinical practice and notes clinical expert feedback that opioids are not used as acute migraine treatment in UK practice, which was also permitted in PROGRESS. However, it does not consider these to be major concerns. See Section 2.3.2 below for further discussion.
Comparators	• Botulinum toxin type A (CM only) • Galcanezumab • Erenumab • Fremanezumab • Eptinezumab (subject to NICE evaluation) • Rimegepant (subject to NICE evaluation)	• Galcanezumab • Erenumab • Fremanezumab	CGRP mAbs (galcanezumab, erenumab, fremanezumab) are deemed to be the appropriate comparators for this appraisal; given that atogepant and the CGRP mAbs are preventive treatments that cover the same patient population which each work in a similar way to suppress CGRP activity, can be self-administered at home, and offer similar health benefits.	The three mAbs currently recommended by NICE in the 3+ TF population for EM and CM have been included in the CS.[8-10] The EAG does not agree with the company's decision not to focus on botulinum toxin type A as a comparator for CM in this appraisal given feedback from the EAG's clinical experts that there is a choice to be made currently between mAbs and botulinum toxin type A in CM in UK clinical practice. However, botulinum

			Eptinezumab (IV CGRP mAb) and rimegepant (oral CGRP receptor inhibitor) have both recently received recommendations from NICE (1 March 2023 and 5 July 2023, respectively).[2, 3] Due to recency of these recommendations, and wide variation in in-hospital administration capabilities for eptinezumab across the UK due to its IV route of administration, clinical experts and market share data have indicated that these drugs do not constitute established clinical practice.[13, 14] Moreover, the NICE recommendations associated with these therapies had not been published at the time of scoping. As such, neither are considered relevant comparators. Clinical experts noted that botulinum toxin type A is not a relevant comparator for atogepant due to the requirement for dedicated in-clinic time and upfront staff investment. It was also noted that the proportion of patients receiving botulinum toxin type A	toxin type A has been included in the NMAs and in the economic model as a scenario analysis. Given final guidance is now available for eptinezumab and rimegepant in the 3+ TF population,[2, 3] the EAG considers their exclusion from the CS may be inappropriate. While the EAG's clinical experts agree that currently their use in UK clinical practice is low, one expert noted that there could be an important decision to be made between rimegepant and atogepant, should atogepant be recommended and an oral option preferred in EM, while the use of eptinezumab may change less substantially given it is considered by the experts to be more resource intensive. The company did not include these treatments in response to CQ A1 but the EAG has incorporated them into its analyses. See Section 2.3.3 for further discussion.

			is likely to decrease for these reasons with market share forecasts indicating that the majority of patients experiencing ≥4 migraine days per month who are receiving treatment, receive CGRP mAbs as a preventive therapy.[12] Market share data further indicate that the large majority of patients across the UK are initiated on CGRP mAbs ahead of botulinum toxin type A, with clinical experts explaining that patients typically initiate on CGRP mAbs currently due to NHS capacity issues associated with botulinum-toxin type A administration and resulting waiting lists.[13, 14] As such, botulinum toxin type A is not considered by the company to be a relevant comparator.	
Outcomes	The outcome measures to be considered include: • Change in frequency of migraine days per month • Change in frequency of headache days per month • Change in severity of headaches and migraines • Change in number of cumulative hours of headache	As per the NICE final scope	N/A	Outcomes covered in the CS for atogepant trials match the NICE final scope. The time-point of 12 weeks for atogepant trials was considered reasonable by the EAG's clinical experts and the EAG considers the outcome definitions to be appropriate, such as the thresholds used to define responders which are in line with comparator appraisals.

	or migraine on headache or migraine days • Changes in acute pharmacological medication given • AEs of treatment • HRQoL			NMAs for multiple outcomes were performed, including efficacy outcomes important to the economic models of comparator appraisals as well as HRQoL, TEAEs and all-cause discontinuation. See further discussion in Section 2.3.4
Economic analysis	• The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. • The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. • Costs will be considered from an NHS and PSS perspective. • The availability of any commercial arrangements for the intervention, comparator and subsequent treatment	• A cost-effectiveness analysis has been conducted in Microsoft Excel to estimate the incremental costs of atogepant versus galcanezumab, erenumab, and fremanezumab • A lifetime time horizon for assessing costs was used • Costs were considered from an NHS and PSS perspective • A PAS for atogepant has been included as part of the analysis	The economic analysis presented is aligned with the final NICE scope for this submission.	The company has stated that atogepant has potential for use in primary care though they have also provided a confidential PAS discount for the treatment. For a treatment to be administered in primary care it must use the public tariff price.

	technologies will be taken into account. • The availability and cost of biosimilar and generic products should be taken into account.			
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • Those with either EM or CM • Subgroups defined by the number of previous prophylactic treatments • Subgroups defined by the frequency of EM (in those with EM)	This submission will focus on patients with ≥3 prior preventive treatment failures in line with the NICE final scope. Subgroup analyses were conducted where applicable. Subgroups defined by the frequency of EM are not provided.	Migraine is a disease continuum in which patients can be classified as having either EM or CM based on the frequency of monthly headache days. The patient population addressed in this submission represents two subgroups of the population specified in the NICE final scope: patients with EM and CM with ≥3 prior preventive treatment failures. This appraisal did not consider subgroups defined by frequency of EM. Evidence presented in the prior appraisal of galcanezumab (TA659) suggests that patients with high frequency EM have a similar disease burden as patients with CM,[9] while published literature have demonstrated that migraines are disabling for patients with 3 or more monthly migraine days.[15] However, due to a lack of consensus on the	Separate clinical and economic analyses have been provided in the CS for EM and CM, in line with comparator appraisals. Subgroups based on the number of prior prophylactic treatments have been explored in the CS for EM given results from ELEVATE are presented separately for the 3+ TF subgroup and the overall trial population of 2-4 TF. NMA results for the 3+ TF subgroup are also presented in the CS for EM. While this was not included in the current CS for CM, clinical data for this subgroup is available within the CSR for PROGRESS. While the EAG's clinical experts note that there may be some distinction between those with low- and high-frequency EM, with the latter potentially experiencing a burden of migraine disability similar to those with CM, there was a difference of opinion regarding whether this distinction is

			definition of, and clinical distinctiveness of high frequency EM, NICE concluded the frequency of migraines (in those with EM) was not an appropriate subgroup for economic analysis. As such, no subgroup analysis has been explored in this submission.	evident in clinical practice. Based on data provided as part of the CCE process earlier in 2023 and a decision made by the committee in TA659, the EAG does not consider further exploration of these subgroups to be important. See Section 2.3.5 for further discussion.
Special considerations, including issues related to equity or equality	N/A	N/A	N/A	Equality considerations are discussed by the company in Section B.1.3.4 of the CS, including a statement that atogepant may help to reduce inequity in access to current treatments that may vary geographically.

*Outside of the scope of this submission, atogepant 10 mg once daily is also licensed for patients who require dose modifications (concomitant use of strong CYP3A4 or OATP inhibitors), or for special populations with severe renal impairment or end-stage renal disease.

Abbreviations: 3+ TF, patients in whom ≥3 prior oral preventive treatments have failed; 2-4 TF, patients in whom 2-4 prior oral preventive treatments have failed; AE, adverse events; CCE, cost-comparison evaluation; CGRP, calcitonin gene-related peptide; CM, chronic migraine; CS, company submission; CSR, clinical study report; CQ, clarification question; CYP, cytochrome P450; EAG, External Assessment Group; EM, episodic migraine; HRQoL, health-related quality of life; IV, intravenous; mAbs, monoclonal antibodies; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; OATP, organic anion transporting polypeptide; PAS, patient access scheme; PSS, Personal Social Services; TA, technology appraisal; TEAE, treatment-emergent adverse events.

2.3.1 Population

The CS positions atogepant for use in adults with migraine who have at least four MMDs and in whom at least three preventive drug treatments have failed. This is narrower than the UK marketing authorisation for atogepant but is in line with the NICE final scope and is deemed reasonable by the EAG as it is in line with the population that the mAbs are recommended for in EM and CM.[4, 8-10] BoNT/A (CM only), eptinezumab (EM and CM) and rimegepant (EM only) are also recommended for the population with at least four MMDs and 3+ TF, although the requirement for MMDs is more strict for BoNT/A given its recommendation for CM only, with patients required to have at least 15 headache days per month of which 8 days are migraine.[1-3]

The main trials focused on in the CS (Section B.2.3) for EM (ELEVATE) and CM (PROGRESS) are not specific to the 3+ TF population, but relevant subgroup data have been provided in the CS for ELEVATE. The same has not been provided for the PROGRESS trial in CM as part of this STA submission given the company highlight the trial was not stratified for prior treatment failures at randomisation, unlike ELEVATE. However, the EAG notes that baseline characteristics and outcome data for this subgroup are available from the clinical study report (CSR) for PROGRESS; the EAG has included this outcome data in this report (Section 3.3). The EAG's clinical experts reviewed the baseline characteristics for the overall trial populations of ELEVATE and PROGRESS and considered them to be a reasonable representation of the UK 3+ TF population. They consider that no major differences would be expected in these characteristics compared with the 3+ TF population; the EAG also compared baseline characteristics between the overall trial populations and 3+ TF populations (Table 6 vs Table 7 in the CS for ELEVATE; Table 7 in the CS vs data provided in the CSR) and notes that there is very little difference for either trial. The most notable difference was within PROGRESS, where for the 3+ TF group values for monthly headache days and monthly acute medication use days (MUDs) were [redacted] compared to the overall trial population. However, the EAG's clinical experts consider the size of these differences unlikely to be important in terms of impact on efficacy.

The EAG notes that failures on prior treatments were based on oral preventive treatments and did not include mAbs or BoNT/A, meaning there is no evidence from atogepant trials in populations that have already failed on a mAb or BoNT/A. One of the EAG's clinical experts highlighted that evidence from a population that has failed mAbs would be required to support the use of atogepant in such as population, given they consider it clinically plausible that it may be less effective in this group. They

are less concerned about its used following failed BoNT/A treatment given the mechanism of action for BoNT/A and atogepant is clearly different. A failed treatment was defined as one in which there was no response by the defined time-point or discontinuation due to intolerability. Given that atogepant has been positioned as an alternative to mAbs in this STA rather than as a subsequent treatment, the EAG does not consider this to be a major limitation but notes that this is something that may need consideration when considering options for patients in clinical practice that have already received mAbs and the order in which treatments should be used. The EAG notes that the same concern may apply for rimegepant and eptinezumab given that the studies (BHV3000-305 for rimegepant and DELIVER for eptinezumab) that the respective NICE appraisals focused on did not include failure on mAbs as one of the treatment failure categories (although BoNT/A was included in the lists for the two studies).[2, 3, 16, 17] However, it may be unlikely that eptinezumab would be used following erenumab, galcanezumab or fremanezumab given it is also a mAb targeting the calcitonin gene-related peptide (CGRP) pathway.

NMAs for efficacy analyses within EM were provided in the CS for the 3+ TF subgroup as well as for the overall migraine population. As noted above, PROGRESS was not stratified for prior treatment failures and efficacy analyses within the 3+ TF population were therefore not provided as part of this STA for CM; however, they were previously provided as part of the cost-comparison evaluation (CCE) process earlier in 2023. At clarification (clarification question [CQ] A9), the EAG requested that these NMAs be provided as part of the STA so that they can be compared. The company did not provide these data and instead reiterated its rationale for not performing NMAs using this subgroup data in this STA. The EAG comments briefly on how the NMA results provided as part of the CCE for this subgroup in CM compare to the company- and EAG-preferred analyses in this report in Section 3.4.3.1. For reasons described further in Section 3.4.1, the EAG considers NMAs for efficacy analyses performed within the overall trial populations to be more robust than those within the 3+ TF (see Key Issue 2 in Table 3); however, it considers a comparison between the two populations useful, with acknowledgement of the additional limitations for the 3+ TF subgroup analyses.

In terms of NMAs performed for other outcomes in the CS, including health-related quality of life (HRQoL), treatment-emergent adverse events (TEAEs) and all-cause discontinuation, for EM and CM analyses were only available within the overall migraine population. This was because of a lack of data for comparator interventions within the 3+ TF subgroup for these outcomes. The EAG considers this to be reasonable and notes that as part of the CCE process earlier in 2023, the company explored HRQoL analyses in 2+ and 3+ TF subgroups in response to clarification; the EAG concluded

that it did not prefer these analyses given data was much scarcer and only allowed comparisons with fremanezumab and/or galcanezumab. See Section 3.4 for further details and critique of the NMAs performed.

The EAG's clinical experts considered it unfortunate that patients with >4 prior treatment failures in ELEVATE and PROGRESS were excluded, given this is a group that would be relevant in UK clinical practice. While the experts consider they would not expect a large difference compared to those with three or four failures, they note that the chance of each successive agent working is reduced which may mean a group that are more complex and less likely to respond have been excluded. The EAG notes that this is not inconsistent with comparator trials focusing on refractory populations (such as FOCUS, CONQUER and LIBERTY), which include those with two to four prior treatment failures.[18-20] For further detail on atogepant clinical trials, see Section B.2.3 of the CS and Section 3.2 below.

2.3.2 Intervention

The intervention in the CS is atogepant (Aquipta™; AbbVie), matching the NICE final scope, which is an oral migraine prevention treatment.[11] The dose covered in the CS is atogepant 60 mg, which is to be taken once daily. UK marketing authorisation has been granted and covers adults with ≥4 MMDs and in whom ≥3 prior oral preventive treatments have failed.[4]

Concomitant medications permitted in the atogepant clinical trials were considered reasonable by the EAG's clinical experts, other than opioids as an acute treatment in CM (PROGRESS), which are not used in UK clinical practice. However, the EAG notes that, based on the clinical study report (CSR), opioids were rarely used in PROGRESS with only [redacted] of it being prescribed for migraine in the placebo group. There were other instances where it was prescribed for other indications such as the common cold, but [redacted] patients per treatment group.

Furthermore, the PROGRESS trial in CM allowed concomitant use of another preventive migraine treatment; the EAG's clinical experts note that while this is fairly uncommon, it may sometimes be done in clinical practice and can improve outcomes. The EAG notes that this was more common in the [redacted] arm ([redacted]% vs [redacted]%). Were the use of concomitant treatments to improve outcomes in this trial, this would potentially have a [redacted] impact given more patients in the [redacted] arm used them. The EAG notes that this is not uncommon among migraine trials as some trials for comparators allowed use of concomitant preventive medications (see Section 3.4.4.1).

2.3.3 Comparators

Within the CS, the three mAbs recommended by NICE for the population of interest are included as comparators for atogepant in EM and CM, as per the final scope.[8-11] While mAbs are recommended for use in EM and CM, the EAG's clinical experts note that capacity issues often mean that mAb services for EM are limited or not yet established.

Use of BoNT/A for CM has not been included as a formal comparator by the company in the CS, for reasons described in Sections B.1.1 and B.1.3.3, although it has been included in the relevant NMAs and as a scenario analysis in the economic model (Appendix O of the CS). The company does not consider BoNT/A to be a relevant comparator in CM given feedback from clinical experts consulted that patients often choose mAbs due to extensive waiting lists for BoNT/A and the need to travel to clinics that administer this treatment.[12, 13] It suggests that BoNT/A use is on the decline according to market share data and IQVIA™ in-hospital pharmacy dispensing data reports that [redacted] of new fourth-line patients received treatment with erenumab, fremanezumab or galcanezumab rather than BoNT/A between the second half of 2022 and first half of 2023 across the UK (the EAG notes that experts consulted by the company estimated this to be 70-80%; see the company's response to CQ B1).[14] Furthermore, the company notes that differences compared to atogepant in terms of requirement for dedicated in-clinic time and upfront staff investment for BoNT/A administration are also reasons that atogepant would not be considered an alternative to BoNT/A.[13] Furthermore, it notes that the exclusion of BoNT/A is in line with the recent NICE appraisal of eptinezumab (TA871), which was recommended for EM and CM.[3]

As discussed earlier in Section 2.2, feedback from the EAG's clinical experts was that BoNT/A is a relevant treatment option in CM. While they acknowledge that waiting lists may exist, this can also be an issue for mAbs. There is considered to be a choice between mAbs and BoNT/A for those who are eligible, which may be made based on patient preferences (for example, willingness to travel to a BoNT/A centre if required or the side effect profile of mAbs) as well as certain contraindications for mAbs that mean BoNT/A would be used. In addition, BoNT/A requires a shorter time off treatment before trying to become pregnant which may also be a factor that patients and clinicians consider. Based on this, the EAG considers BoNT/A to be an equally appropriate comparator in CM that should be considered alongside mAbs. In terms of the eptinezumab appraisal, while the EAG acknowledges that BoNT/A is not mentioned in the final guidance document,[21] it was included in the CS as can be seen from the committee papers.[22] The EAG is unsure of the reason for this but does not consider its

omission from the final guidance document to be an adequate reason for it to be excluded from this STA, particularly given the feedback obtained from the EAG's clinical experts (see Key Issue 1 in Table 2).

The company has excluded eptinezumab and rimegepant as comparators in this STA, citing the recency of their recommendation by NICE and market share data (in addition to clinical expert feedback) indicating that they are not yet established UK clinical practice, with eptinezumab and rimegepant accounting for up to [redacted] and [redacted] of all treated migraine patients within the 3+ TF group, respectively, according to market share data (see Section 4.2.3.2 for a critique of the argument based on market share data; on review of the Clarivate™ reference provided, the EAG considers that the [redacted]% figure likely refers to rimegepant rather than eptinezumab and it could not validate the percentage cited for eptinezumab).[13, 14] Clinical experts consulted by the EAG agreed that the use of these two treatments is very low at the moment in UK clinical practice. However, while feedback from one of the clinical experts also suggested that the use of eptinezumab may not increase substantially in the near future as the expert considered it may be too resource intensive to use in preference to other treatments, particularly oral treatments, they considered rimegepant to be an important comparator given that there may be a decision between rimegepant and atogepant if both are recommended and an oral option is preferred in EM.

While raised by the company, the EAG does not consider the fact that rimegepant is only recommended for EM to be a reason for its exclusion either. The company notes that eptinezumab may be reserved for patients with severe migraine attacks or those unable to self-administer mAbs subcutaneously based on clinical expert feedback as part of the eptinezumab appraisal (Section 3.2 of the final draft guidance for eptinezumab). The EAG's clinical expert feedback suggests similar as one expert described eptinezumab as being more resource intensive.[3] Regardless, the EAG considers it useful for this treatment to be included as a comparator in this appraisal given the recommendation made by NICE is not specific to this population and it is unclear as yet how it will be used in UK clinical practice (see Key Issue 1 in Table 2).[3] The inclusion of eptinezumab and rimegepant as comparators was requested as part of the clarification stage (CQ A1) but the company did not perform this request. Therefore, the EAG has updated NMAs to include data from eptinezumab and rimegepant trials (Section 3.4) and included these treatments as comparators in the economic model (Section 6). The EAG provides a critique of the rationale and evidence supplied by the company to support not including these treatments in Section 3.4.5.

Clinical experts advising the EAG note that in terms of mAbs, in their experience, erenumab is normally the mAb that is used in clinical practice, with galcanezumab used instead if there are any contraindications to using erenumab. The choice between mAbs reflects local formulary committee decisions, which in this instance are based on drug costs as the mAbs are considered to have similar effectiveness. As erenumab has the lowest acquisition cost, it is often the first choice. Galcanezumab is the next least expensive, which is why it is often employed if erenumab is contraindicated. This may be centre-dependent as a clinician that peer reviewed the EAG's report notes that fremanezumab is more easily accessible for them.

No direct evidence comparing atogepant with any of the listed comparators was available and NMAs were instead performed (Section 3.4). Overall, the EAG considers the comparator randomised controlled trials included to be a good representation of the comparator interventions in terms of doses used in practice and does not consider that any have been inappropriately excluded.

2.3.4 Outcomes

Outcomes covered in the CS for atogepant trials match the NICE final scope. The EAG considers that "change in number of cumulative hours of headache or migraine on headache or migraine days" in the NICE final scope may not have been covered in the CS but does not consider this to be a major omission given it was not an outcome key to comparator appraisals.[11]

Outcomes for which NMAs were performed included outcomes that were important in comparator appraisals, such as response based on 50% reduction in MMDs for EM. NMAs were performed for the following outcomes (see Section 3.4 for discussion of these NMAs):

- Change from baseline in MMDs;
- Proportion of patients with 50% reduction in MMDs from baseline (and 30% reduction for CM);
- Change from baseline in days with use of acute MUDs;
- HRQoL outcomes including Headache Impact Test-6 (HIT-6) and three subdomains of the migraine-specific quality of life questionnaire (MSQ);
- TEAEs;
- And all-cause discontinuation.

Of the above outcomes, results for change from baseline in MMDs, proportion with 50% (EM) or 30% reduction in MMDs vs baseline, change from baseline in MUDs and all-cause discontinuation were used in some form in the economic model (see Section 4.2.6). HRQoL data from ELEVATE and PROGRESS were used in the economic model but NMAs were not utilised.

The time-point of 12 weeks for atogepant trials was considered reasonable by the EAG's clinical experts and in line with comparator mAbs (BoNT/A trials assessed response at 24 weeks). It is also the time-point included in the recent recommendations for eptinezumab and rimegepant in terms of assessing response to migraine prevention treatment.[2, 3] Time points reported for trials included in the NMAs varied but were between 12 and 24 weeks in most cases, with some follow-up for TEAEs being longer (see Section 3.4.4.2). The EAG considers the outcome definitions in atogepant trials to be appropriate, such as the thresholds used to define responders which are in line with comparator appraisals.

2.3.5 Subgroups

EM and CM subgroups, and subgroups based on the number of prior prophylactic treatments, listed in the NICE final scope are covered in the submission. While the CS does not present results for the 3+ TF subgroup for CM, or include NMAs for this subgroup, results for this subgroup within the PROGRESS trial are available in the CSR. A comparison of these results is discussed in Section 3.3 for atogepant clinical trials and Section 3.4.3.1 for NMAs; while not provided as part of this STA, NMAs within the 3+ TF population for CM were provided as part of the CCE process for atogepant earlier in 2023. The EAG has not included these results in Section 3.4.3.1 but has commented briefly on how they compared to analyses preferred by the company and the EAG in this STA.

Clinical experts advising the EAG note that high-frequency and low-frequency EM subgroups may represent distinct groups, with those with high-frequency EM possibly experiencing a burden of migraine-related disability more similar to those with CM. However, based on feedback from a clinician peer reviewing this report, the EAG notes that opinion on this differs and it is unclear whether this distinction is evident in clinical practice. As part of the CCE process earlier in 2023, the EAG asked at clarification for efficacy results for these EM subgroups from ELEVATE. Based on the response to this clarification question within the CCE, the EAG is not concerned about major differences existing between these two subgroups. Both subgroups are considered relevant to the appraisal and, given the proportion with high and low frequency EM is similar between atogepant and placebo arms in the overall populations of the atogepant trials, the EAG is not concerned about

the impact of these subgroups on results. Based on this, and the fact that in NICE TA659 for galcanezumab it was concluded that high-frequency EM is not a clinically distinct subgroup,[9] the EAG does not consider further exploration of these subgroups to be important.

In Section B.2.6 of the CS, the company concludes that migraine is a disease continuum and that clinical experts have highlighted that data in patients with EM and CM are complementary and should be viewed holistically. They note that this was also discussed in the NICE appraisal for eptinezumab (TA871) and that clinical experts confirmed that there is no biological rationale for a calcitonin gene-related peptide inhibitor to be effective in only one of the two populations. While the EAG's clinical experts agree that there may be debate about how important differences in migraine burden are between those at the higher end of the EM classification and those at the lower end of the CM classification, they note that efficacy of treatments may reduce with increasing migraine burden (i.e. the potential to reduce MMDs by ≥30% or ≥50% may be more difficult with increased baseline MMD), which could differ for different treatments (i.e. the impact of any differences vs placebo across these groups may be less notable for treatments that are slightly more efficacious than others). Based on this, the EAG considers it appropriate that separate analyses for EM and CM have been performed in this appraisal.

3 Clinical effectiveness

3.1 Critique of the methods review

The company conducted a systematic literature review (SLR) to identify clinical evidence from randomised controlled trials (RCTs) of atogepant or any other pharmaceutical intervention for migraine prevention in episodic migraine (EM) or chronic migraine (CM). Separate SLRs were performed for EM and CM. These RCTs were used to inform network meta-analyses (NMAs), described in Section 3.4. Detailed methods involved in this SLR are described in Appendix D.1 of the company submission (CS) appendices.

The External Assessment Group (EAG) considers these searches to be robust and likely to have captured all relevant RCTs up to the search date; however, it notes that the last update searches were performed in September 2022 (a year prior to this submission) and any relevant RCTs published since then will not have been captured. While the EAG's clinical experts are not aware of any new RCTs published since the last update that would be relevant for inclusion in this SLR, the EAG cannot be sure that RCTs have not been missed as a result; as part of clarification question (CQ) A10, the EAG requested that searches were updated. In response to this, the company performed targeted searches using PubMed; given the time available, the EAG considers this to be a reasonable compromise and it is satisfied that is unlikely that any additional evidence relevant for inclusion in the NMAs was missed. The EAG notes that all RCTs focused on in previous appraisals for comparators relevant to this Single Technology Appraisal (STA) were identified and mentioned in the CS, including eptinezumab and rimegepant RCTs should they be deemed relevant comparators.

The searches for the SLR were broader than the National Institute for Health and Care Excellence (NICE) final scope and the decision problem described in the CS as the whole migraine population was searched for and comparators were not limited to those used after at least three oral preventives had failed. Data extraction was also performed for a broader set of studies than outlined in the decision problem (201 unique studies from 908 publications for EM and 32 unique studies from 596 publications for CM). The list included in the NMAs was in line with the decision problem outlined by the company in terms of comparators, but still wider in terms of population given analyses in the overall migraine population were performed in addition to the group with at least three prior oral preventive treatment failures. A total of 16 and 10 RCTs were identified as relevant

for the NMAs in EM and CM populations, respectively (Section B.2.9 of the CS). This increased to 18 and 12, respectively, when the EAG included rimegepant and eptinezumab studies.

The EAG considers the inclusion criteria used to be reasonable and notes that an issue raised by the EAG as part of the cost-comparison evaluation (CCE) process (exclusion of RCTs solely in Asian populations) was rectified as part of the STA submission, with these RCTs now included in relevant NMAs. The company did not include RCTs covering rimegepant and eptinezumab in NMAs even in response to CQ A1 but the EAG subsequently included them given the discussion in Section 2.2.1 and 2.3.3.

The EAG considers the methodology used in the SLR process to be reasonable, including screening by two independent reviewers and following Cochrane, NICE and PRISMA processes.

Table 13. Summary of EAG's critique of the methods implemented by the company to identify evidence relevant this appraisal

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods
Data sources	Appendix D.1.1	**The EAG considers the sources and dates searched to be comprehensive and appropriate.** Databases searched: • Embase (Embase.com); MEDLINE (Embase.com); MEDLINE In-Process (Pubmed.com); PsychINFO; CDSR and CENTRAL Registries: • Clinicaltrials.gov Conference proceedings: • American Headache Society (2018-2022) • International Headache Society (2017-2022) • European Headache Federation Congress (2018-2022) • American Academy of Neurology (2019-2022) • Migraine Trust International Symposium (2018-2022) Bibliographies of key systematic review and meta-analysis articles were screened to ensure that initial searches captured all relevant clinical studies. Original searches were conducted in May 2020 with multiple update searches performed, including the most recent in September 2022.
Search strategies	Appendix D.1.1	**The EAG considers the search strategies used to be appropriate** The search strategies for the literature review used free-text keywords, MeSH and EMTREE terms for the population and interventions of interest. Search

		filters were used in MEDLINE, Embase and PsychINFO searches to identify RCTs but the EAG is unsure which specific filters were used. The EAG had some concerns about the last SLR updated being performed in September 2022 and whether any additional RCTs relevant to the NMAs in particular have been published since this last update, a year prior to this submission. However, given the results of the targeted searches performed in response to CQ A10 and based on clinical expert feedback, the EAG considers that it is unlikely any have been missed.
Inclusion criteria	Appendix D.1.2, appendix D.2.1 and Section B.2.9.2 of the CS	**The EAG considers the inclusion criteria for the SLR and NMAs to be reasonable** Inclusion criteria for extraction in the SLR were broad and there were few exclusion criteria. Exclusion criteria that were applied at this stage are deemed appropriate by the EAG. To be included in the NMAs, further criteria were applied. The EAG generally considered these to be reasonable and in line with the NICE final scope; however, rimegepant and eptinezumab RCTs were excluded given they were not considered relevant comparators. The company did not include these comparators in response to CQ A1 but the EAG has included them as part of this report. Table 17 in the CS also indicates that RCTs with small sample sizes (fewer than ~30 patients per treatment arm) were considered for exclusion, as were open-label trials. The EAG understands the rationale behind open-label RCTs being excluded, particularly as migraine outcomes are subjective and more likely to suffer from bias introduced as a result of open label RCTs. While excluding RCTs because of small patient numbers may not be ideal, the EAG considers these studies would have a limited impact on results. Tables 9 and 10 of the CS do not appear to contain a full list of RCTs included in the SLR but excluded from NMAs but the EAG notes that none of those listed here were excluded solely because they were open-label and two small BoNT/A RCTs were excluded because of sample size.[23, 24] On review of these RCTs, the EAG does not consider that they would substantially change the available evidence base and they were not included for other appraisals that made comparisons with BoNT/A. In addition, one was a crossover RCT (unlike other included studies which were all parallel RCTs) and the other used a dose that was lower than that recommended by NICE in TA260 (100 units vs 155-195 units). Therefore, the EAG considers the exclusion of these two RCTs to be reasonable.
Screening	Appendix D.1.2	**The EAG considers the methods for screening to be robust** Abstract and title reviews of all references identified from the database searches were reported to be performed independently by two reviewers with any discrepancies resolved by a third reviewer. The same process was applied to articles that were selected for full-text review. Searches of conference proceedings and clinical trial registries were performed by a single reviewer and checked by a second reviewer. Results of the literature screening processes were summarised in a PRISMA diagram.

Data extraction	N/A	**Methods for data extraction in the clinical SLR are not described but processes similar to those described for economic searches may have been used** The EAG notes that a description of the process for extracting studies is not described in Appendix D.1.2 with regards to the clinical SLR. However, it considers it likely that similar processes to those described in Appendix H.3.2, I.2.2 and J.2.2 were performed. This involved one researcher extracting the data and a second researcher independently reviewing all data extracted, which the EAG considers to be reasonable. A third independent individual provided input in cases of uncertainty.
Tool for quality assessment of included study or studies	Appendix D.2.7 and Section B.2.5 of the CS	**The EAG considers the quality assessment tool used for RCTs to be appropriate** The company used the University of York's Centre for Reviews and Dissemination (CRD) checklist for RCTs. These assessments are included in Table 11 of the CS for ELEVATE and PROGRESS (main atogepant trials of interest covered in the CS) and in Tables 33 and 34 of the CS appendices for other included atogepant trials and comparator trials. The EAG notes that the latter two tables include additional studies that were excluded from NMAs, as the criteria for study data extraction was wider than that of the final decision problem set out in the CS.

Abbreviations: BoNT/A, botulinum toxin type A; CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; CQ, clarification question; CS, company submission; EAG, External Assessment Group; EMTREE, Embase subject headings; MeSH, Medical Subject Headings; NICE, National Institute for Health and Care Excellence; N/A, not applicable; NMA, network meta-analysis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial; SLR, systematic literature review; TA, technology appraisal.

3.2 Critique of trials of the technology of interest

Four RCTs involving atogepant are included as part of the CS,[25-28] with all four of these studies included in NMAs within the overall migraine population (see Section 3.4). However, for EM in the CS, the company focuses mostly on ELEVATE given it provides data for the group with at least three prior oral preventive treatment failures (3+ TF) and was stratified at randomisation for this factor. PROGRESS is the only available atogepant RCT within the CM population but results from the overall migraine population are focused on in the CS; while some data for a 3+ TF subgroup were available, the trial was not stratified for this factor at randomisation and the company considers that results within this subgroup cannot be used to draw reliable conclusions based on baseline imbalances between arms and comments from clinical experts that artefactually high placebo rates are present for this subgroup within PROGRESS (see Section B.2.2 of the CS).

The EAG acknowledges the company's concerns about 3+ TF subgroup data from PROGRESS but considers these data useful in providing some insight into outcomes in the subgroup outlined in the decision problem, despite their additional limitations. The EAG has access to these via the clinical study report (CSR) and has included information in its report where required to support decision-making. The EAG notes that information for the overall population and 3+ TF subgroup was provided in the CS for ELEVATE. The company's and EAG's preferred analysis populations for NMAs is discussed in Section 3.4.1.

The EAG notes that a further atogepant RCT in EM is listed as excluded in Table 9 of the CS appendices (NCT03700320; study 3101-302-002).[29] This is because it compares atogepant 60 mg with standard of care migraine preventive treatments, which the EAG considers would include first- to third-line oral options currently recommended by NICE CG150 2021.[30] This differs to all other RCTs included in the NMA (including for comparator treatments), which are compared with placebo and the EAG considers its exclusion from the submission to be reasonable.

While meta-analyses of the three EM atogepant trials could have been presented in the CS rather than focusing on ELEVATE, the EAG does not consider this to be a major omission given the company focuses on the 3+ TF subgroup data for EM in the CS and the other two trials have only a handful or no patients with 3+ TF. All three trials have been included in the overall migraine population NMAs and the EAG presents meta-analysed clinical results from the overall populations of these three trials in Appendix 8.1.

Quality assessments performed by the company for ELEVATE and PROGRESS,[25, 28] the main atogepant RCTs focused on in the CS for EM and CM, respectively, are presented in Table 11 of the CS. The EAG presents its own critique of these studies below in Table 14. Given two additional atogepant RCTs (CGP-MD-01 and ADVANCE) were also included in EM overall population NMAs for health-related quality of life (HRQoL) and/or treatment-emergent adverse events (TEAEs),[26, 27] the EAG has also commented on their quality in this table.

Unlike the company's conclusions, the EAG considers that the included atogepant RCTs have some risk of bias, for example, dropouts are [redacted] for atogepant in ELEVATE, and there are [redacted] in missing data between arms at certain time-points for ELEVATE and PROGRESS, although these are less notable when overall populations are focused on compared to 3+ TF subgroups, which is the EAG's preference as described in Section 3.4.1.

It is unclear if a missing at random assumption, as used in these studies, is appropriate. Although the EAG acknowledge that the robustness of primary outcome (change from baseline [CFB] in monthly migraine days [MMDs]) to this missing at random assumption was assessed to some extent in ELEVATE, PROGRESS and ADVANCE using a copy-reference and jump-to-reference approach, this was not the case for other outcomes, including efficacy outcomes used in the economic model. While the EAG considers that an alternative approach such as reversion to baseline for missing data may provide further insight into the impact of missing data, the company did not provide this in response to CQ A3. Given that similar missing at random approaches have been used in certain studies for comparator treatments (while details for a number of studies were unclear, most studies across EM and CM relied on missing at random assumptions for MMD-related outcome data, with a similar proportion of these analysing observed data only with no imputation as per the atogepant trials and others using alternative methods such as proration/normalisation and/or last observation carried forward methods depending on the level of missing data), and that the sensitivity analyses that have been performed by the company show robustness of the primary outcome to missing data assumption, the EAG does not consider this to be a major limitation.

In addition, subgroup data from PROGRESS for the group with 3+ TF may be at a higher risk of bias given these subgroups were not stratified for at randomisation, with [redacted] and proportion with [redacted] at baseline (see Section 3.3). Despite these limitations, the EAG notes that similar is true for some comparator RCTs included in the NMAs, in terms of assumptions made for missing data (see previous paragraph) and

not being stratified by 3+ TF (none of the comparator studies included in the 3+ TF NMAs for EM stratified for this at randomisation,[18-20] neither did any of the studies included in 3+ TF NMAs for CM as part of the CCE process for atogepant earlier in 2023).[18, 19, 31-34] See Section 3.4.4 for further discussion of differences between studies included in NMAs in this STA.

Overall, the EAG does not consider there to be a large degree of bias associated with the atogepant clinical trials, particularly if the overall migraine populations are focused on.

Table 14. EAG's quality assessment of atogepant clinical trials included in the submission

Question	ELEVATE (EM)[28]	PROGRESS (CM)[25]	CGP-MD-01 (EM)[27]	ADVANCE (EM)[26]
Was randomisation carried out appropriately?	**Yes** Automated IWRS Stratified at randomisation for 3+ TF (subgroups of 2 vs 3-4 treatment class failures)	**Yes** Automated IWRS Not stratified at randomisation for 3+ TF*	**Yes** Automated IWRS Used only for overall migraine population analyses as no efficacy data was reported for those with were reported for patients 3+ TF	**Yes** Automated IWRS Used only for overall migraine population analyses as very few patients in 3+ TF subgroup
Was the concealment of treatme	**Yes** Production of randomisation scheme appears to be separate from those enrolling patients in trial	**Yes** Production of randomisation scheme appears to be separate from those enrolling patients in trial	**Yes** Production of randomisation scheme appears to be separate from those enrolling patients in trial	**Unclear** No details about whether third-party/separate group responsible for randomisation scheme

nt allocated adequate?				
Were the groups similar at the outset of the study in terms of prognostic factors?	**Yes** (overall mITT trial population) Slightly [redacted] between arms in 3+ TF subgroup but [redacted], including continuous outcomes at baseline	**Yes** (overall mITT trial population), although there was a slightly [redacted] proportion using an additional preventive medication during the treatment period in the [redacted] arm ([redacted]% vs [redacted]%) Some [redacted] in 3+ TF subgroup (i.e. [redacted] and proportion with [redacted]†) but others [redacted], including continuous outcomes at baseline (other than MSQ-EF where there was [redacted], with	**Yes** (overall mITT trial population) No 3+ TF subgroup reported	**Yes** (overall mITT trial population) No 3+ TF subgroup used from this trial

		values [redacted] in the placebo group)		
Were the care providers, participants, and outcomes assessors blind to treatment allocation?	**Yes** Said to be double-blind and tablets matched	**Yes** Said to be double-blind and tablets matched	**Yes** Said to be double-blind and tablets matched	**Yes** Said to be double-blind and tablets matched

Were there any unexpected imbalances in dropouts between groups?	**Yes** (from ITT population – proportion discontinuing slightly [redacted] in atogepant group, [redacted]) Slightly [redacted] was due to [redacted] numbers discontinuing due to AE, protocol deviation or lack of efficacy, although these were only differences of [redacted] events per reason Unclear if similar was true for the 3+ TF subgroup	**No** (from ITT population, similar in atogepant 60 mg and placebo groups – [redacted]% vs [redacted]%) Unclear if similar was true for the 3+ TF subgroup	**Yes** (from ITT population – proportion discontinuing [redacted] in atogepant 60 mg group vs placebo, [redacted]) Most of this difference was due to patients [redacted]; withdrawals due to [redacted] between groups	**Yes** (from ITT population – proportion discontinuing [redacted] in atogepant 60 mg group vs placebo, [redacted]) Proportions with each specific reason for discontinuation were, however, [redacted] between arms. Other than [redacted], which occurred [redacted] in the atogepant 60 mg arm vs placebo ([redacted])
Is there any evidence to suggest	**No** Outcome data relevant to the appraisal focused on in CS	**No** Outcome data relevant to the appraisal focused on in CS	**No** Outcome data relevant to the appraisal focused on in CS.	**No** Outcome data relevant to the appraisal focused on in CS.

that the authors measured more outcomes than they reported?				
Did the analysis include an intention-to-	**Yes, some concerns about missing at random assumption** mITT population for efficacy and HRQoL analyses‡ Safety population for AEs§ Missing data handled using MMRM for continuous outcomes – assumed to be MAR, may not	**Yes, some concerns about missing at random assumption** mITT population for efficacy and HRQoL analyses‡ Safety population for AEs§	**Yes, some concerns about missing at random assumption** mITT population for efficacy analyses‡ Safety population for AEs§ [redacted]	**Yes, some concerns about missing at random assumption** mITT population for efficacy and HRQoL analyses‡ Safety population for AEs§ [redacted]

treat analysis? If so, was this appropriate and were appropriate methods used to account for missing	be plausible. Logistic regression used for binary outcomes. In the 3+ TF subgroup at weeks 9-12 for MMD data, [redacted] patients in the atogepant arm had missing data ([redacted], difference of [redacted] patients), while proportions were [redacted] at earlier time-points. There was a similar but [redacted] difference in the overall mITT population ([redacted]%; difference of [redacted] patients)[ll] For HRQoL data in the overall mITT population, missing data was [redacted] between arms at 12 weeks.	Missing data handled using MMRM for continuous outcomes – assumed to be MAR, may not be plausible. Logistic regression used for binary outcomes. In the 3+ TF subgroup for MMD data, while proportions with missing data were slightly [redacted] for placebo at weeks 5-8 and weeks 9-12 ([redacted]), this was based on a difference of [redacted] patients. For the overall mITT population, there was a slight difference in proportions with missing data at weeks 9-12 ([redacted]% in placebo vs atogepant 60 mg groups) but not at earlier time-points[ll]	Detailed information on missing data rates not available.	Detailed information on missing data rates not available.

data?		For HRQoL data in the overall mITT population, missing data was [redacted] between arms at 12 weeks.		
Sample size and power	Planned enrolment of 150 patients per group provided 97% and 95% power to detect a treatment difference for CFB in MMDs vs placebo (-1.7 days for US and -1.6 days for EU, SD 3.5 days). This sample size was also said to have been selected to provide sufficient power for [redacted]. Just over 150 patients per arm were enrolled but the EAG notes that missing data at weeks 9-12 meant that [redacted] patients had available data in atogepant 60 mg (MMD or MUD outcomes) or both treatment arms (HRQoL outcomes). Power calculations were said to have been based on results from	Planned enrolment of 250 patients per group provided ≥96% power to detect a treatment difference between each atogepant dose (assumed equally effective) and placebo for CFB in MMDs (treatment difference assumed to be -2.0 days with 5.5 SD). This sample size was also considered to provide sufficient power for [redacted]. Just over 250 patients were enrolled but the EAG notes that just	Planned enrolment of [redacted] for 60 mg twice daily, 30 mg twice daily and 10 mg once daily, and [redacted] for 60 mg once daily, 30 mg once daily and placebo groups. Assuming treatment difference of [redacted] (SD [redacted]) for the dose relevant to the CS (60 mg atogepant once daily). This was estimated to give a power of [redacted]% for the primary outcome (CFB in MMDs). Numbers outlined above were successfully randomised into the trial, although those completing the trial were less than those specified for each treatment. Power calculations were based on results from other EM prevention studies, including [redacted] Unclear why the specific studies selected were chosen.	Sample size of 218 participants per trial group was calculated to provide at least 98% power to detect a difference of 1.5 migraine days between each of the three atogepant doses (assumed to be equally effective) and placebo for the primary efficacy end point (CFB in MMDs), assuming a standard deviation of 3.5 days for each. Also estimated to provide at least 89% power for first three secondary endpoints (CFB in MHDs, CFB in acute MUDs and 50% MMD reduction). A total of 218 patients for each group were successfully randomised into the trial, although fewer than 218 in each group completed the treatment period. Power calculations were based on results from other EM prevention studies, including CGP-MD-01 for atogepant and selected studies for telcagepant, galcanezumab, fremanezumab and eptinezumab. Unclear why the specific studies selected were chosen.

	[redacted] Unclear why other mAb studies not considered.	under 250 were included in the mITT population for the placebo group. Missing data at weeks 9-12 also meant that data was available from [redacted] in each treatment group for MMD/MUD and HRQoL outcomes. Power calculations were based on assumptions that treatment differences vs placebo will be similar to [redacted] Unclear why [redacted] studies not considered.		This information could not be located in the CSR but was identified in a publication for this study.[35]
Outcome assessment	Migraine outcomes were assessed using eDiaries completed by patients at relevant time-points, which are valid but subjective measures of assessment meaning blinding is particularly important. HRQoL	Migraine outcomes were assessed using eDiaries completed by patients at relevant time-points, which are valid but subjective measures of	Migraine outcomes were assessed using eDiaries completed by patients at relevant time-points, which are valid but subjective measures of assessment meaning blinding is particularly important.	Migraine outcomes were assessed using eDiaries completed by patients at relevant time-points, which are valid but subjective measures of assessment meaning blinding is particularly important. HRQoL outcomes were assessed using validated questionnaires.

	outcomes were assessed using validated questionnaires.	assessment meaning blinding is particularly important. HRQoL outcomes were assessed using validated questionnaires.		

*This trial was stratified based on failing 0 or ≥1 medications with same mechanism of action vs failed 2-4 medications with different mechanisms of action but not for the specific subgroup used in the CS (≥3 prior treatment failures); [†]data provided in response to CQ A5 as part of the CCE process for atogepant earlier in 2023; [‡]mITT defined as patients randomised, receiving at least one dose of study drug, with baseline eDiary data and ≥1 post-baseline 4-week period of eDiary data during double-blind treatment period – of the ITT population, this led to the exclusion of [redacted] and [redacted] in atogepant 60 mg and placebo groups, respectively, in ELEVATE. The equivalent proportions were [redacted] and [redacted] for PROGRESS, [redacted] and [redacted] for CGP-MD-01, and [redacted] and [redacted] for ADVANCE; [§]safety population defined as those with ≥1 dose of study drug, analysed according to treatment received – of the ITT population, this led to the exclusion of [redacted] and [redacted] in atogepant 60 mg and placebo groups, respectively in ELEVATE. The equivalent proportions were [redacted] and [redacted] for PROGRESS, [redacted] for CGP-MD-01, and [redacted] and [redacted] for ADVANCE. It is unclear if any patients switched groups and were analysed in the opposite group to that they were assigned to at randomisation for safety analyses; [‖]data provided in response to CQ A7 as part of the CCE process for atogepant earlier in 2023.

The EAG used the template completed by the company with the addition of rows on sample size and power and outcome assessment.

Abbreviations: 3+ TF, patients in whom ≥3 prior preventive treatments have failed; AEs, adverse events; CCE, cost-comparison evaluation; CM, chronic migraine; CQ, clarification question; CS, company submission; EAG, External Assessment Group; eDiary, electronic diary; EM, episodic migraine; HRQoL, health-related quality of life; ITT, intention to treat; IWRS, interactive web-response system; MAR, missing at random; mITT, modified intention to treat; MMD, monthly migraine day; MMRM, mixed model for repeated measures; MSQ-EF, migraine-specific quality of life questionnaire – emotional function.

3.3 Critique of the clinical effectiveness analysis and interpretation

In Section B.2.6 of the CS, the company outlines results for primary and secondary outcomes of ELEVATE (EM) and PROGRESS trials. While three atogepant RCTs within the EM population were included in the submission for the overall migraine population (see Section 3.2), these are not focused on in the CS given they included no or very few patients with 3+ TF, unlike ELEVATE which included a 3+ TF group which was stratified for at randomisation. For PROGRESS, in the original CS the company only presented results for the overall mITT population, as it notes that the 3+ TF subgroup was not stratified for at randomisation and the results are, therefore, unreliable (see Section 3.2). However, results for both the 3+ TF subgroup and overall mITT population in ELEVATE are included in the CS.

While the EAG agrees that the ELEVATE trial in EM is more relevant to the decision problem population (3+ TF) than ADVANCE and CGP-MD-01 as it includes a proportion of 3+ TF patients and is specifically in those with 2-4 TF, given its preference for NMAs within the mITT population for EM as well as CM (as described in Section 3.4.1), the EAG has also presented results from ADVANCE and CGP-MD-01 within the mITT population. Meta-analysed results are also presented by the EAG in Appendix 8.1. In addition, while the EAG acknowledges the additional bias likely to be associated with 3+ TF subgroup results from PROGRESS, the EAG considers it useful that these results be presented for comparative purposes, given this is the group outlined in the decision problem, and has obtained these results from the PROGRESS CSR.

The EAG considers that the results from the overall population for PROGRESS may be more reliable compared to the 3+ TF subgroup given some larger imbalances were observed for the latter; while the EAG's clinical experts did not consider a notable imbalance in [redacted] white in placebo and atogepant groups, respectively) to be important, the EAG notes that there is a [redacted] in the proportion with ≥18 MMDs within this subgroup ([redacted] in placebo and atogepant groups, respectively; response to CQ A5 as part of the CCE process for atogepant earlier in 2023) which may indicate a difference in migraine burden that could impact relative efficacy outcomes (i.e. more people with higher initial baseline MMDs [redacted] group may mean fewer patients are able to achieve a 30% or 50% reduction in MMDs at follow-up than would have had this been more balanced). There are no major concerns about imbalances for the 3+ TF population from ELEVATE but for reasons described in Section 3.4.1 the EAG also prefers NMAs within the overall migraine population for EM (see Key Issue 2 in Table 3). As noted in Section

2.3.1, the EAG's clinical experts had no major concerns about differences in baseline characteristics between the 3+ TF and overall migraine populations for ELEVATE or PROGRESS; in both cases they consider that either of them would be a reasonable representation of a 3+ TF group.

Of the outcomes described in the sections that follow, data from ELEVATE (3+ TF subgroup for all outcomes) and PROGRESS (overall mITT population for all outcomes) were used in the economic model by the company to inform absolute values for CFB in MMDs, CFB in acute medication use days (MUDs), 50% (EM) or 30% (CM) reduction in MMDs and discontinuation for atogepant. For scenarios using the overall migraine population for EM in the economic model, ADVANCE was used as the source of atogepant data, which the EAG considers to be reasonable. Relative treatment effects from NMAs described in Section 3.4.3 were then used to obtain values for each comparator for use within the economic model (see Section 4.2 for further discussion regarding the economic model). For CM, results for the 50% MMD reduction threshold have also been presented given limited data was available for the 30% threshold in the NMAs (see Section 3.4.3.1), but the EAG notes that 30% is the threshold normally used in CM and is what is used in the base case of the company's economic model. The company performed a scenario analysis in CM where the 50% threshold was used in the economic model instead (see Section 5.1.3). HRQoL outcomes and TEAEs were not used in the economic model but are discussed briefly for completeness.

3.3.1 Migraine day-related outcomes

Migraine day-related outcomes from ELEVATE and PROGRESS that were used to inform the economic model, within the 3+ TF and overall mITT populations, are presented in Table 15 below. For comparison within the EM mITT population, the EAG presents results from ELEVATE alongside ADVANCE and CGP-MD-01 in Table 16 below.

As concluded by the company in Section B.2.6.1 of the CS, the EAG agrees that results in the 3+ TF and overall mITT populations for ELEVATE in EM demonstrate a statistically significant benefit of atogepant compared to placebo in terms of reducing MMDs. Results for EM in these two populations are [redacted] with a slightly [redacted] benefit observed in the 3+ TF subgroup. In terms of CM, the EAG agrees with the company's conclusion that there is a statistically significant difference between atogepant and placebo groups in terms of reducing MMDs, with the benefit observed for atogepant. [redacted], the 3+ TF subgroup results from PROGRESS are [redacted] the overall mITT population, with the point estimate for the difference between treatments suggesting a [redacted] in the 3+ TF subgroup compared to

the overall mITT population; however, the results are [redacted] when this subgroup is considered, which may partially be due to [redacted] in this analysis in addition to the fact that PROGRESS (unlike ELEVATE) was not powered to assess the primary outcome in the 3+ TF subpopulation.

For EM, the same conclusions can be made for the other two outcomes included in Table 15 below; results in both populations are similar in terms of direction and statistical significance, with results [redacted] for atogepant in the 3+ TF subgroup, which is most notable for the ≥50% reduction in MMD outcome. Given the similarity of results between 3+ TF and overall mITT population results in EM from ELEVATE, the EAG considers this provides further support for its preference for the overall migraine population NMAs for the EM population (see Section 3.4.1). The conclusions for other outcomes in Table 15 for CM are also similar to those made for the CFB in MMD outcome; 3+ TF and overall mITT population analyses [redacted] a benefit of atogepant over placebo, but most 3+ TF analyses (with the exception of the CFB in acute MUDs outcome) [redacted]. The remaining outcomes in CM again suggest [redacted] in the 3+ TF subgroup compared to the overall mITT population, with the exception of proportion with ≥30% reduction in MMDs where the OR for the 3+ TF subgroup is [redacted] for atogepant. Nonetheless, the EAG accepts the potential limitations associated with this subgroup in PROGRESS and, overall, considers the use of the mITT population results to be reasonable given they do not differ hugely.

With regards to the three atogepant RCTs in the EM population that are included in NMAs within the migraine population analyses, the EAG notes that across the three outcomes included in Table 16, the most favourable outcomes for atogepant come from the ELEVATE study. However, the EAG notes that results from ELEVATE and ADVANCE are broadly similar in that [redacted] of atogepant 60 mg once daily vs placebo is observed for [redacted]. The same is also true for CGP-MD-01 for the CFB acute MUDs outcome, but not for CFB in MMDs or proportion with ≥50% reduction in MMDs. The EAG is unsure exactly why this may be the case but notes that it may be related to placebo response as it is highest in this study for all three outcomes, with the [redacted]. Nonetheless, the EAG concludes that all three studies suggest a benefit of atogepant 60 mg daily over placebo for these three outcomes in the overall mITT population of included studies, but notes that the [redacted] across the three RCTs. As noted in the introductory text to

Section 3.3, the EAG agrees that ELEVATE is most relevant to the decision problem given it provides data for the 3+ TF subgroup and the whole mITT population is specific to those with 2-4 TF.

Table 15. Primary and secondary MMD day-related outcomes used to inform the economic model – ELEVATE and PROGRESS, 3+ TF and overall mITT populations, across 12-week treatment period – adapted from Tables 12 and 13 of the CS

Outcome	3+ TF subgroup			Overall mITT population		
EM - ELEVATE[28, 36]	Placebo (N=**)	Atogepant 60 mg once daily (N=**)	TE* (95% CI)	Placebo (N=***)	Atogepant 60 mg once daily (N=***)	TE* (95% CI)
CFB in mean MMDs, LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Achievement of ≥50% reduction in mean MMDs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB in mean monthly acute MUDs, LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CM - PROGRESS[25, 37]	**Placebo (N=**)**	**Atogepant 60 mg once daily (N=**)**	**TE*,§ (95% CI)**	**Placebo (N=246)**	**Atogepant 60 mg once daily (N=256)**	**TE* (95% CI)**
CFB in mean MMDs, LS mean (SE)	[redacted]	[redacted]	[redacted]	-5.05 (0.411)	-6.88 (0.406)	**MD -1.82 (-2.89 to -0.75)‡**
Achievement of ≥30% reduction in mean MMDs, n (%)	[redacted]	[redacted]	[redacted]¶	[redacted]	[redacted]	[redacted]‡
Achievement of ≥50% reduction in mean MMDs**, n (%)	[redacted]	[redacted]	[redacted]††	64 (26.0)	105 (41.0)	**OR 2.04 (1.38 to 3.00)‡**
CFB in mean monthly acute MUDs, LS mean (SE)	[redacted]	[redacted]	[redacted]‡‡	-4.10 (0.392)	-6.23 (0.386)	**MD -2.13 (-3.13 to -1.13)‡**

*TE was LSMD for all endpoints apart from the achievement of ≥50% or ≥30% reduction in mean MMDs where it was OR; †p<0.001; ‡p<0.0001; §data obtained from additional tables (Tables 901.3-1.1.3, 901.3-18.1.3, 901.3-2.1.3 and 901.3-4.1.3 for CFB in MMDs,

≥30% reduction in MMDs, ≥50% reduction in MMDs and CFB in acute MUDs, respectively) provided as part of the PROGRESS CSR for the 3+ TF subgroup;[37] ‖p-value = [redacted]; ¶p-value = [redacted]; **for CM, the 50% MMD reduction threshold was not used in the base case of the economic model but was explored by the company in a scenario analysis (Table 67 of the CS); ††p-value = [redacted]; ‡‡p-value = [redacted]. Bolded values indicate statistically significant differences.

Abbreviations: 3+ TF, patients in whom ≥3 prior oral preventive treatments have failed; CFB, change from baseline; CI, confidence interval; CM, chronic migraine; CS, company submission; CSR, clinical study report; EM, episodic migraine; LS, least squares; LSMD, least squares mean difference; MD, mean difference; mITT, modified intention to treat; MMD, monthly migraine days; MUDs, medication use days; OR, odds ratio; SE, standard error; TE, treatment effect.

Table 16. Comparison of migraine day-related outcomes in ELEVATE, ADVANCE and CGP-MD-01 RCTs within the EM mITT population – adapted from Table 12 of the CS and CSRs for ADVANCE and CGP-MD-01

Outcome	ELEVATE[28]			ADVANCE[26,*]			CGP-MD-01[27,†]		
	Placebo (N=[redacted])	Atogepant 60 mg once daily (N=[redacted])	TE‡ (95% CI)	Placebo (N=[redacted])	Atogepant 60 mg once daily (N=[redacted])	TE‡ (95% CI)	Placebo (N=[redacted])	Atogepant 60 mg once daily (N=[redacted])	TE‡ (95% CI)
CFB in mean MMDs, LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Achievement of ≥50% reduction in mean MMDs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB in mean monthly acute MUDs, LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Data was obtained from Tables 11-2, 11-9 and 11-8 for CFB in MMDs, proportion with ≥50% MMD reduction and CFB in acute MUDs, respectively; †data was obtained from Tables 11-2, 11-5 and 11-6 for CFB in MMDs, proportion with ≥50% MMD reduction and CFB in acute MUDs, respectively; ‡TE was LSMD for all endpoints apart from the achievement of ≥50% reduction in mean MMDs where it was OR; §p<0.001; ‖p<0.0001; ¶p-value = [redacted]; **p-value = [redacted]. Bolded values indicate statistically significant differences.

Abbreviations: CFB, change from baseline; CI, confidence interval; CS, company submission; EM, episodic migraine; LS, least squares; LSMD, least squares mean difference; MD, mean difference; mITT, modified intention to treat; MMD, monthly migraine days; MUDs, medication use days; OR, odds ratio; SE, standard error; TE, treatment effect.

3.3.2 Discontinuation

Given NMAs are also performed as part of this submission for all-cause discontinuation (see Section 3.4.3.2), the results of which inform the proportion of patients discontinuing treatment prior to response assessment for comparator treatments in the economic model (see Section 4.2.6.1 of this report and Section B.3.3.2 of the CS), the EAG also touches on the results for discontinuation from atogepant RCTs here.

While the EAG presents discontinuations with the 3+ TF subgroup as well as the overall mITT populations for ELEVATE and PROGRESS in Table 17 below for completeness, it notes that NMAs for EM and CM were only possible within the overall migraine population, given these data were not well reported for comparator RCTs (see Section 3.4.1).

The EAG notes that within the overall mITT population for EM, there does not appear to be a consistent pattern in terms of whether there were more discontinuations in the placebo or atogepant 60 mg once daily group; while it was [redacted] for atogepant in ELEVATE [redacted], the opposite was observed for [redacted]. Within ELEVATE, percentages suggest that there is a [redacted] difference between atogepant and placebo groups in the 3+ TF subgroup compared to the overall mITT population ([redacted] discontinuation for atogepant in both analyses), although the EAG notes that there is a difference of [redacted] events between atogepant and placebo groups in both populations. For CM, the overall mITT population of the PROGRESS trial indicated [redacted] discontinuation in atogepant 60 mg once daily and placebo groups, with there [redacted] based on percentages for the 3+ TF subgroup; however, the EAG notes that there is only a difference of [redacted] events in the 3+ TF subgroup.

Overall, the EAG concludes that while there are some differences in proportions discontinuing for the EM studies ([redacted] for atogepant in two and [redacted] for placebo in one), these are generally based on differences of [redacted] patients, other than the CGP-MD-01 study. For CM, there is limited difference between treatment arms in 3+ TF and overall mITT populations.

Table 17. All-cause discontinuation across atogepant RCTs for EM and CM, 3+ TF and overall mITT populations

Study	3+ TF subgroup		Overall mITT population	
	Placebo, n/N (%)	Atogepant 60 mg once daily, n/N (%)	Placebo, n/N (%)	Atogepant 60 mg once daily, n/N (%)
ELEVATE (EM)[28, 36]	[redacted]	[redacted]	[redacted]	[redacted]
ADVANCE (EM)	N/A	N/A	[redacted]	[redacted]
CGP-MD-01 (EM)	N/A	N/A	[redacted]	[redacted]
PROGRESS (CM)	[redacted]	[redacted]	29/259 (11.2%)	29/262 (11.1%)

Abbreviations: 3+ TF, patients in whom ≥3 prior oral preventive treatments have failed; CM, chronic migraine; EM, episodic migraine; mITT, modified intention to treat; N/A, not applicable; RCT, randomised controlled trial.

3.3.3 Quality of life

HRQoL was included in the CS by reporting results for various validated questionnaires (three subscores of the migraine-specific quality of life questionnaire [MSQ] v2.1 questionnaire and the Headache Impact Test [HIT]-6) assessed in the atogepant RCTs. While NMAs were performed for these outcomes (see Section 3.4.3.3), the results of these NMAs were not used in the economic model. As discussed further in Section 4.2.9, utilities in the economic model are considered by mapping MSQ v2.1 data from the overall mITT populations of ELEVATE and PROGRESS studies to EQ-5D-3L. Given the overall mITT population was used for this purpose in the economic model and was the population used for NMAs of HRQoL outcomes, the EAG only presents mITT results here. However, the EAG agrees with the company's conclusions in Section B.2.6.3 of the CS that within ELEVATE, results for the 3+ TF population are consistent with those in the overall mITT population, although slightly [redacted] for atogepant in the 3+ TF subgroup (but with increased uncertainty). On review of the 3+ data for the PROGRESS trial within the CSR tables provided,[37] the EAG also considers that the same is true for this trial, again with increased uncertainty. The EAG has included data from the ADVANCE and CGP-MD-01 RCTs in EM for comparison, as these were also included in overall migraine population NMAs.

In terms of the results, the EAG agrees with the company's conclusions in Section B.2.6.3 of the CS that overall mITT populations for ELEVATE and PROGRESS demonstrate statistically significant benefits of atogepant 60 mg once daily compared to placebo for the three MSQ v2.1 subscores and HIT-6. The EAG also agrees that these differences are higher than the thresholds considered to be

clinically meaningful for these outcomes according to the sources cited by the company,[38-40] apart from MSQ-EF in PROGRESS for CM where the point estimate was just below the threshold of 7.5 points. While the EAG notes that the results in Table 18 below indicate that [redacted] of atogepant vs placebo was observed in ADVANCE compared to ELEVATE, the results for all outcomes [redacted] the clinically meaningful thresholds reported. The CGP-MD-01 study did not report MSQ v2.1 outcomes; the result for HIT-6 was [redacted] for atogepant compared to ELEVATE and ADVANCE studies as there was [redacted] and the point estimate for the difference vs placebo was [redacted] cited as clinically meaningful by the company.[39, 40]

Overall, the EAG considers that evidence from the atogepant RCTs included in this submission, particularly ELEVATE and PROGRESS, which are focused on by the company, provide evidence that atogepant 60 mg once daily leads to clinically meaningful improvements in HRQoL outcomes compared to placebo.

Table 18. CFB in HRQoL outcomes in atogepant RCTs within the mITT population, EM and CM

Outcome	ELEVATE (EM)[28]			ADVANCE (EM)[26]			CGP-MD-01 (EM)[27]			PROGRESS (CM)		
	Placebo	Atogepant 60 mg once daily	TE* (95% CI)	Placebo	Atogepant 60 mg once daily	TE* (95% CI)	Placebo	Atogepant 60 mg once daily	TE* (95% CI)	Placebo	Atogepant 60 mg once daily	TE* (95% CI)
CFB in mean MSQ-RFP score, LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]
CFB in mean MSQ-RFR score, LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]
CFB in mean MSQ-EF score, LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]
CFB in mean HIT-6 score, LS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

mean (SE)												

*TE was LSMD for all endpoints; †p<0.0001; ‡p<0.001; §p-value = [redacted]. Bolded values indicate statistically significant differences.

Abbreviations: CFB, change from baseline; CI, confidence interval; CM, chronic migraine; EM, episodic migraine; HIT-6, Headache Impact Test-6; HRQoL, health-related quality of life; LS, least squares; LSMD, least squares mean difference; MD, mean difference; mITT, modified intention to treat; MSQ, migraine-specific quality of life questionnaire; MSQ-EF, emotional function subdomain of MSQ; MSQ-RFP, role function-preventive subdomain of MSQ; MSQ-RFR, role function-restrictive subdomain of MSQ; N/A, not applicable; RCT, randomised controlled trial; SE, standard error; TE, treatment effect.

3.3.4 *Safety*

Given adverse events (AEs) are not included in the economic model, the EAG only briefly discusses AEs in this section. AEs for the overall safety populations of ELEVATE and PROGRESS are summarised in Section B.2.10 of the CS. While TEAEs related to treatment were higher in both trials for atogepant 60 mg once daily, the EAG notes that similar proportions in each group experienced serious events or those leading to treatment discontinuation. The biggest differences between atogepant and placebo arms appeared to be for [redacted] in both trials, with more of these events in the atogepant groups. Similar was observed for CGP-MD-01 and ADVANCE atogepant trials.[26, 27]

The EAG's clinical experts are not aware of any AEs of particular concern for atogepant but note that there are certain AEs that can be an issue for monoclonal antibodies (mAbs; erenumab, galcanezumab and fremanezumab) and botulinum toxin type A (BoNT/A) and are more common, such as injection site-related AEs. Omission of AEs from the economic model may be conservative, however, injection site-related AE disutility was indirectly included, by the company applying a utility decrement associated with route of administration (see Section 4.2.7). NMAs for TEAEs were performed as part of the CS (see Section 3.4.3.4) but the EAG notes that usually AEs of a specific severity are included in economic models, rather than any TEAEs, and so the results of these NMAs are not useful in confirming the conclusions made by the EAG's clinical experts. Furthermore, the EAG notes that no AEs of concern for atogepant are reported in the marketing authorisation.[4]

3.4 Summary of the indirect treatment comparison

3.4.1 *Statistical methods and approach*

In the absence of direct evidence comparing atogepant with any of the comparators in the decision problem, NMAs were performed. The EAG focuses on outcomes where NMA results were directly used in the economic model (CFB in MMD, proportion with ≥30 or 50% reduction in MMDs, CFB in acute MUDs and all-cause discontinuation; Sections 3.4.3.1 and 3.4.3.2), but also touches on results of NMAs for HRQoL outcomes and TEAEs (Sections 3.4.3.3 and 3.4.3.4, respectively).

For the EM population, NMAs for MMD-based outcomes were performed in the 3+ TF population (company's preferred analysis) as well as the overall migraine population, but the same was not performed for the CM population. This is because the ELEVATE study in EM stratified for the 3+ TF subgroup at randomisation and this subgroup was said by the company to be adequately powered,

whereas the PROGRESS trial in CM was not stratified for this subgroup or adequately powered within this subgroup. The company states that the lack of stratification in the PROGRESS trial, as well as small sample size, may explain comments from the clinical experts that they consulted that this subgroup within PROGRESS has artefactually high placebo response rates; the company concludes that the 3+ TF subgroup within PROGRESS is not suitable for decision-making and NMAs within the overall migraine population are instead preferred. While NMAs within the 3+ TF population for CM were performed as part of the CCE earlier in 2023, these were not provided as part of this STA; the EAG has touched on these results briefly in Section 3.4.3.1 for CM in terms of how different they are to the company- and EAG-preferred analyses in this report. The EAG agrees with the company's concerns about the 3+ TF subgroup from PROGRESS and the impact this may have on the results of NMAs; however, it considers the same issues apply to EM given many comparator studies were not stratified for 3+ TF. Based on this, the EAG has a preference for NMAs performed within the overall migraine population for EM and CM populations (see Key Issue 2 in Table 3).

For HRQoL, all-cause discontinuation and TEAE NMAs, analyses were performed only in the overall migraine population given a lack of reporting of these outcomes for comparator studies within the 3+ TF population. The EAG considers this to be reasonable and notes that the EAG's concern about the overall migraine population analyses during the CCE has been resolved as part of the STA, as these analyses now include all migraine RCTs rather than excluding those that were specifically in refractory populations (i.e. 2-4 treatment failures). Studies solely in Asian populations were also included in these NMAs, as requested by the EAG during the CCE process. The company also provided HRQoL NMAs within more refractory populations (2+ and 3+ TF groups) as part of the CCE process, which demonstrated that data was much scarcer for these populations, with only one or two comparators being included; the EAG considers that this supports the need for the overall migraine population to be used for these additional outcomes.

The clinical experts advising the EAG note that it may be reasonable to use overall analyses for discontinuation and TEAE outcomes, as they do not expect them to differ across patients with different numbers of treatment failures. One expert noted that if reasons for prior treatment failure included side effects then it may be an issue, as people who experience side effects on one treatment may be at a higher general risk with other treatments. This was the case for the ELEVATE and PROGRESS trials when classifying treatment failure, and the FOCUS, CONQUER and LIBERTY trials, but the proportion failing due to side effects rather than a lack of efficacy is unclear. However, the second expert did not agree with the concerns raised. On balance, the EAG is not concerned that

looking at an overall population rather than focusing only on the 3+ TF subgroup would affect conclusions, particularly as, in most cases where a comparison is possible for the same intervention, relative differences in TEAE rates vs placebo in studies in a general population are similar to those from studies that only include patients with 2-4 prior treatment failures (Tables 17 and 23 of the CS appendices).

The EAG considers the methods used for the NMAs to be appropriate. Fixed (FE) and random effects (RE) models were performed by the company, with RE favoured as the company highlight heterogeneity between the trials included in the NMAs. While the EAG also has a preference for RE analyses in the overall migraine population NMAs given they are generally a better fit and there is reason to believe there is clinical and methodological heterogeneity between trials, the EAG disagrees with the company's preference for RE analyses within the 3+ TF population for EM (see Key Issue 3 in Table 4), given that on rerunning the analyses, in most cases the distribution of between-study heterogeneity was dominated by the priors (uniform [0,5]) that had been set for between-study heterogeneity in the NMAs, which is highlighted as an important issue in points 5 and 6 of a technical support document written by the NICE Decision Support Unit (DSU).[41] In effect, the prior distribution is dictating the uncertainty in the NMAs as there are insufficient data in the analyses to appropriately inform the between-study heterogeneity. The EAG therefore considers that there is not enough data to support the use of RE analysis in the 3+ TF analyses, which is not surprising given in most cases there was only one study per treatment comparison with some having only small subgroups of the original trial included. The EAG also notes that credible intervals (CrIs) for one outcome when RE analyses are used within the EM 3+ TF population are extremely wide (see Section 3.3.1), and while less extreme for other outcomes, CrIs indicate substantial uncertainty for all three MMD-related outcomes in EM within the 3+ TF population, making conclusions difficult. As noted above, the EAG does not have a preference for EM analyses to be conducted within the 3+ TF population.

Within the overall migraine population analyses, RE and FE analyses with adjustment for baseline risk, accounting for differences in placebo responses between studies (discussed as an issue associated with NMAs in this STA in Section 3.4.4.3), were also performed by the company for some outcomes, including MMD-related outcomes and all-cause discontinuation. The company does not favour any of the baseline-adjusted NMA results in the base case of the economic model for either EM or CM populations, stating that, "regression coefficients were not significant and model fit statistics for these models did not show meaningful improvements over unadjusted models". For

MMD-related outcomes in EM, the EAG notes that adjusted versions did not converge in the 3+ TF subgroup, which is the population that the company favoured in its base case for these analyses. While the EAG acknowledges that there may be limited difference between adjusted and unadjusted RE analyses in terms of model fit, it notes that this is not the case for every outcome within EM and CM populations and the EAG has based its decisions about which analysis is most appropriate on model fit as well as other factors such as impact on between-study standard deviation (heterogeneity; see Key Issue 3 in Table 4). The EAG's preferred analyses for each outcome are discussed in the sections that follow.

For discontinuation and TEAE outcomes, NMAs were analysed using both logit and cloglog models. The company has a preference for cloglog models, outlining the potential for the event rates for these types of outcomes to differ with differing study durations, which is an issue for studies included in these NMAs. The EAG considers that cloglog models are a reasonable option for these outcomes based on a guidance document produced by the NICE Guidelines Decision Support Unit.[42] However, the EAG also notes that there is very little difference between logit and cloglog models on the NMA results in most cases, other than TEAEs in CM where differences are more notable but not hugely different (Table 27 of the CS).

The EAG is satisfied that appropriate methods and code have been used for the NMAs included in this STA. While the EAG had issues validating some of the data going into NMAs, the EAG considers that this is because not all of the supplementary papers used to obtain data for secondary outcomes or within certain subgroups have been provided or clearly referenced, making it difficult to locate the data used in the NMAs. The EAG notes that this was primarily an issue for HRQoL outcomes (results of NMAs not used in the economic model), and the EAG was able to validate all of the data for efficacy, TEAE and discontinuation outcomes. On validating the NMAs, the EAG made minor changes to the data analysed where slight errors in input data were identified relative to the publications and more substantial additions were also made by the EAG, for example to include rimegepant and eptinezumab studies given these may be appropriate comparators for this appraisal, as discussed in Section 2.3.3. Any amendments to data analysed for each outcome are discussed in Appendix 8.2.

3.4.2 Included studies

Studies included in the NMAs were RCTs, including phase 2 and phase 3 RCTs. The company performed a quality assessment of all comparator studies, including those for rimegepant and

eptinezumab, which is presented in Tables 33 and 34 of the CS appendices. This assessment was performed for all studies deemed relevant to the SLR, before the final set of studies relevant to this appraisal were selected (see Section 3.1), meaning many more studies are included in these appendix tables. The EAG has presented those relevant to the NMAs in Appendix 8.3. The assessments for all but one study (EVOLVE-1 in EM) suggest that there is low risk of bias for all studies across EM and CM. EVOLVE-1 is stated by the company not to have used appropriate methods for missing data but no further information is provided. The EAG could not identify why this was the case for EVOLVE-1 on review of the primary publication and statistical analysis plan, as there did not appear to be anything different about the methods discussed here compared to other studies.[43]

The EAG has no major concerns about differences in terms of risk of bias that could have an impact on the conclusions of the NMAs, other than differences in analysis methods for missing data already described in Section 3.4.4.2; studies were similar in terms of trial design and all were double-blind, but the EAG notes that the potential for unmasking in trials of BoNT/A due to changes in muscle tone has been previously raised.

When additional rimegepant and eptinezumab studies were included by the EAG, a total of 18 studies in EM and 12 studies in CM were included, although data was not available for all outcomes from each study. Included studies are outlined in Table 19 below. The company further discusses studies included in the NMAs (with the exception of rimegepant and eptinezumab studies) in Section B.2.9.2 and B.2.9.4 of the CS, as well as Section D.2.3 of the CS appendices.

The EAG considers that the doses used in the included comparator studies are in line with those recommended as part of NICE guidance for each treatment.

Table 19. Included studies for EM and CM overall migraine population analyses

Included studies – EM	Relevant treatments
ELEVATE[28]	Atogepant 60 mg
ADVANCE[26]	Atogepant 60 mg
CGP-MD-01[27]	Atogepant 60 mg
LIBERTY[20]	Erenumab 140 mg
STRIVE[44]	Erenumab 140 mg
Sakai 2019[45]	Erenumab 140 mg
EMPOwER[46]	Erenumab 140 mg
CONQUER[19]	Galcanezumab 120 mg

EVOLVE-1[43]	Galcanezumab 120 mg
EVOLVE-2[47]	Galcanezumab 120 mg
Sakai 2020[48]	Galcanezumab 120 mg
PERSIST[49]	Galcanezumab 120 mg
FOCUS[18]	Fremanezumab 225 and 675 mg
HALO EM[50]	Fremanezumab 225 and 675 mg
Sakai 2021[51]	Fremanezumab 225 and 675 mg
Bigal 2015[52]	Fremanezumab 225 mg
BHV3000-305[17]	Rimegepant 75 mg
PROMISE-1[53]	Eptinezumab 100 and 300 mg
Included studies – CM	**Relevant treatments**
PROGRESS[25]	Atogepant 60 mg
Tepper 2017[32]	Erenumab 140 mg
CONQUER[19]	Galcanezumab 120 mg
REGAIN[31]	Galcanezumab 120 mg
FOCUS[18]	Fremanezumab 225 and 675 mg
HALO CM[54]	Fremanezumab 225 and 675 mg
Sakai 2021[55]	Fremanezumab 225 and 675 mg
Bigal 2015[56]	Fremanezumab 225 mg
PREEMPT-1[33]	Botulinum toxin type A
PREEMPT-2[34]	Botulinum toxin type A
PROMISE-2[57]	Eptinezumab 100 and 300 mg
Dodick 2019[58]	Eptinezumab 100 and 300 mg

Abbreviations: EM, episodic migraine; CM, chronic migraine.

3.4.3 Results

3.4.3.1 MMD-based outcomes

For these outcomes, the company preferred RE unadjusted analyses in the 3+ TF population for EM and RE unadjusted analyses in the overall migraine population for CM for reasons outlined in Section 3.4.1. All of these NMA results were used to inform the economic model (note that 50% MMD reduction for CM was used in a scenario analysis in the economic model instead of the 30% MMD reduction threshold). As described in Section 3.4.1, the EAG's preferred analyses are within the overall migraine population for EM as well as CM, and the EAG has additional concerns about using RE analyses in the 3+ TF population for EM (which is the company's preference), given there appears to be insufficient data in the analyses to appropriately inform the between-study heterogeneity and

may be introducing additional and unwarranted uncertainty in the results, which is particularly notable for the ≥50% MMD reduction outcome for EM in Table 20 below with extremely wide and difficult to interpret CrIs (the most extreme CrI ranges from [redacted]; see Key Issue 2 in Table 3).

In general, within the overall migraine population analyses, the EAG has a preference for RE analyses given these are a better fit than FE models and there is reason to believe clinical and methodological heterogeneity exists across the included studies (see Section 3.4.4). Furthermore, while model fits for RE unadjusted and adjusted analyses are similar, in most cases the adjusted analyses reduced between-study heterogeneity; where this was true or where there was very little difference in between-study heterogeneity and other model fit statistics, the EAG prefers RE adjusted analyses (see Key Issue 3 in Table 4). Exceptions to this are as follows:

- 30% MMD reduction in CM – FE unadjusted preferred as there appear to be issues with between-study heterogeneity being driven by priors which would make an RE analysis inappropriate (as noted earlier for 3+ TF analyses in EM), and the FE adjusted analysis did not converge;
- CFB in MUDs in CM – RE unadjusted preferred as model fit statistics are similar for unadjusted and adjusted versions, and the adjusted version appears to increase between-study heterogeneity.

Company- and EAG-preferred analyses for EM and CM populations are presented in Table 20 and Table 21, respectively. The EAG's analyses include rimegepant and eptinezumab data where available (note that data were not reported for some outcomes and that rimegepant is only relevant to the EM population).

Feedback from the EAG's clinical experts was that it is difficult to assess whether differences in mean CFB for MMDs and acute MUDs between treatments are clinically meaningful, given each patient will be different and may consider different levels of MMD (or acute MUDs) reduction beneficial or not. They note that the proportion of patients with ≥50% (EM) or ≥30% (CM) reduction in MMDs are most informative in terms of assessing differences in the efficacy of treatments, as these are the thresholds used in clinical practice to determine response.

Episodic migraine

For EM, the company's preferred analyses are associated with increased uncertainty compared to the EAG's preferred analyses, as expected given fewer studies with data within the 3+ TF population are available and smaller sample sizes analysed within each of the studies that do report data. The company's preferred results may be conservative for comparisons against the two fremanezumab doses relative to the estimates from the EAG's preferred analyses, but the opposite appears to be true for erenumab and galcanezumab comparisons as [redacted] are not as large based on point estimates in the EAG's preferred NMAs. All of the company's preferred NMAs are associated with uncertainty in terms of direction of effect (no statistically significant differences), with wide CrIs making it unclear whether outcomes are better or worse with atogepant, as well as uncertainty about the size of any impact.

While results from most of the EAG's preferred NMAs also suggest no statistically significant differences, the EAG notes that uncertainty is reduced and erenumab can be included for the CFB in acute MUDs outcome when the overall migraine population analysis is used. As data for erenumab are not available within the 3+ TF population for CFB in acute MUDs, the company used a conversion factor (see response to CQ B5) to obtain an estimate for this comparator that could be used in the economic model (atogepant vs erenumab: median CFB [redacted]. This is conservative relative to the estimate the EAG obtained from its preferred NMAs and used in its base case (see Section 6).

The EAG considers that the point estimates obtained from its preferred NMAs (RE adjusted) indicate only [redacted] in terms of CFB in MMDs ([redacted] for all comparisons), suggested [redacted] vs all comparators in terms of proportion with ≥50% reduction in MMDs and [redacted] for the CFB in acute MUDs outcome, with the exception of comparisons against erenumab and the two eptinezumab doses, where [redacted] are indicated. While the company's preferred NMAs also indicate fairly [redacted] between treatments in terms of CFB in MMD and acute MUDs outcomes, these differences are [redacted] in the EAG's preferred analyses and results for the two fremanezumab doses are quite different compared to the EAG's preferred analyses (more conservative in the company's preferred analyses). The EAG considers its preferred NMAs to be more robust and, therefore, more appropriate for use in the economic model. While the EAG was able to rerun NMAs with rimegepant and eptinezumab studies included, data for rimegepant were not available for the CFB in acute MUDs outcome. To allow inclusion in the economic model, the EAG made the assumption that rimegepant efficacy with regards to this

outcome is the same as atogepant (see Section 4.2.6.4). Unadjusted FE versions of the company's preferred analyses (within the 3+ TF population for EM) can be found in Table 26 of the CS appendices; results are very similar to unadjusted RE analyses but with CrIs that are narrower. Unadjusted RE versions of the EAG's preferred analyses are presented in Appendix 8.2.1; these results are similar to the adjusted RE results in that differences are [redacted], but point estimates for the ≥50% reduction in MMDs outcome do not always [redacted] in these analyses and there are no [redacted] for any comparators for the CFB in acute MUDs outcome.

Table 20. Relative effect of atogepant 60 mg once daily vs comparators in EM for MMD outcomes – EAG- and company-preferred analyses

Atogepant 60 mg once daily vs	Company-preferred NMA*	EAG-preferred NMA†
CFB in MMD, MD (95% CrI)		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
Rimegepant 75 mg every other day	-	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]
≥50% reduction in MMDs, OR (95% CrI)		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
Rimegepant 75 mg every other day	-	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]
CFB in acute MUDs, MD (95% CrI)		
Erenumab 140 mg once monthly	-‡	[redacted]

Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
Rimegepant 75 mg every other day	-	-[§]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]

*Company preferred NMAs for all MMD-related outcomes in EM are from the NMAs performed specifically using 3+ TF data in this population. RE unadjusted analyses are preferred for all outcomes; [†]EAG-preferred NMAs for all MMD-related outcomes in EM are from the NMAs performed in the overall migraine population. For all three outcomes, the EAG prefers results from RE adjusted analyses. The EAG reran NMAs to include data for rimegepant and eptinezumab given, as described in Section 2.3.3, they may be considered important comparators; [‡]no data for erenumab 140 mg were available to include within the NMA for the CFB in acute MUDs outcome within the 3+ TF population. The company used a conversion factor (see CQ B5) to obtain data for erenumab to use in the economic model (median CFB [redacted] for atogepant vs erenumab; see Table 46 of the CS); [§]rimegepant could not be included in the NMA for CFB in acute MUDs when rerun by the EAG given this outcome was not reported for the only available rimegepant study.

Outputs from the NMAs are means for the CFB outcomes and median OR for the proportion with ≥50% reduction in MMD from baseline. Bold values indicate statistically significant differences.

Abbreviations: 3+ TF, patients in whom ≥3 prior oral preventive treatments have failed; CFB, change from baseline; CrI, credible interval; CQ, clarification question; CS, company submission; EAG, External Assessment Group; EM, episodic migraine; MD, mean difference; MMD, monthly migraine days; MUDs, medication use days; NMA, network meta-analysis; OR, odds ratio; RE, random effects;

Chronic migraine

For CM, the EAG's preferred NMAs are also associated with less uncertainty compared to the company's preferred analyses. While the company's preferred analyses may be slightly conservative for CFB in MMDs and ≥50% reduction in MMDs for comparisons vs mAbs, this is not the case for the comparison against BoNT/A. For ≥30% reduction in MMDs and CFB in acute MUDs outcomes, the point estimates of the company's preferred analyses are more favourable for atogepant compared to the results from EAG-preferred analyses (other than vs galcanezumab). The EAG and company both have a preference for the RE unadjusted analysis for the CFB in acute MUDs outcome, which explains the similarity of these results. Slight differences may be due to minor errors corrected by the EAG before NMAs were run (see Section 8.2.2). There were no statistically significant differences vs any of the comparators in the company's preferred analyses, but some were identified for the [redacted] outcome in the EAG's preferred analyses.

Based on the EAG's preferred analyses, the EAG considers that point estimates suggest fairly [redacted] between atogepant and comparators in terms of CFB in MMDs and CFB in

acute MUDs, with point estimates either favouring atogepant or there being a difference of [redacted] in the opposite direction. While comparisons against the two fremanezumab doses indicate [redacted] for the ≥30% reduction in MMDs outcome, the EAG considers this analysis to be limited given the fact that a FE unadjusted analysis had to be used due to insufficient data to inform between-study heterogeneity for this outcome and the adjusted analyses did not converge. The EAG notes that results for the ≥50% MMD reduction threshold are similar in that point estimates suggest the fremanezumab doses may [redacted] than atogepant, but the extent of the difference is reduced and differences [redacted]; an RE analysis with adjustment for baseline risk was able to be performed for this outcome, which the EAG considers to be more robust than the unadjusted FE analysis performed for the ≥30% threshold. Based on point estimates, results for the ≥50% reduction in MMD outcome suggest that atogepant is [redacted] achieving this outcome vs all comparators other than galcanezumab, although there remains uncertainty based on CrIs.

To be included in the economic model, the company used a conversion factor to calculate estimates of the odds ratios (ORs) for erenumab 140 mg and BoNT/A that may be observed had data for the ≥30% MMD reduction outcome been available for inclusion in the NMAs. The EAG considers the methodology used for this, as described in response to CQ B5, to be reasonable in terms of obtaining point estimates given that there are no data for these comparators, but notes that it is an assumption that should be considered to be associated with substantial uncertainty, given it uses an average of the ratios observed for comparators with available data and it is not possible to determine if this is robust across all comparators. The conversion factor calculated based on point estimates was also applied to the CrIs from the company's ≥50% MMD reduction analysis to calculate 95% CrIs for the comparators with missing data for the ≥30% MMD reduction outcome. This results in the 95% CrIs for erenumab and BoNT/A being much narrower compared to the three comparators that had data and were included in the ≥30% MMD reduction NMA (for example, the 95% CrI estimated for erenumab is [redacted], whereas that obtained from the NMA for fremanezumab 225 mg is [redacted]). The EAG considers that obtaining separate conversion factors for point estimates and the upper and lower values of the CrI would lead to CrIs for erenumab and BoNT/A that are more similar to those obtained from the company's preferred NMA for ≥30% MMD reduction for comparators with available data.

While the EAG was able to rerun NMAs with eptinezumab studies included, data for eptinezumab were not available for the ≥30% reduction in MMDs outcome. The EAG recalculated the conversion factors described above using its preferred analyses for the ≥30% (FE unadjusted) and ≥50% (RE adjusted) NMAs to calculate ORs to be used for erenumab 140 mg and BoNT/A, and also did the same to allow inclusion of eptinezumab for the ≥30% threshold. The EAG used the same method as the company by applying the same conversion factors to the CrIs for each comparator, but notes that when separate conversion factors were calculated for the EAG's preferred analyses, estimated CrIs were either unchanged or differed by only 0.01. Estimated ORs and CrIs used by the company and the EAG for comparators with missing ≥30% MMD reduction data in CM are presented in Table 22 below. The EAG acknowledges the uncertainty associated with these ORs and CrIs but notes that options are limited given the lack of data for these comparators.

Unadjusted RE versions of the EAG's preferred analyses for CFB in MMDs and ≥50% reduction in MMDs are presented in Appendix 8.2.2; these results are very similar to company's preferred results in Table 21 below given the company preferred unadjusted RE analyses, with minor differences likely due to minor corrections made by the EAG to the data analysed or random sampling.

While not presented as part of this STA, the company provided results from 3+ TF population NMAs within CM as part of the CCE process for atogepant earlier in 2023. The EAG does not have a preference for these results and has not presented them here given limitations raised by the company (which the EAG agrees with) but notes that the point estimates obtained from these analyses were generally [redacted] for atogepant compared to both the EAG- and company-preferred NMAs presented in Table 21 below, albeit with [redacted] based on CrIs, potentially associated with more bias and based on more scarce data. Differences between the analyses in terms of CFB in MMDs [redacted] exist for the ≥30 and ≥50% MMD reduction outcomes.

Table 21. Relative effect of atogepant 60 mg once daily vs comparators in CM for MMD outcomes – EAG- and company-preferred analyses

Atogepant 60 mg once daily vs	Company-preferred NMA*	EAG-preferred NMA†
CFB in MMD, MD (95% CrI)		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]

Galcanezumab 120 mg once monthly	[redacted]	[redacted]
BoNT/A	[redacted]	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]
≥30% reduction in MMDs, OR (95% CrI)		
Erenumab 140 mg once monthly‡	-	-
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
BoNT/A‡	-	-
Eptinezumab 100 mg once every three months‡	-	-
Eptinezumab 300 mg once every three months‡	-	-
≥50% reduction in MMDs, OR (95% CrI)		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
BoNT/A	[redacted]	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]
CFB in acute MUDs, MD (95% CrI)		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
BoNT/A	[redacted]	[redacted]

Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]

*Company preferred NMAs for all MMD-related outcomes in CM are from the NMAs performed in the overall migraine population. RE unadjusted analyses are preferred for all outcomes; †EAG-preferred NMAs for all MMD-related outcomes in EM are from the NMAs performed in the overall migraine population. The EAG's preference is RE adjusted analyses for CFB in MMDs and ≥50% reduction in MMDs, FE unadjusted for ≥30% reduction in MMDs and RE unadjusted for CFB in acute MUDs. The EAG reran NMAs to include data for eptinezumab given, as described in Section 2.3.3, it may be considered an important comparator in CM; ‡no data for erenumab 140 mg, BoNT/A or 100 mg or 300 mg doses of eptinezumab were available to include within the NMA for the ≥30% MMD reduction outcome within the overall migraine population in CM.

Outputs from the NMAs are means for the CFB outcome and median OR for the proportion with ≥50% reduction in MMD from baseline. Bold values indicate statistically significant differences.

Abbreviations: BoNT/A, botulinum toxin type A; CFB, change from baseline; CM, chronic migraine; CrI, credible interval; EAG, External Assessment Group; FE, fixed effects; MD, mean difference; MMD, monthly migraine days; MUDs, medication use days; NMA, network meta-analysis; OR, odds ratio; RE, random effects.

Table 22. Relative effect of atogepant 60 mg once daily vs comparators in CM for ≥30% MMD reduction – ORs estimated for comparators with no data for this threshold

Atogepant 60 mg once daily vs	Company estimation*	EAG estimation†
≥30% reduction in MMDs, OR (95% CrI)		
Erenumab 140 mg once monthly	[redacted]	[redacted]
BoNT/A	[redacted]	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]

*Based on the company's preference for RE unadjusted analyses for ≥30% and ≥50% MMD reduction outcomes (inverted versions of values in Table 42 of the CS and Table 119 of the CS appendices); †based on the EAG's preference for an FE unadjusted analysis for ≥30% MMD reduction and an RE adjusted analysis for ≥50% MMD reduction.

ORs for atogepant 60 mg vs placebo for ≥30% and ≥50% MMD reduction outcomes were also used in the calculations and were as follows for company- and EAG-preferred analyses: company, [redacted] for ≥30% and [redacted] for ≥50%; EAG, [redacted] for ≥30% and [redacted] for ≥50%. The company obtained a conversion factor of 1.24 which was applied to the ≥50% ORs for the comparators (ORs divided by 1.24) with missing ≥30% data. The equivalent conversion factor obtained by the EAG using its preferred analyses was 1.82. To calculate 95% CrIs, the company applied the same conversion factor (1.24); the EAG did the same using the conversion factor it calculated.

Abbreviations: BoNT/A, botulinum toxin type A; CM, chronic migraine; CrI, credible interval; CS, company submission; EAG, External Assessment Group; FE, fixed effects; MMD, monthly migraine days; OR, odds ratio; RE, random effects.

3.4.3.2 All-cause discontinuation

As noted above in Section 3.4.3.1, within the overall migraine population analyses, the EAG has a preference for RE analyses given these are on the whole a better fit than FE models and there is

reason to believe clinical and methodological heterogeneity exists across the included studies (see Section 3.4.4).

For discontinuation, model fits for RE unadjusted and adjusted analyses were similar but the adjusted analysis in EM led to reduced between-study heterogeneity, resulting in the EAG preferring this analysis (see Key Issue 3 in Table 4). For CM, model fit statistics regardless of adjustment but the adjusted version appears to increase between-study heterogeneity; therefore, the EAG's preference is for the unadjusted RE analysis in this population. The company's preference is for RE unadjusted analyses in both cases. As noted in Section 3.4.1, the company's preference is for cloglog models, which the EAG considers to be reasonable. Cloglog models were, therefore, used by the EAG when running analyses to include additional comparators. Results of the company's and EAG's preferred analyses of discontinuation are presented below in Table 23.

While the EAG and company preferred the RE unadjusted analyses for all-cause discontinuation in CM, the EAG notes that there are some apparent differences in the values estimated between the two analyses (largest for erenumab, but also notable for galcanezumab). The EAG did not make any changes to the data analysed by the company for this outcome and notes that results for erenumab and galcanezumab are more in line with those obtained in the EAG's analysis when it reran the analysis using the company's data spreadsheet. The EAG, therefore, considers that these may be errors in reporting in Table 27 of the CS for this analysis.

For EM, the EAG's preferred NMA results lead to point estimates suggesting slightly [redacted] discontinuation for atogepant compared to the four mAbs in the company's preferred NMAs. Results suggest similar for the comparisons against eptinezumab 100 mg and 300 mg, while discontinuation may be [redacted] for atogepant compared to rimegepant. For CM, the EAG and company's preferred analysis was the same and results almost identical; point estimates suggest that discontinuation may be [redacted] for atogepant compared to some comparators (erenumab, fremanezumab 675 mg and galcanezumab) but [redacted] compared with the remaining treatments. Across EM and CM, some of the differences between treatments are [redacted], with hazard ratios (HRs) only [redacted]. Furthermore, the EAG notes that there is uncertainty in all estimates, given CrIs cross 1.00 and are fairly wide in either direction. As noted earlier, HRs were used to inform discontinuation up to 12 weeks in the economic model (see Section 4.2.6.1).

Alternative RE analyses performed by the EAG for discontinuation in the two populations are presented in Appendix 8.2.3. The RE unadjusted analysis for EM aligns well with the company's results in Table 23 below (as expected given it is the same analysis) and there are no large differences in results for the adjusted RE analysis in CM compared with the EAG- and company-preferred RE unadjusted analysis in Table 23 below.

Table 23. Relative effect of atogepant 60 mg once daily vs comparators in EM and CM for discontinuation (cloglog analyses) – EAG- and company-preferred analyses

Atogepant 60 mg once daily vs	Company-preferred NMA*	EAG-preferred NMA†
EM, HR (95% CrIs)		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
Rimegepant 75 mg every other day	-	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]
CM, HR (95% CrIs)		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
BoNT/A	[redacted]	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]

*The company's preferred NMAs for discontinuation in EM and CM are the RE unadjusted analyses within the overall migraine population; †the EAG's preferred NMA for discontinuation in EM is the RE adjusted analysis, while for CM it is the RE unadjusted analysis (as per the company's preference). The EAG reran NMAs to include data for rimegepant and eptinezumab given, as described in Section 2.3.3, they may be considered important comparators; ‡when the EAG reran the company's analysis using the exact same spreadsheet, it obtained an estimate that was more in line with the EAG's estimate ([redacted]); §when the EAG reran the company' s analysis using the exact same spreadsheet, it obtained an estimate that was more in line with the EAG's estimate ([redacted]).

Outputs from the NMAs are median HR for the company analyses; the EAG was only able to obtain mean HRs for comparisons between atogepant and other treatments, but was able to verify that means and medians are likely to be

similar given mean and median HRs for all treatments vs placebo could be obtained and were similar. Bold values indicate statistically significant differences.

Abbreviations: BoNT/A, botulinum toxin type A; CM, chronic migraine; CrI, credible interval; EAG, External Assessment Group; EM, episodic migraine; HR, hazard ratio; NMA, network meta-analysis; RE, random effects.

3.4.3.3 Health-related quality of life outcomes

The company performed NMAs for a number of HRQoL outcomes, including three subdomains of the MSQ v2.1 questionnaire and HIT-6. The results of these NMAs did not inform the economic model and the EAG discusses them only briefly here. The EAG reran the NMAs to validate the results and included eptinezumab and rimegepant studies where possible; however, HRQoL outcomes were poorly reported for these two comparators. The EAG did not identify any corrections required to data included in the HRQoL analyses performed by the company, but was not able to validate all of the data analysed given supplementary papers were not provided.

As noted above in Section 3.4.3.1, within the overall migraine population analyses, the EAG has a preference for RE analyses given these are on the whole a better fit than FE models and there is reason to believe clinical and methodological heterogeneity exists across the included studies (see Section 3.4.3.3). Adjusted analyses were not performed by the company for HRQoL outcomes so the results presented below in Table 24 are from unadjusted RE analyses.

The results of the analyses rerun by the EAG (presented in Table 24 below) are in line with those presented by the company on the whole; however, there are some slight discrepancies for certain outcomes and comparators. The EAG considers that these could be due to a mixture of random sampling variation and the EAG needing to run certain NMAs using contrast rather than arm-based data to allow the inclusion of eptinezumab or rimegepant studies. The EAG does not consider that any of these differences would change conclusions. See Table 26 of the CS (and Appendix O of the CS for BoNT/A) for comparison to the company-reported results for HRQoL outcomes.

Higher MSQ v2.1 scores indicate better outcome, while the opposite is true for HIT-6. For EM, point estimates suggest [redacted] outcome for atogepant or very small differences across the HRQoL scores compared to all comparators where data was available, some of which are statistically significant differences. Some of these differences are larger than the thresholds referenced by the company and described in Section 3.3.3 as indicative of clinically important differences. The EAG notes that data were only available for one outcome for rimegepant and no HRQoL outcome data were

available for eptinezumab in EM, and fewer comparators were available for the HIT-6 outcome. For CM, differences appear to be smaller between atogepant and comparators, with some point estimates in favour of comparator treatments rather than atogepant. Only one of these point estimates appears to be above the thresholds cited by the company as being indicative of clinically important differences.

The EAG concludes that, point estimates suggest that there could be benefits of atogepant vs comparators in terms of HRQoL outcomes in EM and that results are more mixed in CM, with differences in either direction here unlikely to be clinically meaningful based on thresholds cited by the company. However, the EAG notes that uncertainty in these conclusions remains based on CrIs as well as the fact that these NMAs were not adjusted for placebo differences unlike other outcomes discussed in Section 3.4.3.1 and 3.4.3.2.

Table 24. Relative effect of atogepant 60 mg once daily vs comparators in EM and CM for HRQoL outcomes – RE unadjusted analyses, EAG results

Atogepant 60 mg once daily vs	EM, MD (95% CrI)	CM, MD (95% CrI)
CFB in MSQ-RFR		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
BoNT/A	N/A	[redacted]
Rimegepant 75 mg every other day	[redacted]	N/A
Eptinezumab 100 mg once every three months*	-	-
Eptinezumab 300 mg once every three months*	-	-
CFB in MSQ-RFP		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
BoNT/A	N/A	[redacted]

Rimegepant 75 mg every other day†	-	N/A
Eptinezumab 100 mg once every three months*	-	-
Eptinezumab 300 mg once every three months*	-	-
CFB in MSQ-EF		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
BoNT/A	N/A	[redacted]
Rimegepant 75 mg every other day†	-	N/A
Eptinezumab 100 mg once every three months*	-	-
Eptinezumab 300 mg once every three months*	-	-
CFB in HIT-6		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly‡	-	-
BoNT/A	N/A	[redacted]
Rimegepant 75 mg every other day†	-	N/A
Eptinezumab 100 mg once every three months§	-	[redacted]
Eptinezumab 300 mg once every three months§	-	[redacted]

*No data was available for eptinezumab in terms of MSQ v2.1outcomes in EM or CM; †no data was available for rimegepant in terms of the MQS-EF, MSQ-RFP or HIT-6 questionnaires in EM; ‡no data was available for galcanezumab in terms of the HIT-6 questionnaire in either EM or CM; §no data was available for eptinezumab in terms of the HIT-6 questionnaire in EM.

Outputs from the NMAs are mean CFB values as run by the EAG. Bold values indicate statistically significant differences.

Abbreviations: BoNT/A, botulinum toxin type A; CFB, change from baseline; CM, chronic migraine; CrI, credible interval; EAG, External Assessment Group; EM, episodic migraine; HIT-6, Headache Impact Test-6; HRQoL, health-related quality of life; MD, mean difference; MSQ, migraine-specific quality of life questionnaire; MSQ-EF, emotional function subdomain of MSQ; MSQ-RFP, role function-preventive subdomain of MSQ; MSQ-RFR, role function-restrictive subdomain of MSQ; N/A, not applicable; NMA, network meta-analysis; RE, random effects.

3.4.3.4 Adverse events

The company also performed NMAs to analyse TEAEs across treatments within the overall migraine population. Given that no AEs were included in the economic model, the EAG does not discuss these in detail here. The EAG reran the NMAs to validate the results and included eptinezumab and rimegepant studies. The EAG did not identify any corrections required to data included in the TEAE analyses performed by the company. The results of the analyses rerun by the EAG are in line with those presented by the company on the whole, but the HR for erenumab in EM is higher in the results presented in the CS compared to when rerun by the EAG. The EAG is unsure whether this is variation due to sampling or whether there was a reporting error in Table 27 of the CS for erenumab.

As noted above in Section 3.4.3.1, within the overall migraine population analyses, the EAG has a preference for RE analyses given these are on the whole a better fit than FE models and there is reason to believe clinical and methodological heterogeneity exists across the included studies (see Section 3.4.3.3). Adjusted analyses were not performed by the company for TEAEs so the results presented below in Table 25 are from unadjusted RE analyses. As discussed for discontinuation (Section 3.4.3.2), cloglog analyses were preferred by the company for TEAEs.

The results based on point estimates for EM suggest that there may be slightly [redacted] rates of TEAEs for atogepant compared to fremanezumab 675 mg, galcanezumab 120 mg and eptinezumab 100 mg, with the opposite observed vs other comparators. For CM, the results suggest slightly [redacted] rates of TEAEs for atogepant compared to all comparators. However, the EAG acknowledges the uncertainty based on CrIs for all but one of the outcomes below. Given that, as discussed in Section 3.3.4, most AEs for atogepant were symptoms such as [redacted], the EAG is not concerned about the omission of AEs from the economic model.

Table 25. Relative effect of atogepant 60 mg once daily vs comparators in EM and CM for TEAEs (cloglog analyses) – RE unadjusted analyses, company and EAG results

Atogepant 60 mg once daily vs	Company results	EAG results
EM, HR (95% CrIs)		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]

Galcanezumab 120 mg once monthly	[redacted]	[redacted]
Rimegepant 75 mg every other day	-	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]
CM, HR (95% CrIs)		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
BoNT/A	[redacted]	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]

Outputs from the NMAs are median HR for the company analyses; the EAG was only able to obtain mean HRs for comparisons between atogepant and other treatments, but was able to verify that means and medians are likely to be similar given mean and median HRs for all treatments vs placebo could be obtained and were similar. Bold values indicate statistically significant differences.

Abbreviations: BoNT/A, botulinum toxin type A; CM, chronic migraine; CrI, credible interval; EAG, External Assessment Group; EM, episodic migraine; HR, hazard ratio; RE, random effects; TEAEs, treatment-emergent adverse events.

3.4.4 Critique of the indirect treatment comparison

In section B.2.9.4 of the CS, the company highlight various differences between trials included in the NMA. These are discussed in the subsections that follow, as well as any additional issues identified by the EAG. While the EAG notes that many of the issues described below lead to uncertainty in the NMAs, the same issues have been raised in other NICE appraisals in migraine, most recently for rimegepant (TA906),[2] where many of the same studies were included in overall migraine population analyses. These issues are one reason for the EAG's preference for RE analyses where possible, to capture this increased uncertainty. These concerns are collectively captured in Key Issue 4 (Table 5) as uncertainty within the NMAs that may not be fully captured by analysis methods used (such as using RE analyses with or without adjustment for baseline risk) but that are considered to unresolvable limitations based on data available from comparator studies.

3.4.4.1 *Differences in study populations included and concomitant treatments*

Studies included in the NMAs differed in terms of the number of prior treatment failures. Some studies only focused on patients with two to four prior treatment failures (ELEVATE, FOCUS, CONQUER, LIBERTY),[18-20, 28] while others included any patient regardless of prior treatment failure. The EAG notes that some studies (including the PROGRESS and ELEVATE trials for atogepant) excluded patients with a certain number of treatment failures (e.g. four or more failures in the PROGRESS and ELEVATE trials, as well as FOCUS, CONQUER and LIBERTY trials,[18-20, 25, 28] or more than two failures in other studies such as HALO-EM and the only available trial for rimegepant (BHV3000-305).[50] Given that clinical experts advising the EAG consider prior treatment failures to be a factor that could impact the efficacy of preventive treatments for migraine, this could be an important source of clinical heterogeneity between trials, particularly within the overall migraine population analyses. The impact of prior treatment failures on safety outcomes may be less important based on feedback from the EAG's clinical experts discussed in Section 3.4.1.

Most studies included in the NMAs did not stratify randomisation by number of prior treatments and there is potential for imbalance in patient characteristics between trial arms; this was not an issue for ELEVATE as this trial was stratified for this factor, but [redacted] in PROGRESS and it is unclear for comparator trials given characteristics for this subgroup are not well reported.

For EM overall migraine analyses preferred by the EAG, some variation in mean age across studies was identified but the EAG considers the range of means between ~37 and ~46 years may not have a large impact on results (Figures 29 and 30 of the CS appendices). Distribution of sex across studies was largely consistent (Figures 31 and 32 of the CS appendices) but there were some substantial differences in terms of race, which is the result of some studies focusing solely on Asian population (Figures 33 and 34 of the CS appendices); the EAG is not too concerned about differences in race distribution across studies as feedback from the EAG's clinical experts was that there is no reason to expect the efficacy of drugs to differ in Asian vs non-Asian populations. There was variation for baseline MMDs across EM studies, ranging from a mean of ~7.5 days to ~11.5 days (Figures 35 and 36 of the CS appendices); while it is possible that baseline MMDs could impact the ability of individuals to achieve a ≥50% reduction in MMDs, the EAG is unsure as to the impact on relative efficacy outcomes given randomisation should ensure baseline MMDs are similar within each trial

for intervention and placebo groups. The EAG notes that the only available study for rimegepant also included a proportion of patients with CM (23%) rather than EM.[17]

Similar variation was observed for trials within the overall migraine population analyses for CM (Figures 45 to 52 of the CS appendices), with mean baseline MMD values ranging from ~15.5 to 19.5 days in this population. The EAG also reviewed rimegepant and eptinezumab studies that were added to the NMAs and values for these studies fell within the ranges already highlighted in the CS appendix figures, apart from mean age in Dodick 2019 which was slightly lower than the other studies originally included in the NMAs for CM (~37 years vs ~40-46 years).[17, 53, 57, 58]

The use of concomitant preventive therapies during the trial also differed; some studies excluded their use while others did not. Those allowing its use for EM included two of the mAb studies identified and the rimegepant study and eptinezumab studies in this population; the remaining mAb studies and all of the atogepant studies did not allow concomitant use of preventive migraine treatments. For CM, the PROGRESS trial for atogepant, three mAb studies and the two eptinezumab studies allowed the use of concomitant preventive migraine treatments (none of the BoNT/A studies allowed these to be used). The EAG considers this to be an area that may introduce uncertainty but the extent of any impact on results is unclear.

3.4.4.2 Differences in outcome definitions and time-points

Timepoints used for each study in the NMA varied, with this being reported at 12 weeks most commonly. For overall migraine population analyses in EM and CM, data for MMD-related and HRQoL outcomes were most commonly reported as an average across weeks 1-12 or values at 12 weeks for MMD-related and HRQoL outcomes but in some cases follow-up was up to 24/26 weeks or an average across weeks 9 to 12 was reported (Table 15 of the CS appendices and Appendix 8.4.1 of this report).

For discontinuation and TEAE, follow-up at 12 or 24 weeks was mostly available for discontinuation but time-points ranged between 12 and 49 weeks for TEAEs. It is unclear how this may affect results but it is a limitation of the data available from comparator studies. While this may not be ideal, the EAG is not concerned this would have a large impact on results given that when requested as part of the CCE process, an exploratory NMA analysis including only studies with 12-week data demonstrated similar results.

The company reports variation in the definition of endpoints across trials included in the NMA, particularly for MMD-related outcomes. The EAG acknowledges these differences and consider them to be a limitation of the data available across trials. Most variation appeared to be with regards to the length of time required for a migraine day to be confirmed (e.g. ≥4 continuous hours, ≥2 continuous hours or ≥30 min) and symptoms or features of migraine required to be present were, overall, similar. The likely impact of these different definitions on results is unclear.

The EAG also notes that definitions within individual trials for all-cause discontinuation (e.g. study withdrawal vs treatment discontinuation) and TEAEs (any adverse event vs TEAEs specifically) may differ slightly between trials. The EAG considers this to be based on available data reported across studies and is not concerned that these would have a large impact on results but acknowledge that it is a potential source of methodological heterogeneity.

For the change from baseline outcomes (e.g. CFB in MMDs, acute MUDs and HRQoL outcomes) the EAG notes that in EM and CM, most studies used mean values obtained from least squares regression. However, this was not consistent across all studies and may be another potential source of methodological heterogeneity. Differences in the approach to missing data may also be an important factor to consider (for example, some have used imputation while others have only analysed available data), although the EAG notes that it is another unavoidable difference given different studies have opted for different methods and the company is limited to data that is publicly available for comparator studies. For ≥30% and ≥50% MMD reduction outcomes, the EAG notes that methods of analysis in terms of missing data also differed across studies, with some assuming that those discontinuing for any reason were non-responders and others not making this assumption, which could introduce uncertainty within these NMAs. The observed effectiveness of treatments in the trials assuming non-response on discontinuation may be reduced compared to trials using less conservative assumptions.

3.4.4.3 Placebo rate differences

The EAG agrees with the company that differences in placebo rates across included studies are an issue, particularly for MMD-related outcomes. The EAG's clinical experts confirmed that varying placebo efficacy across migraine trials is an issue and makes it difficult to compare two individual studies. The EAG acknowledges these differences as a potential source of uncertainty within the NMAs, but given its preference for most MMD-related outcomes in EM and CM is RE analyses adjusted for baseline (placebo) risk, it considers these analyses should reduce the impact of these

differences (see Section 3.4.3.1). The exceptions were for the ≥30% MMD reduction outcome in CM as adjusted versions of this NMA would not converge and CFB in MUD in CM, as adjustment for baseline risk actually increased heterogeneity within the network based on between-study standard deviation values. The EAG notes that adjusted versions of analyses for HRQoL outcomes or TEAEs were not performed. The EAG considers that outcomes such as discontinuation and TEAEs may be less impacted by differences in placebo rates given they are less subjective outcomes; adjusted versions were performed for discontinuation but not for TEAEs (Section 3.4.3.2 and 3.4.3.4).

3.4.5 EAG critique of rimegepant and eptinezumab evidence provided by the company

In response to CQ A1, the company puts forward additional rationale to support the exclusion of rimegepant and eptinezumab as comparators from this appraisal, as well as some comparative evidence for atogepant vs rimegepant and eptinezumab. This issue is covered in Key Issue 1 in Table 2.

The company reiterates its statements in the CS that market shares for rimegepant and eptinezumab are currently low and are expected to remain low ([redacted] for rimegepant and [redacted] for eptinezumab) among patients eligible for NICE-recommended fourth line preventive therapies in 2024 based on Clarivate™ forecast data, suggesting the situation will not have changed by the time the committee meeting for this appraisal has been held. Feedback from clinical experts that the company consulted also suggested challenges in the local implementation of each treatment, such as the need to set up services for in-clinic infusion of eptinezumab. The company's clinical experts also suggest it would be unlikely for an infusion-based treatment requiring in-clinic time to be prioritised by services over a home-administered treatment, meaning atogepant would likely be positioned ahead of eptinezumab. One of the EAG's clinical experts agreed with this as they noted that it may be considered too resource intensive to be routinely used in preference to other available treatments. However, regarding rimegepant, they noted that there is potential for its low usage to change in the near future and, should atogepant be recommended and oral options preferred for an individual patient, it is likely that clinicians would be making a decision between atogepant and rimegepant in EM. Therefore, it may be particularly important to compare atogepant and rimegepant in this appraisal, which the EAG has done as part of this report. Given that eptinezumab is recommended in the same population as outlined for atogepant in this appraisal, the EAG has also explored its inclusion as part of this report, but it acknowledges that it may be less important than the other comparators included based on the feedback received.

Nonetheless, the company has provided some evidence to support the idea that conclusions would not change if either of these treatments had been included in the submission. This includes a matching-adjusted indirect comparison (MAIC) between rimegepant and atogepant that was presented at a recent conference (American Headache Society 2023) and a naïve comparison of results from one atogepant trial in EM and CM to one eptinezumab trial in each population.

For the anchored MAIC involving rimegepant,[59] the EAG confirms that the results suggest that atogepant may be more effective in reducing migraine frequency (CFB in MMDs) and in improving HRQoL outcomes (MSQ-RFR) compared to rimegepant. It also notes that non-statistically significant differences were identified suggesting reduced risk of TEAEs for atogepant but increased risk of discontinuation compared to rimegepant. Given the details of this analysis are only available in the form of a poster, information required to fully critique this MAIC is not available. Methods of aligning the atogepant population to the rimegepant trial population appear to have been performed, with ADVANCE (EM) and PROGRESS (CM) studies for atogepant being pooled in order to include a mixed EM/CM population in line with BHV3000-305, and adjustment for various treatment effect modifiers has been performed. The rationale for performing a MAIC rather than a standard indirect comparison was that there are differences between the populations enrolled in ADVANCE (EM) and PROGRESS (CM) studies for atogepant and the BHV3000-305 trial, which the EAG acknowledges in Section 3.4.4.1. While the EAG acknowledges that these results suggest that atogepant may improve efficacy and HRQoL outcomes compared to rimegepant, with small differences for TEAEs and discontinuation, the EAG considered it useful to also explore this via inclusion in NMAs as these do not break the randomisation of the original trials. The EAG notes that similar conclusions may be made based on the point estimates of the NMA results obtained but that differences were [redacted] for efficacy outcomes (Section 3.4.3).

While the EAG acknowledges the company's conclusions that the naïve comparisons suggest that the efficacy of atogepant and eptinezumab is likely to be comparable (Tables 1 and 2 of the response to CQ A1), there are limitations associated with these naïve analyses, including the fact that not all available trials for each treatment are included. The EAG considers the inclusion of eptinezumab in NMAs in Section 3.4.3 to make better use of the available data for each treatment, with results suggesting that for EM they may be comparable or there may be [redacted] for atogepant, but with estimates for some outcomes in CM [redacted] atogepant.

While the company notes that costs for atogepant and rimegepant are [redacted], and that costs for atogepant may be [redacted] than for eptinezumab, the EAG considers their inclusion in the economic model to be a more robust measure of whether the inclusion of these comparators would impact cost-effectiveness results and decisions.

3.4.6 EAG conclusions from the indirect treatment comparison

- NMAs performed to inform relative effects for atogepant compared to mAbs and BoNT/A (and eptinezumab and rimegepant in the EAG's preferred analyses) are deemed to be reasonable by the EAG, but they are not without limitations, including differences between included studies described in Section 3.4.4 (see Key Issue 4 in Table 5) and limited data for some analyses;
- the EAG considers it important that BoNT/A, rimegepant and eptinezumab are considered as comparators within the appraisal (see Key Issue 1 in Table 2) and has included data for rimegepant and eptinezumab in the relevant NMAs;
- the EAG has a preference for efficacy analyses (MMD-related outcomes) performed in the overall migraine population for EM and CM, whereas the company prefers NMAs within the 3+ TF subgroup for these outcomes in EM, and the EAG's preferred NMA model (i.e. FE or RE analyses with or without adjustment for baseline risk) differs to the company's for many outcomes (see Section 3.4 and Key Issues 2 and 3 in Table 3 and Table 4);
- based on the point estimates from the EAG's preferred analyses in EM, the EAG considers that atogepant may be associated with [redacted] other treatments in terms of MMD-related efficacy outcomes and HRQoL, or that there is only a [redacted] comparator treatments, with no major concerns about differences in discontinuation or TEAEs. However, uncertainty with regards to this exists based on 95% CrIs from the NMAs (see Section 3.4.3);
- for CM, point estimates for MMD-related efficacy outcomes and HRQoL were generally [redacted] compared to within the EM population, with many point estimates [redacted] comparator treatments rather than atogepant, although the differences for CFB outcomes were fairly small and may not be clinically meaningful. However, for most outcomes uncertainty exists for all comparators based on 95% CrIs from the NMAs. While some [redacted] comparator treatments were identified for the ≥30% MMD reduction outcome, the EAG notes the limitations of this analysis given an FE analysis was preferred by the EAG due to limited data, which may mean

CrIs are inappropriately narrow. There are no major concerns about differences between treatments in terms of discontinuation and TEAEs (see Section 3.4.3);

- the EAG considers the results from the NMAs to be the best available evidence on which to base decisions about the relative clinical effectiveness of atogepant vs other treatments, but notes that limitations remain in terms of clinical and methodological heterogeneity of studies included and the applicability of the EAG's preferred analyses to the 3+ TF migraine population (see Key Issues 2 and 4 in Table 3 and Table 5). The EAG considers that while overall migraine population analyses may represent a deviation from the decision problem population, the robustness of the NMAs and the results obtained from them are improved as a result.

3.5 Conclusions of the clinical effectiveness section

Evidence for atogepant in the population specified in the decision problem (3+ TF) is available for EM and CM populations from ELEVATE and PROGRESS RCTs (Section 3.3), respectively. Evidence from these studies was considered to be at some risk of bias (see Section 3.2) but similar issues were identified for some comparator studies used in NMAs. The EAG notes that both trials exclude patients with >4 treatment failures, which the experts advising the EAG note is unfortunate given this is a patient group seen in clinical practice (Section 2.3.1).

Given that the EAG prefers NMAs performed within the overall migraine population for EM and CM (Section 3.4.1), it notes that ADVANCE and CGP-MD-01 RCTs for EM are also of relevance. The results presented in Section 3.3 indicate that across the three EM RCTs and single CM RCT for atogepant, atogepant appears to lead to benefits in terms of efficacy and HRQoL compared to placebo, some of which are [redacted]. While for EM the extent of the differences varies across the three studies, they are consistent in that point estimates suggest benefits for atogepant. For EM and CM, results were often [redacted] for atogepant in the 3+ TF subgroup compared to the overall trial population, although they did not always [redacted] in PROGRESS potentially due to the reduced sample size and lack of stratification at randomisation for this factor.

While the EAG's preference for NMAs within the overall migraine population in EM and CM (also the company's preference for the CM population) represents a deviation from the decision problem in

terms of population as the NMAs include data that are not specific to the 3+ TF population (see Key Issue 2 in Table 3), the EAG's clinical experts consider the baseline characteristics of the overall trial populations from ELEVATE and PROGRESS to be a reasonable representation of the UK 3+ TF population, with no major differences expected in these characteristics compared with the 3+ TF population. The EAG also considers the overall migraine population NMAs to be more robust given it avoids issues with lack of stratification for prior treatment history and allows the inclusion of more data. For some outcomes in each population, the EAG has a preference for an alternative NMA model compared to the company (i.e. RE adjusted instead of RE unadjusted in most cases; see Key Issue 3 in Table 4).

Conclusions from the NMA results are summarised in Section 3.4.6; the NMAs are not without their limitations (Section 3.4.4; see Key Issue 4 in Table 5) but the EAG considers them to be reasonable for decision-making. The results suggest that atogepant may have [redacted] in EM or [redacted], with the results being more mixed for CM (many differences may be considered [redacted] but differences for ≥30% and ≥50% MMD reduction outcomes are more notable for some comparators). The EAG notes that these conclusions are based on point estimates and that uncertainty remains for most NMAs given results were [redacted]. The EAG has included rimegepant and eptinezumab as additional comparators, as discussed in Sections 2.2.1, 2.3.3 and 3.4.5 (see Key Issue 1 in Table 2).

4 Cost effectiveness

The company's deterministic base case results for episodic migraine (EM) are given in Table 26. In the company's base case EM model results, the monoclonal antibodies (mAbs) are associated with higher costs and similar quality-adjusted life years (QALYs) compared to atogepant. Based on willingness-to-pay (WTP) thresholds of £20,000 or £30,000 per QALY, atogepant could be considered cost-effective compared to each mAb as the incremental cost-effectiveness ratios (ICERs) are above these WTP thresholds and the incremental net health benefits (NHBs) are positive.

The company's deterministic base case results for chronic migraine (CM) are given in Table 27. In the company's base case CM model results, the mAbs are associated with higher costs and marginally higher QALYs compared to atogepant. Based on WTP thresholds of £20,000 or £30,000 per QALY, atogepant could be considered cost-effective compared to each mAb as the ICERs are above these WTP thresholds and the incremental NHBs are positive.

Table 26. Company's pairwise deterministic base case results (EM)

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)	Inc. NHB (£20,000/ QALY WTP threshold)	Inc. NHB (£30,000/ QALY WTP threshold)
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Galcanezumab 120mg once monthly	£33,666	13.69	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Erenumab 140mg once monthly	£28,299	13.68	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Fremanezumab 225mg once monthly	£31,383	13.74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-

Fremanezumab 675mg once every three months	£32,976	13.75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*SW quadrant ICER (atogepant is cheaper and less effective than the comparator)

Abbreviations: EM, episodic migraine; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

Table 27. Company's pairwise deterministic base case results (CM)

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)	Inc. NHB (£20,000/ QALY WTP threshold)	Inc. NHB (£30,000/ QALY WTP threshold)
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Galcanezumab 120mg once monthly	£47,490	10.86	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Erenumab 140mg once monthly	£39,404	10.87	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Fremanezumab 225mg once monthly	£40,991	10.86	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Fremanezumab 675mg once every three months	£41,222	10.86	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*SW quadrant ICER (atogepant is cheaper and less effective than the comparator)

Abbreviations: CM, chronic migraine; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

4.1 EAG comment on the company's review of cost effectiveness evidence

The company carried out three separate systematic literature reviews (SLRs), to identify existing:

- Economic evaluations for the prevention of migraines;
- Health-related quality of life (HRQoL) evidence (health state utility values [HSUVs]) in the prevention of migraines; and
- Cost and resource use evidence in the prevention of migraines conducted in the UK.

Searches were initially run in August 2020 and were last updated in November 2022 for the economic evaluation and HRQoL evidence. Searches for cost and resource use were originally conducted on in January 2022 and last updated in November 2022. A summary of the External Assessment Group's (EAG's) critique of the methods implemented by the company to identify relevant evidence is presented in Table 28. Due to time constraints, the EAG was unable to replicate the company's searches and appraisal of identified abstracts.

Table 28. EAG's critique of company's systematic literature review (migraine prevention)

SLR step	Section of CS in which methods are reported			EAG assessment of robustness of methods
	Cost effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Data sources	Section 1 of Appendix H	Section 1 of Appendix I	Section of Appendix J	Electronic databases included: MEDLINE, MEDLINE In-Process, Embase, econLit and HTAD and NHS EED (searched simultaneously through the CRD platform). The company also searched conference proceedings, HTA websites and grey literature sources.
Search terms	Table 46-59 Section 2.5 of Appendix H	Table 71-80 Section 1.5 of Appendix I	Table 88-97 Section of Appendix J	**Appropriate.** For all applicable searches the search terms to capture economic studies are based on the validated SIGN filter set.
Inclusion criteria	Table 60 in Section of Appendix H	Table 81 in Section of Appendix I	Table 98 in Section of Appendix J	**Appropriate.** For the economic evaluations review, the company could have considered rimegepant and eptinezumab NICE final scope. The EAG also notes that the company could have been more specific regarding the inclusion criteria in the HRQoL review to identify QoL measures. The company stated "Any HSUVs" were included but do not provide a comprehensive list of what this includes or excludes.

				For example, at present it is not clear if a study that used MSQ values directly would be excluded or included; all studies included that use MSQ are mapped to EQ-5D.
Screening	Section 4 Appendix H	Section 3 Appendix I	Section 3 Appendix J	**Appropriate.**
Data extraction	Table 64 in Section 5 of Appendix H	Table 84 in Section 5 of Appendix I	Table 103 in Section 4 of Appendix J	**Appropriate.** For the economic evaluations review, 39 unique studies from 46 publications were extracted. For the HRQoL review, 44 unique studies were extracted. For the cost and resource use studies, 16 were extracted.
QA of included studies	Table 68 and 70 in Section 5 of Appendix H	No QA only assessment of appropriateness for cost-effectiveness evaluation	No QA only assessment of appropriateness for cost-effectiveness evaluation	**Appropriate.**

Abbreviations: AWMSG, All Wales Medicines Strategy Group; CADTH, Canadian Agency for Drugs and Technologies in Health; CEA, cost-effectiveness analysis; CRD, University of York's Centre for Reviews and Dissemination; CS, company submission; EAG, External Assessment Group; HRQoL, health-related quality of life; HSUVs, health state utility values; HTA, Health Technology Assessment; HTAD, Health Technology Assessment Database; MSQ, Migraine Specific Questionnaire; NCPE, National Centre for Pharmacoeconomics; NHS EED, National Health Service Economic Evaluation Database; NICE, National Institute for Health and Care Excellence; QA, quality assessment; ScHARRHUD, University of Sheffield School of Health and Related Research Health Utilities Database; SIGN, Scottish Intercollegiate Guidelines Network; SLR, systematic literature review; SMC, Scottish Medicines Consortium.

The EAG notes that eight cost-effectiveness studies for EM and six for CM considered the UK NHS perspective. The EAG notes that the company states that a Scottish NHS perspective is aligned to decision making in England for EM health technology assessment (HTA) studies but states that this perspective does not align with English decision making for CM HTA studies.

Three were National Institute for Health and Care Excellence (NICE) technology appraisals (TAs) in EM (TA764/TA631, TA659 and TA682)[8-10] and four were NICE TAs in CM (TA260, TA764/TA631, TA659 and TA682)[1]. The EAG notes that the NICE submission for rimegepant (TA906)[2] and eptinezumab (TA871)[3] were not included. The semi-Markov model structure described by the galcanezumab (TA659) was adopted by the company. The key differences between these modelling assumptions and those used in the other NICE submissions are discussed further in Section 4.2.4. Across all the health economic studies, the most common time horizon used was 10-years, with a range of 1- to 3-month cycles.

Of the 20 extracted and unique EM HRQoL studies, six reported migraine-specific quality of life questionnaire (MSQ) mapped to EQ-5D values, one collected data from the Health Utilities Index (HUI)-3, one used exclusively SF-36D and 12 report EQ-5D values directly. Of the 22 extracted and unique EM HRQoL studies, seven reported MSQ mapped to EQ-5D values, 12 report EQ-5D values directly and the remaining used alternate elicitation methods. These studies were not used to inform the base case as the company elicited MSQv2 data from the key clinical trials of atogepant (ELEVATE and PROGRESS). Please refer to Section 4.2.9 for further details on the HRQoL data applied in the model.

The company considered the cost and resource use data from the galcanezumab and erenumab appraisals to be the most appropriate source for informing the economic analysis. Please refer to Section 4.2.10 for further details on the cost and resource use data applied in the model.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 29 summarises the EAG's appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base-case analysis, with reference to the NICE final scope outlined in Section 2.3.

Table 29. NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes.
Perspective on costs	NHS and PSS	Yes.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes.
Synthesis of evidence on health effects	Based on systematic review	Yes.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-	Health effects were expressed in QALYs. The EQ-5D does not appear to be appropriate to

	5D is the preferred measure of HRQoL in adults.	measure HRQoL in this population as patients may not have a migraine when they complete the EQ-5D. The MSQ is preferred as it has a 4-week recall period. Study BHV3000-305 included MSQv2 responses from patients which the company mapped to EQ-5D utilities.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes.
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Yes. MSQv2 was mapped to EQ-5D-3L utilities using a validated algorithm developed by Gillard *et al.* 2012,[60] which uses a UK valuation set.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	The company utilised HCRU estimates accepted in previous NICE appraisals in migraine prevention (TA631/TA764 and TA682), these estimates were obtained from the NHWS. Unit costs were derived from the BNF, PSSRU and NHS References Costs.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes.

Abbreviations: BNF, British National Formulary; EAG, External Assessment Group; HCRU, healthcare resource use; HRQoL, health-related quality of life; HSUVs, health state utility values; MSQ, Migraine Specific Questionnaire; NHS, national health service; NHWS, National Health and Wellness Survey; PSS, personal social services; QALY, quality adjusted life year

4.2.2 Population

The population considered in the NICE final scope consists of adults with migraine who have discontinued/failed on at least 3 oral preventative drug treatments (3+TF). The company focuses on two specific patient populations within this, “episodic migraine” (EM) and “chronic migraine” (CM). EM includes patients who have at least four migraine days per month but fewer than 15 headache

days per month whereas CM includes all patients with ≥15 headache days per month and ≥8 migraine days per month.

The proposed target populations is in line with the NICE final scope and marketing authorisation.[11] The company's target population is also consistent with the BASH guideline[61] and recent NICE recommendations for the comparator treatments (monoclonal antibody [mAb] calcitonin gene-related peptide [CGRP] antagonists – erenumab 140 mg [TA682], galcanezumab [TA659] and fremanezumab [TA631/TA764]).[8-10]

The company used clinical effectiveness data for atogepant from the ADVANCE[26] or ELEVATE[28] study for the EM population and the PROGRESS[25] study for the CM population to inform the economic analysis. The results of a network meta-analysis (NMA) were used to inform comparator treatment outcomes relative to atogepant.

The ADVANCE study included the total EM patient population with [redacted] in the atogepant 60 mg arm and [redacted] in the placebo group. ELEVATE focused on EM patients with 2 to 4 previous preventative treatment failures (TF) and contained a subgroup based on 3+ TF, in line with the target population laid out in the NICE final scope.[11] Within this 3+ TF subgroup of ELEVATE, [redacted] patients were in the placebo arm and [redacted] in the atogepant 60 mg arm. The PROGRESS study included the total CM patient population with 246 in the placebo arm and 256 in the atogepant arm. There was a subgroup of patients with 3+ TF in this trial but with only [redacted] in the atogepant arm and [redacted] in the placebo it was not seen as sufficiently powered to obtain accurate efficacy estimates for these patients. As a result, the base case CM data for atogepant is based on a population that differs from the NICE final scope. Baseline characteristics that can be used in the model are listed in Table 30, with the ADVANCE data representing an optional scenario and the data from ELEVATE and PROGRESS representing the base case for the EM and CM populations, respectively.

Table 30. Baseline characteristics for populations used in economic model

Characteristic	EM (overall mITT) ADVANCE	EM (3+ TF mITT) ELEVATE	CM (overall mITT) PROGRESS
Age, mean	***	***	42.1
Proportion female, %	***	***	87.5%
Pooled baseline MMDs (SD)	***	***	***
Pooled baseline monthly acute MUDs (SD)	***	***	***

4.2.2.1 EAG comment

As previously stated in section 3.4.1, the EAG considers the overall modified intention to treat (mITT) is a more appropriate population to use in the EM arm of the model. This is due to a lack of available 3+ TF data for comparator randomised controlled trials (RCTs) used in the NMA. Therefore, the EAG base case uses the overall mITT population from ADVANCE.

4.2.3 Interventions and comparators

4.2.3.1 Intervention

The economic analysis investigates the cost-effectiveness of atogepant (Aquipta™; AbbVie) 60 mg every day; a small molecule, orally administered CGRP antagonist. As per the SmPC, atogepant is indicated for the prophylaxis treatment of EM and CM patients. UK marketing authorisation has been granted and covers adults with ≥4 monthly migraine days (MMDs) and in whom ≥3 prior oral preventive treatments have failed.[4]

The intervention has a list price of £463.68 per 28-tablet pack. The company have applied a confidential patient access scheme (PAS) discount of [redacted] bringing the cost per pack down to [redacted]. The company have also noted in the submission that atogepant has potential for use in primary care. The EAG notes that the pharmaceutical price regulation scheme[62] states that treatments used in primary care are unlikely to be able to apply a PAS.

4.2.3.2 Comparators

The comparators listed in the NICE final scope are:

- Erenumab;
- Galcanezumab;
- Fremanezumab;
- Botulinum toxin type A (BoNT/A , in CM only);
- Eptinezumab (subject to NICE evaluation); and,
- Rimegepant (subject to NICE evaluation)

Although rimegepant and eptinezumab have both received approval from NICE for use in routine commissioning, the company excluded these as comparators. The company have provided three key justifications for this decision:

1. The low predicted market share for 2023 of the respective treatments; up to [redacted] for rimegepant and [redacted] for eptinezumab,[13] in the relevant population (see section 4.2.2), along with clinical expert opinion suggests these treatments are not part of established care in the UK.
2. The populations these treatments target are not fully aligned with atogepant. Rimegepant is restricted to EM patients only and eptinezumab will likely be reserved for patients with severe migraine attacks, or have difficulty administering other mAb treatments, due to its intravenous (IV) administration.
3. The requirement for IV administration further limits the population eligible for treatment due to lack of access to suitable hospital facilities.
4. While eptinezumab and rimegepant are recommended by NICE, these recommendations had not been published at the time of scoping (the EAG notes that they were, however, listed in the final scope subject to NICE evaluation).

Despite this, in response to a clarification request the company have provided limited efficacy data comparing atogepant to eptinezumab and rimegepant, this is included in section 3.4.5 and 4.2.6.

In addition, the company excludes BoNT/A from their base case analysis, including it as a scenario only. This decision was made as the treatment is predicted to decline following the introduction mAbs and they state that this is in line with TA871.

Two regimens of fremanezumab are recommended by NICE: 225 mg monthly and 675 mg every three months (quarterly).[10] These were included in the company's NMA and economic analysis. For erenumab, the modelled dose reflected the dose recommended by NICE in TA682;[8] 140 mg every 4 weeks. For galcanezumab, the modelled dose reflected the dose recommended in the BNF (120 mg monthly dose after a 240 mg initial loading dose), which aligns with clinical trial evidence informing TA659.[9] The EAG also notes that these doses reflect the clinical trials informing the NMA.

4.2.3.3 EAG comment

The EAG disagrees with the decision to exclude rimegepant and eptinezumab. Firstly, the market share estimates are based on an assumption that [redacted]. This assumption is sourced

from the resource impact template uploaded for fremanezumab, which has been removed from the NICE website. This template has been superseded by the resource template for rimegepant and does not contain this assumption. According to the data provided by the company [redacted] out of [redacted] patients ([redacted]) are expected to receive rimegepant in 2023, which represents a significant uptake considering the treatment was approved in May and is only available for EM. The EAG clinical experts predict a notable uptake in rimegepant, although not much change is expected with the use of eptinezumab. A slow or limited uptake does not seem like a reasonable justification for excluding a treatment; if the medication is in the final scope, has NICE approval and can be provided to the same patient population.

In addition, a treatment being a comparator to only a subgroup of the intended patients does not exclude it from being used as a comparator, as evidenced by BoNT/A featuring as a comparator in prior submissions for eptinezumab, erenumab, galcanezumab, and fremanezumab.

As a result, the EAG has attempted to incorporate a scenario utilising rimegepant and eptinezumab as comparators.

The EAG also disagrees with the company's claim that BoNT/A is not a relevant treatment comparator for atogepant and that this decision is in line with TA871. The EAG could not find evidence that BoNT/A was not considered a relevant comparator in the NICE appraisal for eptinezumab as it appears to have been included in base case results and it is mentioned in the FAD as one of the 4 currently available treatment options (for CM)[21, 63].

Aside from the exclusion of these treatments, the EAG considers the comparators included in the economic analysis to be appropriate.

4.2.4 Modelling approach and model structure

The company developed a *de novo* cost-effectiveness model in Microsoft Excel® to evaluate the incremental cost-utility of atogepant versus erenumab, fremanezumab, and galcanezumab, in adults with EM and CM, with BoNT/A added as an additional comparator scenario for adults with CM. The model is a semi-Markov most similar to the NICE submission for galcanezumab (TA659).[64] The model has a 28-day cycle which means 3 cycles precede the 12-week assessment period. There are six health states, two of the health states are defined by their position prior to response assessment and three are defined by their position post response assessment with one death state. The model

structure is presented in Figure 2. The model also includes a health state for background mortality; however, this does not differ across treatment arms.

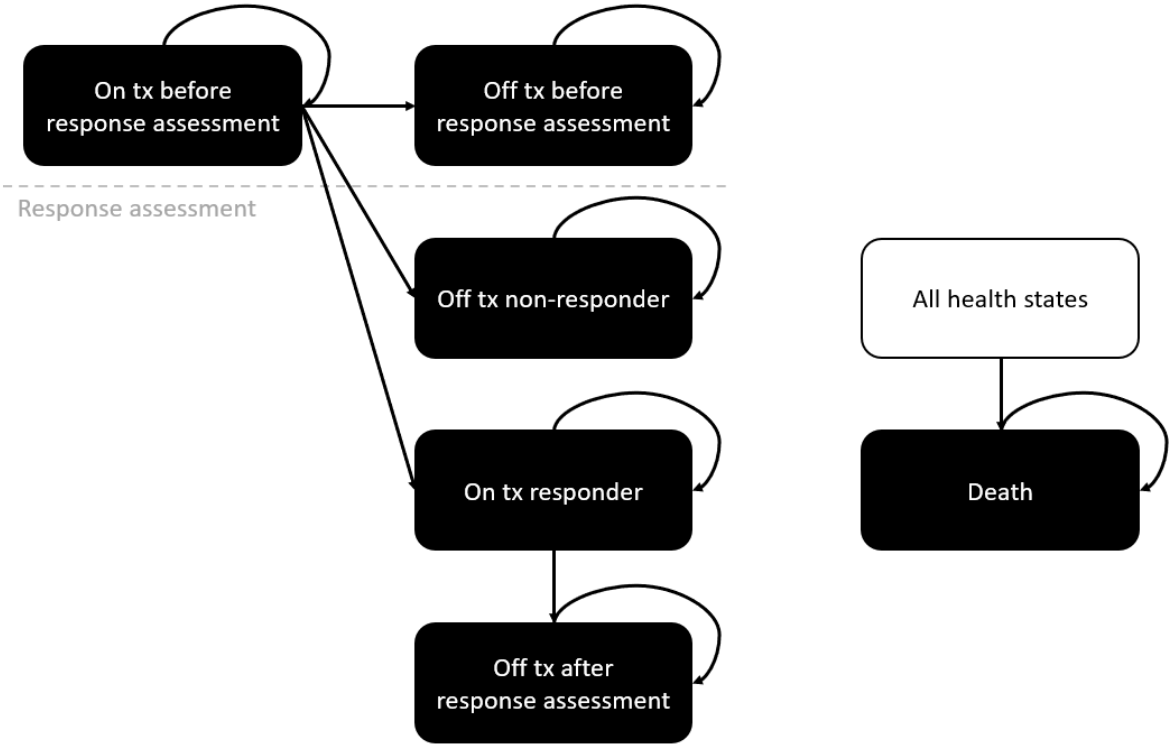
Assessment period

At the start of the model, patients initiate treatment on atogepant, erenumab, fremanezumab, galcanezumab or botulinum toxin type A (CM only) for a period of 12 weeks. This on treatment initiation state is "On tx before response assessment". Patients can discontinue in the cycles prior to the response assessment to "Off tx before response assessment" in which a patient will remain until death. For patients still on treatment, response is then assessed after the 12-week trial period (or 24-week period for BoNT/A) and defined as a ≥50% (for EM) and ≥30% (for CM) MMD reduction from baseline (see Section 4.2.6).

Post-assessment period

Non-responders immediately discontinue treatment at 12 weeks, consistent with previous NICE appraisals in migraine prevention (TA764/TA631, TA659 and TA682). Non-responders enter the Markov model in the off-treatment non-responder health state and responders continue treatment and enter the Markov model in the on-treatment responder health state. Patients who discontinue after this will enter the Off tx after response assessment health state. Utility for these health states is determined by average MMDs assumed to be distributed using a Poisson distribution.

Figure 2. Overview of the semi-Markov model for migraine prevention (reproduced from Figure 24 of the CS)



4.2.4.1 EAG comment

The EAG considers the company's model structure and modelling approach to be generally in line with those accepted in previous NICE appraisals in migraine prevention (TA764/TA631, TA659 and TA682).

A significant difference in the treatment waning assumption when compared to most prior submissions was identified and this is outlined in Table 31, based on committee preferences reported in the final guidance (note that the eptinezumab appraisal is excluded from the table as it was approved based on a cost-comparison).

Table 31. Treatment waning assumptions in previous NICE migraine prevention technology appraisals accepted at the final committee meetings

TA	Non-responders to BSC	Responders to BSC	Non-responders to active treatment at 12-weeks	Responders to active treatment who stay on treatment	Responders to active treatment who discontinue treatment
Company	NA	NA	Return to baseline MMDs immediately	Treatment effect maintained	Return to baseline MMDs immediately

Rimegepant TA906	NA	NA	Wane back to baseline MMDs over 12 months	Treatment effect maintained	Wane back to baseline MMDs over 12 months
Erenumab TA682 (FAD Section 3.17 and 3.21)	Return to baseline MMDs immediately	Return to baseline MMDs at the end of year 1 immediately	Return to baseline MMDs immediately	Treatment effect maintained	Return to baseline MMDs immediately
Fremanezumab TA764/TA631 (FAD Section 3.16)	Return to baseline MMDs immediately*	Wane back to baseline MMDs over 12 months	Wane back to baseline MMDs over 12 months	Treatment effect maintained	Return to baseline MMDs immediately*
Galcanezumab TA659 (Technical report, Issue 5)	Return to baseline MMDs immediately*	Wane back to baseline MMDs over 12 months	Wane back to baseline MMDs over 12 months (treatment-specific waning)*	Treatment effect maintained	Wane back to baseline MMDs over 12 months (treatment-specific waning)

*This assumption is not explicitly stated but could be inferred

Abbreviations: ACM, appraisal committee meeting; BSC, best supportive care; FAD, final appraisal determination; MMDs, monthly migraine days; NA, not applicable; NICE, National Institute for Health and Care Excellence; TAs, technology appraisals

As highlighted in Table 31, the company's assumptions regarding reversions to baseline MMD is in line with erenumab, in which its exclusion was a conservative assumption when comparing the treatment to BSC. In all other previous submissions, the reversion to baseline takes 12 months. This approach favours the more effective treatment. It may also be in line with fremanezumab, though it is not clear from the text in TA764/TA631.

As a result, the EAG requested the company provide scenario analysis assuming a 12-month gradual loss of treatment benefit and explain their rationale for the immediate reversion to baseline. The company provided this analysis but stated that there is no evidence available to show a placebo effect persists following treatment discontinuation, indicating this case was argued in the fremanezumab submission. The company note that the model includes an assumption that placebo responders in the "MMDs" input sheet retain their 'treatment effect'. In addition, they claim that the assumption of immediate reversion to baseline MMDs following discontinuation of active treatments is a conservative assumption.

Immediate reversion to baseline is conservative when comparing active treatment comparators such as atogepant or erenumab to BSC, but the impact of the same assumption when the comparator is another active treatment is uncertain. In the scenario analysis results provided by the company, the only recorded change in NHB was a 0.01 reduction when comparing atogepant to fremanezumab

(225mg) in EM. The company's assumption that placebo response is maintained would be conservative, but this does not impact results since BSC is not a comparator treatment.

The company is correct that the committee decided against including a continued treatment response following discontinuation in the fremanezumab appraisal (TA764/TA631). Furthermore, figure 1 in Vernieri *et al.* 2021[65] suggests benefits from discontinuing CGRP treatments are lost relatively quickly. Patients who discontinue mAbs experience a ≥50% response rate decline to 31.9% in EM and 34.3% in CM at the 2-month follow-up, from a peak of 73.3% and 60.6% whilst on treatment. A multicentre observational study on erenumab discontinuation, Schiano di Cola *et al.* 2021,[66] reaffirms this conclusion, although it remains uncertain whether this assumption is also true for atogepant and/or rimegepant.

As a result, the EAG will only incorporate post discontinuation treatment effect waning used in TA906 and TA659 as a scenario. This scenario compared to the base case is illustrated in Table 32. Note that although a user defined transition period may be inputted as "0 cycles" the model applies a minimum 1 cycle transition period.

Table 32. Health state transition period EAG and company

Health state	Base case MMD assumptions		Company transition period	TA906 and TA659 scenario transition period
	Start	End		
On treatment before response assessment	Pooled baseline MMDs	Pooled baseline MMDs	3 cycles (12 weeks)	3 cycles (12 weeks)
Off treatment before response assessment	Treatment-specific non-responder MMDs[a]	Pooled baseline MMDs	0 cycles (4 weeks)	13 cycles (1 year)
Off treatment non-responder	Treatment-specific non-responder MMDs	Pooled baseline MMDs	0 cycles (4 weeks)	13 cycles (1 year)
On treatment responder	Treatment-specific responder MMDs	Treatment-specific responder MMDs	18 cycles (72 weeks)	18 cycles (72 weeks)'
Off treatment after response assessment	Treatment-specific responder MMDs	Pooled baseline MMDs	0 cycles (4 weeks)	13 cycles (1 year)
Death	None		NA	NA

Abbreviations: IV: intravenous; MMD: monthly migraine day; NA: not applicable; SC: subcutaneous; TA: technology appraisal.

In addition, this scenario will also be included in a combined scenario that attempts to match the assumptions used in TA906. The modelling assumptions in this submission depart from prior

submissions in a number of key areas. To provide a consistent comparison with prior assessments a scenario has been created that matches the assumptions of the most recent submission in this area (TA906).

4.2.5 Perspective, time horizon and discounting

The model was conducted from the perspective of the UK NHS and Personal Social Services (PSS), in line with the NICE reference case.

The time horizon of the model was 60 years. Based on a starting age of 41.7-43.5 years (depending on if the EM or CM population is selected), patients would be over 100 years old at the end of the time horizon, meaning the time horizon is effectively lifetime.

The cycle length in the model was 28 days to align with the schedule of MMD reporting in the randomised control trials. A simple half cycle correction, taking the average of the two consecutive cycles, was applied to the model trace.

Finally, an annual discount rate of 3.5% was applied to both costs and benefits, in line with the NICE reference case.

4.2.5.1 EAG comment

In previous submissions for galcanezumab and rimegepant, it has been identified that women are predominately impacted by migraine and prevalence is significantly reduced after menopause, making a lifetime time horizon potentially inappropriate. However, given the high rates of discontinuation across all treatment arms this is likely to have minimal impact. At the end of the 20-year time horizon, less than 0.1% of patients remain on atogepant.

4.2.6 Treatment effectiveness

4.2.6.1 Assessment period discontinuation

The treatment effect is modelled according to the proportion of patients achieving a 50% reduction in MMD from baseline for EM or a 30% reduction MMD for CM, consistent with previous NICE appraisals in migraine prevention (TA764/TA631, TA659 and TA682). The probabilities for achieving response or discontinuing prior to the assessment period were derived from an NMA and results were expressed in terms of odds ratios (ORs) and/or hazard ratios (HRs).

The HRs obtained from the NMA and used to inform discontinuation prior to response assessment in the model, are summarised in Table 32. The NMA results used to establish treatment response are shown in Table 34. Atogepant was used as the baseline treatment in the economic analysis (i.e., the treatment ORs are compared to atogepant).

Table 33. Hazard ratios for discontinuation before response assessment (reproduced from table 18 of CQ)

	EM		CM	
	HR (95% CrI)	Probability of disc.	HR (95% CrI)	Probability of disc.
Atogepant 60 mg once daily (reference)	[redacted]	[redacted]	[redacted]	[redacted]
Galcanezumab 120 mg once monthly *	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg once every four weeks	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 225 mg once monthly †	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]	[redacted]	[redacted]

*Galcanezumab regimen is a 240 mg loading dose followed by 120 mg once a month. † Fremanezumab regimen is 675 mg initial dose followed by 225 mg once a month. *this was marked as once monthly in CS but has been updated to match dosing schedule used in the model.

Abbreviations: CM: chronic migraine; CrI: credible interval; CS: company submission; disc.: discontinuation; EM: episodic migraine; HR: hazard ratio.

Table 34. Hazard ratios for response and corresponding probabilities applied in the base case (reproduced from table 41 and 42 of CS)

Treatment	Random-effects model (EM)		Random-effects model (CM)	
	OR (95% CrI)	Response probability	OR (95% CrI)	Response probability
Atogepant 60 mg	1	46.2%	1	59.0%
Galcanezumab 120 mg	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 225 mg	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 675 mg*	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CM: chronic migraine; CrI, credible interval; CS: company submission; EM: episodic migraine; OR, odds ratio (treatment vs atogepant)

4.2.6.2 *Monthly migraine day (MMD) distributions*

Health-state related QoL in the model was determined by MMDs. When a patient transitions to a new health state, in order to represent waning, a mean MMD is applied to the start and end of the transition to that health state. These transitions are represented in Table 35. The mean MMD for the start is applied in the joining cycle and the mean MMD for the end, in the company's base case, is applied in the subsequent cycle (though the option is available to extend this transition period). Treatment-specific non-responder MMDs were assumed equal across all active treatments.

Table 35. MMD assumptions made per health state (preproduced from table 43 of CS)

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

Abbreviations: CS, company submission; MMD, monthly migraine days.

A Poisson distribution is used in conjunction with mean MMD in order to establish the distribution of MMDs for a patient. The utility formula laid out in section 4.2.9 is then used to convert this to HRQoL values for a health state. Treatment specific change from baseline (CFB) values derived from the NMA are shown in Table 36, these values were used to obtain treatment specific MMDs for the comparator treatments.

Table 36. Change from baseline in mean MMDs across the 12-week treatment period to atogepant and relevant comparators in EM and CM

	EM (RE)		CM (RE)	
	Median CFB (95% CrI)	Mean MMDs	Median CFB (95% CrI)	Mean MMDs
Atogepant 60 mg once daily (reference)	***	***	***	***
Galcanezumab 120 mg once monthly	***	***	***	***
Erenumab 140 mg once every four weeks	***	***	***	***
Fremanezumab 225 mg once monthly	***	***	***	***

Fremanezumab 675 mg once every three months	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EM: episodic migraine; CM: chronic migraine; CFB: change from baseline; CrI: credible interval; EM: episodic migraine; MMDs: monthly migraine days; OR: odds ratio; RE: random effects

To prevent clinically implausible MMD results arising from the NMA, the company added a restriction that prevented mean MMDs for treatment responders falling below 1. This was further explained by the company, at clarification, that without this limitation galcanezumab responders in EM would have negative MMDs or 100% of these patients would have 0 MMDs if the restriction was set to 0.

4.2.6.3 Long-term discontinuation

Following the 12-week assessment patients remain at risk of discontinuation. During the clarification stage the company provided further details on how this was calculated. This was based on LTS-302 in EM. Patients on atogepant remained on treatment a mean time of 291.6 days with 173 patients discontinued and 546 total patients. Using the 28 day cycle length the company used the below formula to calculate long term discontinuation (applied to EM and CM and all treatment arms):

$$Rate\ per\ day = {-\ln\left(1-\frac{173}{546}\right)}/{291.6}$$

$$Rate\ per\ cycle = 1 - e^{(-Rate\ per\ day \times 28)} = 3.59\%$$

4.2.6.4 EAG comment

As previously noted in section 3.4 the EAG seeks to update, alter and add to the NMA values used in the model. To recap, these updates include:

- Add rimegepant and eptinezumab as part of the preferred base case (the EAG reran NMAs to include data for rimegepant and eptinezumab);
- Use the total mITT population for efficacy outcomes for both EM and CM (as opposed to the 3+ TF population for EM patients);
- Preference for random effects (RE) adjusted analysis for CFB MMDs and ≥50% reduction in MMDs in CM, and fixed effects (FE) unadjusted analysis for ≥30% reduction in MMDs in CM;
- Preference in EM for the RE adjusted analysis for CFB in MMDs, ≥50% reduction in MMDs, CFB in acute medication use days (MUDs) and discontinuation.

Table 37. Relative effect of atogepant 60 mg once daily vs comparators for MMD outcomes – EAG- and company-preferred analyses

Atogepant 60 mg once daily vs	Company-preferred NMA	EAG-preferred NMA
EM CFB in MMD, MD (95% CrI)		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
Rimegepant 75 mg every other day	-	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]
EM ≥50% reduction in MMDs, OR (95% CrI)		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
Rimegepant 75 mg every other day	-	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]
EM, discontinuation pre assessment period HR (95% CrIs)		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
Rimegepant 75 mg every other day	-	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]
CM CFB in MMD, MD (95% CrI)		

Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
BoNT/A	[redacted]	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]
CM ≥30% reduction in MMDs, OR (95% CrI) - company base case		
Erenumab 140 mg once monthly	[redacted]*	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
BoNT/A	[redacted]*	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]
CM ≥50% reduction in MMDs, OR (95% CrI)		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
BoNT/A	[redacted]	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]
CM, discontinuation pre assessment period HR (95% CrIs)		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]

Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
BoNT/A	[redacted]	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]

*Obtained using conversion factors

Abbreviations: BoNT/A, botulinum toxin type A; CFB, change from baseline; CM, chronic migraine; CrI, credible interval; CQ, clarification question; CS, company submission; EAG, External Assessment Group; EM, episodic migraine; HR, hazard ratio; MD, mean difference; MMD, monthly migraine days; NMA, network meta-analysis; OR, odds ratio; RE, random effects;

The EAG disagreed with the company's clinically plausible limit of 1 MMD. While it is evidently true that negative MMDs are implausible, it is not reasonable to use unexpected results from the NMA to justify an arbitrary limit. Furthermore, in the EAG base case analysis, using updated/preferred NMA results, the responder MMDs do not result in the same issue of 100% of patients having 0 MMDs, with the lowest mean responder MMDs in EM being 0.014 and 0.4555 for fremanezumab 225mg and 675mg, respectively.

In the most recent submission for this therapy area (TA906), MMD of responders and non-responders was assumed conditionally independent of treatment (i.e., MMD was solely dependent on responder status, treatment was not a relevant factor). There is some justification for making the same assumption given that CFB in MMD for all treatments in EM and CM is not statistically significant; however if this standard was consistently applied it would also disqualify most other efficacy inputs. Given this, the EAG has only included this as a scenario around the EAG base case and utilised it in a scenario that consistently utilizes the same assumptions as TA906.

The EAG's clinical experts advised that a lower rate of discontinuation would be expected in CM due to the higher rate of severity of the disease. In addition, the company's method of calculating this rate appears flawed as this calculation assumes approximately 173 patients will discontinue every 291.6 days in order to obtain a rate of discontinuation. However, given 291.6 is the mean time to discontinuation and 173 is the total number of patients that discontinue this is an implausible assumption. A more plausible assumption would be that half of 173 patients discontinued at 291.6 days, although this would involve assuming equivalence between the median patient discontinuing treatment and the mean time on treatment. In addition, the average treatment duration value is limited due to the cut off time of the study meaning that this places an arbitrary limit on how high

treatment duration can be, biasing the outcome. As a result, the long-term discontinuation rate from TA659 (0.44% per cycle)[64], provided by the company as a scenario, appears the most appropriate for use in the EAG base case. Note that whilst the company states this value is sourced from TA682, this appears to be an error as the 12 week discontinuation rate used in the erenumab submission was 2.38%[8].

4.2.7 Adverse events

The company did not directly include adverse events in the model given no patients experienced serious adverse events (Grade ≥3) in the phase III treatment studies (ELEVATE, PROGRESS and ADVANCE) and they have not been incorporated into previous submissions (TA260, TA659, TA682, TA764, TA871, TA906). The company also considered this to be a conservative assumption given the potential for injection site reactions, constipation and hypersensitivity reactions with mAbs.

However, the company have indirectly included AE disutility associated with injections by attaching a utility decrement for SC (subcutaneous) or IM (intramuscular) administration from Matza *et al*. 2019.[67] A disutility of 0.011 for SC and 0.0735 for IM was applied. The paper included utility for migraine patients and members of the general population taking oral treatments (propranolol, topiramate, and amitriptyline), receiving 31-39 injections once every 3 months (representing BoNT/A) and receiving 1 injection per month (representing mAb treatments). The average difference in utility, for migraine patients and general population patients, between the oral treatment and the injectables is what was used to derive the disutility. Utility was derived via interviewers completing a time-trade-off (TTO) task.

4.2.7.1 EAG comment

The EAG heard from its clinical experts that they were unaware of any specific serious adverse events associated with atogepant. The EAG accepts that it is likely a conservative assumption to exclude AEs, although the Matza *et al*. 2019 source effectively incorporates any injection-related disutility.

The EAG does not consider that the Matza paper represents an appropriate source for administration related disutility. The utility difference between 1 injection per month and oral medication was not statistically significant and a disutility associated with injection was not incorporated into the rimegepant appraisal (TA906).[2] This would suggest use of this disutility for SC

administration has not been sufficiently demonstrated and is inconsistent with the most recent/comparable NICE submission.

Furthermore, the paper did not use EQ-5D utility from patients actively receiving treatment. Utilities were instead elicited, from migraine sufferers and the general population, using a TTO task with a 10-year time horizon and health state vignettes described to interviewees. Given this, it is unclear whether the 0.0735 utility decrement derived for botulinum toxin type A is comparable to a 0.0735 decline in EQ-5D utility score.

4.2.8 Mortality

In both EM and CM, the company only included all-cause mortality, as per prior NICE TAs in migraine prevention (TA906, TA764, TA659 and TA682). To further support this approach, the company referred to a published meta-analysis, which found no association between migraine and all-cause mortality.[68]

The company obtained all-cause general population mortality from UK national life tables provided by the Office for National Statistics (ONS). Data from Years 2018 to 2020 were used to inform the model. These probabilities were age and sex adjusted according to the baseline patient characteristics in the atogepant studies. The life years gained in all company model runs was [redacted] years in EM and [redacted] years in CM.

4.2.8.1 EAG comment

The EAG found that the life table values used in the model differ to the qx, lx and dx column in the latest release of the ONS life tables (2018-20). The difference between the values is minor, as shown in Table 38, Table 39 and Table 40, but it is unclear where the company derived their general population mortality values since their inputs do not match any of the values within any of the last three ONS releases. The EAG base case uses the updated life tables to match the latest ONS data. The life years gained in all model runs remained [redacted] years in EM but decreased marginally to [redacted] years in CM following this change.

Table 38. ONS lifetables 2018-20 qx versus company inputs

	ONS national life table 2018-20		Company mortality input	
Age	Male	Female	Male	Female
0	0.004224	0.003503	0.004244	0.003519
1	0.000229	0.000214	0.000231	0.000211

2	0.000127	0.000114	0.000128	0.000113
3	0.000102	0.000095	0.000099	0.000093
4	0.000086	0.000064	0.000090	0.000061
5	0.000074	0.000074	0.000077	0.000079
6	0.000085	0.000071	0.000081	0.000069
7	0.000067	0.000055	0.000068	0.000051
8	0.000069	0.000058	0.000065	0.000053
9	0.000060	0.000051	0.000062	0.000056
10	0.000078	0.000066	0.000073	0.000065
Abbreviations: ONS; Office of National Statistics.				

Table 39. ONS lifetables 2018-20 lx versus company inputs

Age	ONS national life table 2018-20		Company mortality input	
	Male	Female	Male	Female
0	100000	100000	100000	100000
1	99578	99650	99576	99648
2	99555	99628	99553	99627
3	99542	99617	99540	99616
4	99532	99608	99530	99607
5	99524	99601	99521	99601
6	99516	99594	99513	99593
7	99508	99587	99505	99586
8	99501	99581	99499	99581
9	99494	99576	99492	99576
10	99488	99570	99486	99570
Abbreviations: ONS; Office of National Statistics.				

Table 40. ONS lifetables 2018-20 dx versus company inputs

Age	ONS national life table 2018-20		Company mortality input	
	Male	Female	Male	Female
0	422	350	424	352
1	23	21	23	21
2	13	11	13	11
3	10	9	10	9
4	9	6	9	6
5	7	7	8	8
6	8	7	8	7

7	7	5	7	5
8	7	6	6	5
9	6	5	6	6
10	8	7	7	7

Abbreviations: ONS; Office of National Statistics.

4.2.9 Health-related quality of life

The company used a mapping regression from Gillard *et* al. 2012 to convert MSQ v2.1 values from the placebo and atogepant arms of the ELEVATE and PROGRESS trials to EQ-5D values. These individual patient data (IPD) EQ-5D utility values was then regressed against MMD and response for the EM and CM groups separately in order to obtain the regression shown in Table 41.

Table 41. Regression models for mapped EQ-5D-3L utility (copy of table 47 in CS)

MMDs and treatment	EM		CM	
	Coeff	SE	Coeff	SE
Intercept	***	***	***	***
MMD	***	***	***	***
Response	***	***	***	***

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

With MMDs derived for each health state, as described in section 4.2.6.2, along with this regression applied, the company obtained HRQoL values for each health state/treatment.

Age-related utility decrements were included in the prevention model based on the algorithms reported in Health Survey for England (HSE) 2014 data[69].

4.2.9.1 EAG comment

During the clarification stage, the company was asked to rerun the regression using "on treatment" in place of "response" to match the previous submission TA906 and avoid issues of multicollinearity. The company stated that it was not possible to dynamically define treatment status this way, as it would require recalculating mean monthly migraine days for time periods were taking atogepant versus after they discontinued . Given that "on treatment" is likely to be aligned with responder status the EAG expects the absence of this regression will have minimal impact.

In scenarios that include eptinezumab, where a treatment disutility is applied for other treatments, a 0.005 disutility is used for each IV administration, in line with TA871 NICE submission[3].

4.2.10 Resource use and costs

The company has proposed a confidential patient access scheme (PAS) discount of approximately [redacted] on the list price, and all results presented in this report are inclusive of the discount. Confidential PAS discounts are available for fremanezumab, erenumab, galcanezumab, and eptinezumab. Furthermore, there is a CMU (Confidential Medicines Unit) price available for BoNT/A.

As such, the EAG has produced a confidential appendix to the EAG report. Analyses in the confidential appendix include the company base case results, scenario analyses and EAG base case and scenario analyses.

4.2.10.1 Drug acquisition and administration costs

Treatment costs and dosages are provided in Table 42. The 28-day ongoing treatment cost is an approximate average of the per cycle costs applied in the model since the model applies cost of treatments only in cycles where a new pack/dose was required. Fremanezumab, for example, is administered once monthly (as opposed to once every four weeks if it were once per cycle), meaning that the full cost per pack is applied from cycles 0 to 11 but no cost is applied in cycle 12.

No administration cost is associated with atogepant since it is administered orally. All mAb treatments have an initial cost in the first cycle for SC administration, following this it is assumed that 10% of patients who have issues self-administering will incur this cost every cycle. The cost for SC administration is £21.50 based on 30 minutes of Band 5 nurse time from the PSSRU 2022.[70] The administration cost for multiple intramuscular (IM) injections (required for BoNT/A) is £226.41 per appointment, based on the cost of a consultant lead neurology service for non-admitted face-to-face follow-up attendance.[71]

Table 42. Treatment costs for prevention (adapted from Table 49 of the CS)

Treatment	Dose	Cost per pack or vial	28-day initial treatment cost	28-day ongoing treatment cost
Atogepant	60mg once daily	List price £463.68 [redacted]	£463.68 [redacted]	£463.68 [redacted]
Erenumab	140 mg once every four weeks	£386.50	£386.50	£386.50
Fremanezumab	225 mg once monthly	£450.00	£450.00*	£414.00
Fremanezumab	675 mg once every three months	£1,350	£1,350	£414.00
Galcanezumab	120 mg once monthly with 240 mg initial dose	£450.00	£900.00*	£414.00
Botulinum toxin type A (CM only)	155–195 U (200 U assumed in the model as vial sharing is assumed not feasible) once every 12 weeks	£276.40	£276.40	£92.13

Abbreviations: CM, chronic migraine; CS, company submission; U, units

In addition to the intervention and comparator, acute medications are also costed for based on the trial results and the results from the NMA. The trial provides a baseline value for MUD (medication use days) for atogepant of [redacted] in CM and [redacted] in EM. This is then utilised in conjunction with the relative effects from the NMA to estimate MUDs for the comparators. As previously noted, the NMA has been updated to include rimegepant and eptinezumab; the updated results for MUD alongside the company base case are shown Table 43 and the acute medication costs and usage rates shown in Table 44. Due to a lack of available data, rimegepant was assumed to have equal MUD to atogepant.

Table 43. Relative effect of atogepant 60 mg once daily vs comparators for MUD outcomes – EAG- and company-preferred analyses

Atogepant 60 mg once daily vs	Company-preferred NMA	EAG-preferred NMA
CFB in acute MUDs, MD (95% CrI)		
Erenumab 140 mg once monthly	-	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
Rimegepant 75 mg every other day	-	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]
CM CFB in acute MUDs, MD (95% CrI)		
Erenumab 140 mg once monthly	[redacted]	[redacted]
Fremanezumab 225 mg once monthly	[redacted]	[redacted]
Fremanezumab 675 mg once every three months	[redacted]	[redacted]
Galcanezumab 120 mg once monthly	[redacted]	[redacted]
BoNT/A	[redacted]	[redacted]
Eptinezumab 100 mg once every three months	-	[redacted]
Eptinezumab 300 mg once every three months	-	[redacted]

*95% CrI assumed

Outputs from the NMAs are means for the CFB outcome. Bold values indicate statistically significant differences.

Abbreviations: BoNT/A, botulinum toxin type A; CFB, change from baseline; CM, chronic migraine; CrI, credible interval; EAG, External Assessment Group; EM, episodic migraine; MD, mean difference; MUDs, medication use days; NMA, network meta-analysis.

Table 44.Acute medication use costs (reproduced from table 53 in the CS)

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

Abbreviations: CS, company submission; U, units

Commercial arrangements are available for most of the comparators. Table 45 shows the source of commercial arrangement that has been used for each treatment in the confidential appendix. The results from Figure 3 to Figure 11, Table 52 to Table 55 and Table 60 to Table 63 from sections 5 and 6 have been replicated in the confidential appendix using confidential commercial arrangements. In addition, Table 56 and Table 57 have been replicated in the same way, with additional scenarios provided by the company at CQs added.

Table 45. Source of prices for confidential appendix.

Treatment	Formulation	Source
Atogepant	60mg 28 tablets	PAS
Galcanezumab	120 mg/1 ml solution for injection	PAS
Erenumab	140 mg/1 ml solution for injection	PAS
Fremanezumab	225 mg/1.5 ml solution for injection	PAS
Fremanezumab	675 mg/4.5 ml solution for injection	PAS
Eptinezumab	100 mg/mL	PAS
Rimegepant	75mg 8 tablets	List price
Botulinum toxin type A	200 units	CMU
Ibuprofen	400 mg 84 tablets	eMIT

Thomapyrin N® - company used price of aspirin with metoclopramide as a proxy	900 mg/10 mg 6 sachets	
Sumatriptan	50 mg 6 tablets	eMIT
Paracetamol	500 mg 32 tablets (company) 500 mg 100 tablets (EAG)	eMIT
Abbreviations: BNF, British national formulary; CMU, confidential medicines unit; eMIT, electronic market information tool; PAS, Patient access scheme,		

4.2.10.2 Treatment monitoring costs

All mAb patients are costed for a headache specialist visit in the first cycle, while atogepant has a 50:50 split between a headache specialist or a general neurologist visit. Clinical follow up visits are assumed to occur in primary care for atogepant and by a general neurologist for the mAbs. These professionals' unit costs are shown in Table 46.

Table 46. Monitoring unit costs

Resource	Unit cost
Headache specialist	£226.41
General neurologist	£184.23
General practitioner	£41.00

4.2.10.3 Health care resource use cost per migraine

The company states that health care resource use is taken from the National Health and Wellness Survey (NHWS) data as published in Vo *et al.* 2018[72]. However, the original data source appears to be NHWS data on file analysed as part of the erenumab submission (shown in table 58 and 59 of the original TA682 submission) [8,].

Nevertheless, this matches the dataset used in multiple recent submissions (rimegepant, erenumab fremanezumab, galcanezumab)[2, 8, 10, 64], the resource use can be seen listed in Table 47. These resource use values are then multiplied by the costs listed in Table 48.

Table 47. HCRU data from the NHWS (reproduced from table 51 in the CS)

Number of MMDs	Resource use per MMD				
	GP visit	A&E visit	Hospitalisation	Nurse specialist visit	Neurologist visit
0	0.202	0.030	0.023	0.063	0.003
1–3	0.288	0.067	0.042	0.102	0.015

4–7	0.413	0.058	0.040	0.175	0.013
8	0.553	0.092	0.040	0.048	0.038
9–14	0.553	0.092	0.052	0.048	0.038
15–28	0.585	0.117	0.052	0.127	0.073

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

Table 48. Disease management unit costs (reproduced from table 52 in the CS)

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

Abbreviations: A&E, accident and emergency; CS, company submission; GP, general practitioner; HRG, healthcare resource group.

4.2.10.4 EAG comment

As stated in section 4.2.3, the EAG considers that rimegepant and eptinezumab should be included in the analysis. The costs for these treatments used in the EAG analysis are listed in Table 49 and are sourced from the British national formulary (BNF)[73].

Table 49. Treatment costs of additional comparators

Treatment	Dose	Cost per pack or vial	28-day initial treatment cost	28-day ongoing treatment cost
Rimegepant	75mg every other day	£103.20	£361.20	£361.20
Eptinezumab	100mg once every 12 weeks	£1,350	£1,350	£450

Rimegepant is administered orally, therefore it has no administration cost. Eptinezumab is administered via intravenous (IV) injection, which requires a professional in every instance. The cost used for this was £174.04, taken from the eptinezumab NICE submission[3].

There is no specific source for the percentage of patients who have difficulty self-administering, although EAG's clinical experts agreed with the company that approximately 10% seemed reasonable. The sensitivity of the results to this assumption has been explored in EAG scenario analyses using 5% and 15% in section 6.2.

For acute medication costs, the company did not use the latest available eMIT costs. As a result, the EAG have updated the acute medication costs using the eMIT data from July 2022 to December 2022, as shown in Table 50. There has since been an update to eMIT costs released on the 5th of October 2023, though since this was released after the company submission this has not been used.

Table 50.Acute medication use costs update using eMIT

Acute Medication	CS strength	CS pack size	CS Pack cost	EAG strength	EAG pack size	EAG pack cost	EAG source
Ibuprofen	400 mg	84 tablets	£3.25	400 mg	84 tablets	£1.10	eMIT
Thomapyrin N*	One sachet	6 sachets	£6.61*	900mg/10 mg	6 tablets	£6.61*	BNF: List price for Migramax
Sumatriptan	50 mg	6 tablets	£1.03	50 mg	6 tablets	£0.79	eMIT
Paracetamol	500 mg	32 tablets	£0.22	500 mg	100 tablets	£0.88	eMIT

*Company used price of aspirin with metoclopramide as a proxy
Abbreviations: BNF, British National Formulary; CS, company submission; EAG, External Assessment Group; eMIT, electronic market information tool.

Given HCRU includes neurologist and GP visits, there is a potential issue of double counting by incorporating monitoring costs. In addition, the EAG's clinical experts expected that as it is a new treatment a period of time would be required when it was exclusively monitored by specialist care before any transfer of care could be possible to primary care. This is in line with previous expectations for monitoring of rimegepant explained in TA906. In addition, the company has additional savings from including 50% of atogepant patients as being prescribed in primary care. Since the company intends to apply for a confidential PAS this would not be possible, as treatments that are eligible for a PAS must be prescribed in secondary care.

The EAG has opted to exclude monitoring costs in line with the most recent submission for rimegepant (TA906) and to avoid the potential issue of double counting. Health state costs include neurologist and GP visits and there is no indication from the source that these rates of resource use excluded monitoring.

In the eptinezumab submission (TA871), the submitting company presented an analysis of the updated NHWS survey results to apply in their model for informing resource use rates by MMD. The source of these data was a report commissioned by the company and has not been published; however, the annual resource use by MMD frequency was made publicly available in the committee papers for TA871. These values, adjusted to per cycle rates, are shown in Table 51.

Table 51. per cycle HCRU data from the TA871

Number of MMDs	Resource use per MMD					
	GP visit	A&E visit	Hospitalisation	Nurse specialist visit	Neurologist visit	Psychiatrist visits
0	0.000	0.000	0.000	0.000	0.000	0.000
1–3	0.057	0.020	0.010	0.008	0.006	0.008
4–7	0.058	0.023	0.012	0.011	0.008	0.011
8–14	0.059	0.023	0.014	0.009	0.012	0.009
15–28	0.064	0.027	0.016	0.014	0.018	0.014

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

Given this is the most recent available data, these rates of resource use would be the most appropriate values to inform the model. However, since the per cycle resource values appear to differ significantly from those used in previous submissions and the EAG cannot access and verify the original source, this has been provided as an additional scenario analysis around the EAG base case.

5 Cost effectiveness results

5.1 Company's base case results

5.1.1 Deterministic results

Table 52 and Table 53 shows the company's deterministic base case for episodic migraine (EM) and chronic migraine (CM), comparing each of the three monoclonal antibodies (mAbs) to atogepant. As shown in Table 52, mAbs are associated with higher costs and similar quality-adjusted life years (QALYs). Based on willingness-to-pay (WTP) thresholds of £20,000 or £30,000 per QALY, atogepant could be considered cost-effective compared to each mAb as the incremental cost-effectiveness ratios (ICERs) are above these WTP thresholds and the incremental net health benefits (NHBs) are positive. The company made minor corrections to the network meta-analyses (NMAs) following clarification questions which resulted in the updated model results presented in this section.

Table 52. Company's pairwise deterministic base case results (EM)

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)	Inc. NHB (£20,000/ QALY WTP threshold)	Inc. NHB (£30,000/ QALY WTP threshold)
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Galcanezumab 120mg once monthly	£33,647	13.69	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Erenumab 140mg once monthly	£28,260	13.68	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Fremanezumab 225mg once monthly	£31,394	13.74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant 60mg once daily	[redacted]	[redacted]					

Fremanezumab 675mg once every three months	£32,980	13.75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*SW quadrant ICER (atogepant is cheaper and less effective than the comparator)

Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

Table 53. Company's pairwise deterministic base case results (CM)

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)	Inc. NHB (£20,000/ QALY WTP threshold)	Inc. NHB (£30,000/ QALY WTP threshold)
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Galcanezumab 120mg once monthly	£47,530	10.87	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Erenumab 140mg once monthly	£39,510	10.87	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Fremanezumab 225mg once monthly	£40,993	10.86	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Fremanezumab 675mg once monthly	£41,220	10.86	[redacted]	[redacted]†	[redacted]	[redacted]	[redacted]

*SW quadrant ICER

†Value of [redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

5.1.2 *Probabilistic results*

The company performed probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around base case results. Generally, probabilities were varied using a normal distribution unless it was necessary to constrain the variation (i.e. if a value couldn't be negative or exceed 1).

The PSA results provided by the company, arising from 1,000 simulations, are reproduced in Table 54. The External Assessment Group (EAG) considers these results to be similar to the company's deterministic results.

Table 54. Company's revised probabilistic base case results (EM)

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)	Inc. NHB (£20,000/ QALY WTP threshold)	Inc. NHB (£30,000/ QALY WTP threshold)
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Galcanezumab 120mg once monthly	£33,714	13.69	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Erenumab 140mg once monthly	£28,277	13.67	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Fremanezumab 225mg once monthly	£31,466	13.73	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Fremanezumab 675mg once every three months	£33,047	13.74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*SW quadrant ICER (atogepant is cheaper and less effective than the comparator)

Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

Table 55. Company's revised probabilistic base case results (CM)

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)	Inc. NHB (£20,000/ QALY WTP threshold)	Inc. NHB (£30,000/ QALY WTP threshold)
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Galcanezumab 120mg once monthly	£47,569	10.87	[redacted]	[redacted]	1,314,438*	0.66	0.44
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Erenumab 140mg once monthly	£39,452	10.88	[redacted]	[redacted]	420,750*	0.25	0.16
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Fremanezumab 225mg once monthly	£40,919	10.87	[redacted]	[redacted]	1,255,618*	0.33	0.22
Atogepant 60mg once daily	[redacted]	[redacted]	-	-	-	-	-
Fremanezumab 675mg once monthly	£41,180	10.86	[redacted]	[redacted]	-50,434,768	0.35	0.23

*SW quadrant ICER (atogepant is cheaper and less effective than the comparator)

†Value of [redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

5.1.3 *One-way sensitivity analysis*

The company carried out one-way sensitivity analyses (OWSAs) to assess the impact of varying the key parameters between the upper and lower 95% credible intervals or confidence intervals of the mean value. The tornado plot figures presented by the company in the company submission (CS; figures 38-45) were not correctly updated, resulting in many of the lower/upper bound NHB results exceeding the chart axis range. In addition, the model has since been updated following clarification. As a result the EAG have rerun the OWSA for EM and CM and present the results in Figure 3 to

Figure 10.These plots include the 10 most influential parameters resulting from the OWSA, comparing each mAb and botulinum toxin type A (BoNT/A) with atogepant. The ICER was most sensitive to unit cost of treatments, response rates and discontinuation.

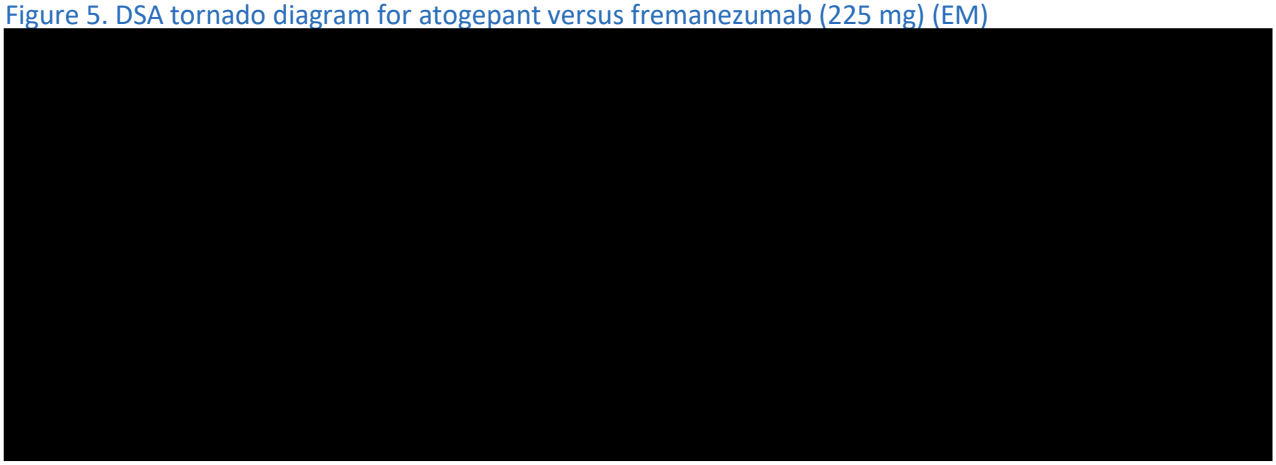
Figure 3. DSA tornado diagram for atogepant versus erenumab (140 mg) (EM)

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

Figure 4. DSA tornado diagram for atogepant versus galcanezumab (120 mg) (EM)

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

Figure 5. DSA tornado diagram for atogepant versus fremanezumab (225 mg) (EM)



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

Figure 6. DSA tornado diagram for atogepant versus fremanezumab (675 mg) (EM)

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

Figure 7. DSA tornado diagram for atogepant versus erenumab (140 mg) (CM)

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

Figure 8. DSA tornado diagram for atogepant versus galcanezumab (120 mg) (CM)

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

Figure 9. DSA tornado diagram for atogepant versus fremanezumab (225 mg) (CM)

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

Figure 10.DSA tornado diagram for atogepant versus fremanezumab (675 mg) (CM)

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

Figure 11. DSA tornado diagram for atogepant versus BoNT/A (CM)

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

5.1.4 Scenario analysis

The company undertook a series of scenario analyses to assess the impact of applying alternative assumptions to key model parameters. The scenarios run by the company are presented in Table 56 and Table 57. The largest decrease in the NHB (favoring the mAbs) was observed for using an alternate responder definition of ≥50% response definition for CM and exclusion of disutility associated with administration for EM, although in both cases atogepant could still be considered cost-effective at £20,000 and £30,000 WTP thresholds.

Table 56. Scenario analyses (EM) – atogepant PAS price (deterministic results) (reproduced from table 35 in company CQ response)

#	Description	Galcanezumab (120 mg)			Erenumab (140 mg)			Fremanezumab (225 mg)			Fremanezumab (675 mg)		
		Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs)[a]
Base Case		[redacted]	[redacted]	0.26	[redacted]	[redacted]	0.10	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.19
1	Missing NMA data equal to average mAb	[redacted]	[redacted]	0.26	[redacted]	[redacted]	0.10	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.19
2	Consider natural history of migraine	[redacted]	[redacted]	0.26	[redacted]	[redacted]	0.10	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.19
3a	Discontinuation before response assessment assumed to be a one-off probability at the response assessment timepoint	[redacted]	[redacted]	0.27	[redacted]	[redacted]	0.10	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.19
3b	Discontinuation after response assessment informed by alternative value	[redacted]	[redacted]	0.98	[redacted]	[redacted]	0.37	[redacted]	[redacted]	0.59	[redacted]	[redacted]	0.75
3c	Long-term discontinuation based on	[redacted]	[redacted]	0.39	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.22	[redacted]	[redacted]	0.29

	fremanezumab (1.95% per cycle)												
3d	Long-term discontinuation based on galcanezumab (0.79% per cycle)	[redacted]	[redacted]	0.70	[redacted]	[redacted]	0.27	[redacted]	[redacted]	0.42	[redacted]	[redacted]	0.53
4	Use of regression model 2 for utilities	[redacted]	[redacted]	0.26	[redacted]	[redacted]	0.09	[redacted]	[redacted]	0.16	[redacted]	[redacted]	0.20
5	Exclusion of disutility associated with SC or IM administration routes	[redacted]	[redacted]	0.26	[redacted]	[redacted]	0.09	[redacted]	[redacted]	0.13	[redacted]	[redacted]	0.17
6a	Monitoring costs 1	[redacted]	[redacted]	0.26	[redacted]	[redacted]	0.09	[redacted]	[redacted]	0.14	[redacted]	[redacted]	0.18
6b	Monitoring costs 2	[redacted]	[redacted]	0.27	[redacted]	[redacted]	0.11	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.20
7	EM overall population	[redacted]	[redacted]	0.42	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.18	[redacted]	[redacted]	0.20
8	Use of trial-observed MMD distributions	[redacted]	[redacted]	**0.27**	[redacted]	[redacted]	**0.10**	[redacted]	[redacted]	**0.16**	[redacted]	[redacted]	**0.19**
9	Assuming a gradual loss of benefit over 1 year	[redacted]	[redacted]	**0.26**	[redacted]	[redacted]	**0.10**	[redacted]	[redacted]	**0.14**	[redacted]	[redacted]	**0.19**
10	All treatments have equal MMD distributions for	[redacted]	[redacted]	**0.27**	[redacted]	[redacted]	**0.10**	[redacted]	[redacted]	**0.16**	[redacted]	[redacted]	**0.19**

	responders (based on atogepant data)												
11	HRQoL regression based on MMDs alone	[redacted]	[redacted]	**0.25**	[redacted]	[redacted]	**0.09**	[redacted]	[redacted]	**0.15**	[redacted]	[redacted]	**0.21**

*NHB calculated at a WTP threshold of £30,000. Note: Baseline risk-adjusted analyses were removed given that the NMA exploring ≥50% reduction in MMDs following baseline risk-adjustment did not converge (per CS appendices Table 26).
Abbreviations: CGRP: calcitonin gene-related peptide; EM: episodic migraine; mAbs: monoclonal antibodies; NMA: network meta-analysis; PAS: patient access scheme; SC: subcutaneous; TA: technology appraisal; tx: treatment.

Table 57. Scenario analyses (CM) – atogepant PAS price (deterministic results) (reproduced from table 36 in company CQ response)

#	Description	Galcanezumab (120 mg)			Erenumab (140 mg)			Fremanezumab (225 mg)			Fremanezumab (675 mg)		
		Inc. costs (£)	Inc. QALYs	NHB (QALYs) [a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs) [a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs) [a]	Inc. costs (£)	Inc. QALYs	NHB (QALYs) [a]
Base Case		[redacted]	[redacted]	0.43	[redacted]	[redacted]	0.16	[redacted]	[redacted]	0.22	[redacted]	[redacted]	0.23
12	Missing NMA data equal to average mAb	[redacted]	[redacted]	0.43	[redacted]	[redacted]	0.18	[redacted]	[redacted]	0.22	[redacted]	[redacted]	0.23
13	Consider natural history of migraine	[redacted]	[redacted]	0.43	[redacted]	[redacted]	0.16	[redacted]	[redacted]	0.22	[redacted]	[redacted]	0.24
14a	Discontinuation before response assessment assumed to be a one-off probability at the response assessment timepoint	[redacted]	[redacted]	0.43	[redacted]	[redacted]	0.16	[redacted]	[redacted]	0.22	[redacted]	[redacted]	0.23

14b	Discontinuation after response assessment informed by alternative value	[redacted]	[redacted]	1.85	[redacted]	[redacted]	0.70	[redacted]	[redacted]	0.96	[redacted]	[redacted]	0.97
14c	Long-term discontinuation based on fremanezumab (1.95% per cycle)	[redacted]	[redacted]	**0.68**	[redacted]	[redacted]	**0.26**	[redacted]	[redacted]	**0.35**	[redacted]	[redacted]	**0.36**
14d	Long-term discontinuation based on galcanezumab (0.79% per cycle)	[redacted]	[redacted]	**1.30**	[redacted]	[redacted]	**0.49**	[redacted]	[redacted]	**0.67**	[redacted]	[redacted]	**0.68**
15	Use of regression model 2 for utilities	[redacted]	[redacted]	0.44	[redacted]	[redacted]	0.17	[redacted]	[redacted]	0.23	[redacted]	[redacted]	0.24
16	Exclusion of disutility associated with SC or IM administration routes	[redacted]	[redacted]	0.42	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.20	[redacted]	[redacted]	0.22
17	≥50% response definition	[redacted]	[redacted]	0.34	[redacted]	[redacted]	0.11	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.17
18a	Monitoring costs 1	[redacted]	[redacted]	0.43	[redacted]	[redacted]	0.16	[redacted]	[redacted]	0.21	[redacted]	[redacted]	0.23
18b	Monitoring costs 2	[redacted]	[redacted]	0.44	[redacted]	[redacted]	0.17	[redacted]	[redacted]	0.23	[redacted]	[redacted]	0.24
19	Use of trial-observed MMD distributions	[redacted]	[redacted]	0.44	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.18	[redacted]	[redacted]	0.20

20	Assuming a gradual loss of benefit over 1 year	[redacted]	[redacted]	0.43	[redacted]	[redacted]	0.16	[redacted]	[redacted]	0.22	[redacted]	[redacted]	0.23
21	All treatments have equal MMD distributions for responders (based on atogepant data)	[redacted]	[redacted]	0.44	[redacted]	[redacted]	0.15	[redacted]	[redacted]	0.18	[redacted]	[redacted]	0.20
22	HRQoL regression based on MMDs alone	[redacted]	[redacted]	0.44	[redacted]	[redacted]	0.17	[redacted]	[redacted]	0.24	[redacted]	[redacted]	0.25

*NHB calculated at a WTP threshold of £30,000. Note: Baseline risk-adjusted analyses were removed as per the response to clarification question A5.
Abbreviations: CGRP: calcitonin gene-related peptide; EM: episodic migraine; mAbs: monoclonal antibodies; NMA: network meta-analysis; PAS: patient access scheme; SC: subcutaneous; TA: technology appraisal; tx: treatment.

5.2 Model validation and face validity check

In the CS, the company stated that expert clinical validation was sought throughout the model development in order to validate key inputs. In addition, technical validation was undertaken by an independent modelling team. Further, extreme value testing has been performed to investigate and ensure robustness of model behaviours for wide range of input parameter values.

The EAG considers that the company's model validation and face validity checks were generally extensive and robust.

6 Additional economic analysis undertaken by the EAG

6.1 Model corrections

The External Assessment Group (EAG) identified one error in the model. As explained in Section 4.2.8, the most recent life tables uploaded to the Office for National Statistics (ONS) website (2021) do not appear to match the table in the company submitted model. As such, the EAG has updated the life tables to match the latest ONS release. This was the only correction applied to the model. Corrected vs original model results for episodic migraine (EM) are shown in Table 58 and chronic migraine (CM) is shown in Table 59.

Table 58. Company's revised deterministic base case results (EM)

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)	Inc. NHB (£20,000/ QALY WTP threshold)	Inc. NHB (£30,000/ QALY WTP threshold)
Original company base case							
Atogepant 60mg once daily	[redacted]	[redacted]	–	–	–	–	–
Galcanezumab 120mg once monthly	33,647	13.69	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140mg once monthly	28,260	13.68	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 225mg once monthly	31,394	13.74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 675mg once every three months	32,980	13.75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated company base case							
Atogepant 60mg once daily	[redacted]	[redacted]	–	–	–	–	–
Galcanezumab 120mg once monthly	£33,954	13.92	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140mg once monthly	£26,805	13.91	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 225mg once monthly	£30,233	13.97	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 675mg once every three months	£31,554	13.99	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*SW quadrant ICER (atogepant is cheaper and less effective than the comparator)

Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

Table 59. Company's revised deterministic base case results (CM)

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)	Inc. NHB (£20,000/ QALY WTP threshold)	Inc. NHB (£30,000/ QALY WTP threshold)
Original company base case							
Atogepant 60mg once daily	[redacted]	[redacted]	–	–	–	–	–
Galcanezumab 120mg once monthly	£47,530	10.87	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140mg once monthly	£39,510	10.87	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 225mg once monthly	£40,993	10.86	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 675mg once every three months	£41,220	10.86	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BoNT/A	£34,107	10.743	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated company base case							
Atogepant 60mg once daily	[redacted]	[redacted]	–	–	–	–	–
Galcanezumab 120mg once monthly	£47,428	10.83	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140mg once monthly	£39,409	10.84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 225mg once monthly	£40,892	10.83	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 675mg once every three months	£41,119	10.82	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BoNT/A	£34,007	10.712	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*SW quadrant ICER (atogepant is cheaper and less effective than the comparator)

[redacted]

Abbreviations: BoNT/A, botulinum toxin type A; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

6.2 EAG scenario analysis

In section 4 of this report, the EAG identified changes to the model that would be preferred or warrant further exploration. These scenarios were each explored individually and included:

1. Removal of monitoring costs 4.2.10.4;
2. Removal of injection related disutility 4.2.7.1;
3. Alternate long-term discontinuation source from TA659 (0.44%) 4.2.6.3;
4. 12-month waning post disc treatment 4.2.4.1;
5. Updated National Health and Wellness Survey (NHWS) resource use values 4.2.10.4;
6. No monthly migraine day (MMD) reduction difference in responders between treatments 4.2.6.4;
7. Responder MMD restricted to 0, EM only 4.2.6.4;
8. 5% of patients require assistance in administering subcutaneous (SC) injection
9. 15% of patients require assistance in administering SC injection
10. Updates to the network meta-analyses (NMAs) - Using modified intention to treat (mITT) population for EM, addition of rimegepant and eptinezumab, alternate use of random effects/fixed effects (RE/FE) and adjusted/unadjusted where justified 4.2.6.4;
11. Assumptions to match TA906 (combination of scenario 1, 2, 4, 6, 7 and 10).

Results for these scenarios are shown in Table 60 for EM and Table 61 for CM.

Table 60. Results of the EAG's scenario analyses (episodic migraine)

Results per patient	Epti (7)	Rim (6)	Ere (5)	Gal (4)	Fre (3)	Fre (2)	Ato (1)	Incremental value					
								(1-7)	(1-6)	(1-5)	(1-4)	(1-3)	(1-2)
Company corrected base case													
Total costs	NA	NA	£28,183	£33,571	£32,904	£31,318	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	NA	13.64	13.65	13.71	13.70	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Removal of monitoring costs													
Total costs	NA	NA	£27,393	£32,739	£31,771	£30,280	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	NA	13.64	13.65	13.71	13.70	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Removal of injection related disutility													
Total costs	NA	NA	£28,183	£33,571	£32,904	£31,318	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	NA	13.65	13.66	13.72	13.71	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
12-month waning post-discontinuation in line with rimegepant submission													
Total costs	NA	NA	£28,147	£33,509	£32,832	£31,247	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	NA	13.64	13.67	13.72	13.71	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]

ICER (£/QALY)								NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Health care resource use utilising updated NHWS from eptinezumab submission													
Total costs	NA	NA	£13,162	£20,357	£18,063	£16,715	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	NA	13.91	13.92	13.99	13.97	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
No MMD reduction difference for responders between treatments													
Total costs	NA	NA	£26,742	£33,954	£31,725	£30,358	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	NA	13.91	13.92	13.97	13.96	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Responder MMD restricted to 0													
Total costs	NA	NA	£26,805	£33,777	£31,551	£30,068	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	NA	13.91	13.93	13.99	13.98	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
5% of patients require assistance in administering subcutaneous (SC) injection													
Total costs	NA	NA	£26,792	£33,940	£31,547	£30,214	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	NA	13.91	13.92	13.99	13.97	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
15% of patients require assistance in administering subcutaneous (SC) injection													

Total costs	NA	NA	£26,817	£33,967	£31,561	£30,252	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	NA	13.91	13.92	13.99	13.97	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Updates to the NMA - Using MITT population for EM, addition of rimegepant and eptinezumab, alternate use of RE/FE and adjusted/unadjusted where justified.													
Total costs	£30,439	£24,202	£28,401	£36,709	£29,480	£29,114	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	13.94	13.94	13.94	13.94	13.95	13.95	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assumptions to match TA906													
Total costs	£29,198	£23,178	£27,250	£35,515	£28,380	£28,003	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	13.97	13.96	13.97	13.97	13.97	13.97	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* SW quadrant ICER (atogepant is cheaper and less effective than the comparator)

Abbreviations: BoT, botulinum toxin type A, Epti, eptinezumab; Ere, erenumab; Fre, fremanezumab; Gal, galcanezumab; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; Rim, rimegepant

Table 61. Results of the EAG's scenario analyses (chronic migraine)

Results per patient	Epti (7)	Bot (6)	Ere (5)	Gal (4)	Fre (3)	Fre (2)	Ato (1)	Incremental value					
								(1-7)	(1-6)	(1-5)	(1-4)	(1-3)	(1-2)
Company corrected base case													

Total costs	NA	£34,007	£39,409	£47,428	£41,119	£40,892	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	10.71	10.84	10.83	10.82	10.83	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)									[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Removal of monitoring costs													
Total costs	NA	£34,007	£38,228	£46,294	£39,902	£39,658	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	10.71	10.84	10.83	10.82	10.83	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Removal of injection related disutility													
Total costs	NA	£34,007	£39,409	£47,428	£41,119	£40,892	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	10.82	10.85	10.85	10.84	10.85	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12-month waning post-discontinuation in line with rimegepant submission													
Total costs	NA	£33,943	£39,335	£47,351	£41,058	£40,829	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	10.73	10.86	10.86	10.85	10.85	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health care resource use utilising updated NHWS from eptinezumab submission													
Total costs	NA	£14,976	£20,429	£28,462	£22,064	£21,850	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	10.71	10.84	10.83	10.82	10.83	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER (£/QALY)								NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No MMD reduction difference between treatments													
Total costs	NA	£34,016	£39,461	£47,492	£41,130	£40,932	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	10.71	10.83	10.82	10.82	10.82	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5% of patients require assistance in administering subcutaneous (SC) injection													
Total costs	NA	£34,007	£39,389	£47,410	£41,113	£40,872	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	10.71	10.84	10.83	10.82	10.83	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15% of patients require assistance in administering subcutaneous (SC) injection													
Total costs	NA	£34,007	£39,430	£47,446	£41,125	£40,913	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	10.71	10.84	10.83	10.82	10.83	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updates to the NMA - Using MITT population for EM, addition of rimegepant and eptinezumab, alternate use of RE/FE and adjusted/unadjusted where justified.													
Total costs	£41,837	£34,390	£39,778	£46,697	£41,646	£41,244	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	10.82	10.72	10.83	10.80	10.80	10.80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assumptions to match TA906													

Total costs	£40,681	£34,396	£38,514	£45,461	£40,239	£39,867	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	10.84	10.85	10.87	10.85	10.86	10.86	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* SW quadrant ICER (atogepant is cheaper and less effective than the comparator)

Abbreviations: BoT, botulinum toxin type A, Epti, eptinezumab; Ere, erenumab; Fre, fremanezumab; Gal, galcanezumab; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; Rim, rimegepant

6.3 EAG preferred assumptions

The EAG's preferred assumptions are listed in the bullet points below. Table 62 and Table 63 provides cumulative impact these assumptions have on the incremental cost-effectiveness ratio (ICER) for episodic migraine. The preferred assumptions are:

- Removal of monitoring costs 4.2.10.4;
- Removal of injection related disutility 4.2.7.1;
- Alternate long-term discontinuation source from TA659 (0.44%) 4.2.6.3;
- Responder MMD restricted to 0 (only impacts EM), 4.2.6.4;
- Acute medication costs updated, 4.2.10.4;
- Updates to the NMA - Using mITT population for EM, addition of rimegepant and eptinezumab, alternate use of RE/FE and adjusted/unadjusted where justified 4.2.6.4.

Table 62. Results of the EAG's cumulative preferred assumptions (episodic migraine)

Results per patient	Epti (7)	Rim (6)	Ere (5)	Gal (4)	Fre (3)	Fre (2)	Ato (1)	Incremental value					
								(1-7)	(1-6)	(1-5)	(1-4)	(1-3)	(2-2)
Company corrected base case													
Total costs	NA	NA	£28,183	£33,571	£32,904	£31,318	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	NA	13.64	13.65	13.71	13.70	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Removal of monitoring costs													
Total costs	NA	NA	£27,393	£32,739	£31,771	£30,280	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	NA	13.64	13.65	13.71	13.70	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Removal of injection site disutility													
Total costs	NA	NA	£27,393	£32,739	£31,771	£30,280	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	NA	13.65	13.66	13.72	13.71	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Alternate LT disc source													

Total costs	NA	NA	£37,008	£57,481	£57,005	£51,125	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	NA	13.84	13.93	14.23	14.16	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Responder MMD restricted to 0													
Total costs	NA	NA	£37,008	£56,878	£57,005	£51,125	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	NA	13.84	13.95	14.23	14.16	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Updated acute medication costs													
Total costs	NA	NA	£36,808	£56,678	£56,822	£50,939	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	NA	13.84	13.95	14.23	14.16	[redacted]	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Updates to the NMA - Using MITT population for EM, addition of rimegepant and eptinezumab, alternate use of RE/FE and adjusted/unadjusted where justified.													
Total costs	£55,233	£30,790	£48,222	£83,849	£50,471	£49,737	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	14.40	14.35	14.46	14.45	14.50	14.52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*SW quadrant ICER (atogepant is cheaper and less effective than the comparator)

Abbreviations: BoT, botulinum toxin type A, Epti, eptinezumab; Ere, erenumab; Fre, fremanezumab; Gal, galcanezumab; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; Rim, rimegepant

Table 63. Results of the EAG's cumulative preferred assumptions (chronic migraine)

Results per patient	Epti (7)	Bot (6)	Ere (5)	Gal (4)	Fre (3)	Fre (2)	Ato (1)	Incremental value					
								(1-7)	(1-6)	(1-5)	(1-4)	(1-3)	(2-2)
Company corrected base case													
Total costs	NA	£34,007	£39,409	£47,428	£41,119	£40,892	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	10.71	10.84	10.83	10.82	10.83	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]†	[redacted]
ICER (£/QALY)								NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Removal of monitoring costs													
Total costs	NA	£34,007	£38,228	£46,294	£39,902	£39,658	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	10.71	10.84	10.83	10.82	10.83	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]†	[redacted]
ICER (£/QALY)								NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Removal of injection site disutility													
Total costs	NA	£34,007	£38,228	£46,294	£39,902	£39,658	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	10.82	10.85	10.85	10.84	10.85	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Alternate LT discontinuation source													
Total costs	NA	£41,681	£63,119	£97,385	£68,855	£69,467	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	11.47	11.64	11.62	11.58	11.61	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated acute medication costs													
Total costs	NA	£41,361	£62,818	£97,087	£68,546	£69,161	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	NA	11.47	11.64	11.62	11.58	11.61	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updates to the NMA-Using MITT population for EM, addition of rimegepant and eptinezumab, alternate use of RE/FE and adjusted/unadjusted where justified.													
Total costs	£72,104	£43,366	£64,621	£93,493	£71,092	£70,872	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	11.53	11.57	11.59	11.45	11.46	11.49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)								[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*SW quadrant ICER (atogepant is cheaper and less effective than the comparator)

[redacted]Abbreviations: BoT, botulinum toxin type A, Epti, eptinezumab; Ere, erenumab; Fre, fremanezumab; Gal, galcanezumab; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; Rim, rimegepant

6.4 Conclusions of the cost effectiveness sections

As stated in section 4.2.10 fremanezumab, erenumab, galcanezumab, eptinezumab and BoNT/A all have confidential prices that have not been used in the analysis. Conclusions on comparisons to these treatments may differ when these alternate prices are applied. Rimegepant is the only comparator used which does not have a confidential price, therefore conclusions on cost-effectiveness of atogepant versus rimegepant will remain unchanged.

Overall, in the company's base case analysis, atogepant is significantly less expensive and approximately as effective as mAb comparators, leading to south-west quadrant ICERs of around [redacted] per quality-adjusted life year (QALY) for the next best mAb comparator in EM and around [redacted] per QALY in CM. BoNT/A was the only treatment that appeared to be less expensive than atogepant but atogepant could still be considered to be cost-effective with a North-East quadrant ICER of [redacted].

However, the inclusion of rimegepant by the EAG has shown it to be a critical comparator for atogepant in terms of cost-effectiveness. Atogepant could be considered cost-effective versus rimegepant at a willingness-to-pay-threshold (WTP) threshold of £30,000 but not at a cost-effectiveness threshold of £20,000, since rimegepant is less costly and less effective using the company base case for scenario analysis (EM only). In addition, the cumulative impact of EAG preferences has resulted in BoNT/A becoming a more cost-effective treatment for the treatment of CM, with a south-west quadrant ICER of [redacted]. However, given the small incremental cost and QALYs involved, and the large standard errors in the effectiveness derived from the NMA, this result comes with significant uncertainty. It should also be noted that the EAG's clinical experts have stated that BoNT/A is currently being used less frequently in favour of easier to administer treatments, although this may be just an issue of availability of services to provide BoNT/A.

The EAG considers the model structure and modelling assumptions to be generally appropriate and match other migraine prevention models submitted for appraisal by the National Institute for Health and Care Excellence (NICE). The EAG maintains that rimegepant and eptinezumab are relevant comparators currently approved by NICE and so should be included in analysis going forward.

7 References

1. National Institute for Health and Care Excellence (NICE). Botulinum toxin type A for the prevention of headaches in adults with chronic migraine [TA260]. . Available from: https://www.nice.org.uk/guidance/TA260. Date accessed: Oct 23.
2. National Institute for Health and Care Excellence (NICE). Rimegepant for preventing migraine [TA906]. . Available from: https://www.nice.org.uk/guidance/ta906. Date accessed: Oct 23.
3. National Institute for Health and Care Excellence (NICE). Eptinezumab for preventing migraine [TA871]. . Available from: https://www.nice.org.uk/guidance/ta871. Date accessed: Oct 23.
4. Medicines and Healthcare Products Regulatory Agency. Atogepant - Summary of Product Characteristics, 2023. Available from: https://mhraproducts4853.blob.core.windows.net/docs/fb517a0a566e1d2ca7046f48f40b89703b34f718 Date accessed: Oct 23.
5. International Headache Society. The International Classification of Headache Disorders, 3rd edition. *Cephalalgia* 2018; **38**: 1-211.
6. Katsarava Z, Manack A, Yoon MS, Obermann M, Becker H, Dommes P, et al. Chronic migraine: classification and comparisons. *Cephalalgia* 2011; **31**: 520-9.
7. National Migraine Centre. What is migraine? . Available from: http://www.nationalmigrainecentre.org.uk/migraine-and-headaches/migraine-and-headache-factsheets/what-is-migraine/. Date accessed: Oct 22.
8. National Institute for Health and Care Excellence (NICE). Erenumab for preventing migraine [TA682]. Available from: https://www.nice.org.uk/guidance/ta682. Date accessed: Oct 23.
9. National Institute for Health and Care Excellence (NICE). Galcanezumab for preventing migraine; resource impact template. Technology appraisal guidance (TA659). . Available from: https://www.nice.org.uk/guidance/ta659. Date accessed: Oct 23.
10. National Institute for Health and Care Excellence (NICE). Fremanezumab for preventing migraine [TA764]. . Available from: https://www.nice.org.uk/guidance/TA764. Date accessed: Oct 23.
11. National Institute for Health and Care Excellence (NICE). Atogepant for preventing migraine [ID5090]. Final scope 2023. Available from: https://www.nice.org.uk/guidance/gid-ta10992/documents/final-scope. Date accessed: Oct 23.
12. AbbVie Data on File. Atogepant in Migraine UK Advisory Board Meeting Report. 2022.
13. AbbVie Data on File. Clarivate™ Market Forecast Assumptions Migraine. 2020.
14. AbbVie Data on File. IQVIA HPA/BPI Combined Overview Unit Data Report. 2023.
15. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology* 2007; **68**: 343-9.
16. Ashina M, Lanteri-Minet M, Pozo-Rosich P, Ettrup A, Christoffersen CL, Josiassen MK, et al. Safety and efficacy of eptinezumab for migraine prevention in patients with two-to-four previous preventive treatment failures (DELIVER): a multi-arm, randomised, double-blind, placebo-controlled, phase 3b trial. *The Lancet Neurology* 2022; **21**: 597-607.
17. Croop R, Lipton RB, Kudrow D, Stock DA, Kamen L, Conway CM, et al. Oral rimegepant for preventive treatment of migraine: a phase 2/3, randomised, double-blind, placebo-controlled trial. *The Lancet* 2021; **397**: 51-60.
18. Ferrari MD, Diener HC, Ning X, Galic M, Cohen JM, Yang R, et al. Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial. *The Lancet* 2019; **394**: 1030-40.
19. Mulleners WM, Kim BK, Láinez MJA, Lanteri-Minet M, Pozo-Rosich P, Wang S, et al. Safety and efficacy of galcanezumab in patients for whom previous migraine preventive medication from two to

four categories had failed (CONQUER): a multicentre, randomised, double-blind, placebo-controlled, phase 3b trial. *Lancet Neurol* 2020; **19**: 814-25.
20. Reuter U, Goadsby PJ, Lanteri-Minet M, Wen S, Hours-Zesiger P, Ferrari MD, et al. Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study. *The Lancet* 2018; **392**: 2280-7.
21. National Institute for Health and Care Excellence (NICE). Final draft guidance: Eptinezumab for preventing migraine, 2023. Available from: https://www.nice.org.uk/guidance/ta871/documents/final-appraisal-determination-document. Date accessed: Oct 23.
22. National Institute for Health and Care Excellence (NICE). Single Technology Appraisal: Eptinezumab for preventing migraine [ID3803] - Committee Papers, 2023. Available from: https://www.nice.org.uk/guidance/ta871/documents/committee-papers. Date accessed: Oct 23.
23. Cady R, Turner I, Dexter K, Beach ME, Cady R, Durham P. An exploratory study of salivary calcitonin gene-related peptide levels relative to acute interventions and preventative treatment with onabotulinumtoxinA in chronic migraine. *Headache* 2014; **54**: 269-77.
24. Freitag FG, Diamond S, Diamond M, Urban G. Botulinum toxin type A in the treatment of chronic migraine without medication overuse. *Headache* 2008; **48**: 201-9.
25. AbbVie Data on File [CONFIDENTIAL]. Study 303 PROGRESS CSR. 2022.
26. AbbVie Data on File [CONFIDENTIAL]. Study 301 ADVANCE CSR. 2020.
27. AbbVie Data on File [CONFIDENTIAL]. CGP-MD-01 CSR. 2019.
28. AbbVie Data on File [CONFIDENTIAL]. Study 304 ELEVATE CSR. 2022.
29. Clinicaltrials.gov. Study to Evaluate the Safety and Tolerability of Treatment With Atogepant 60 mg Daily for the Prevention of Migraine in Participants With Episodic Migraine (NCT03700320), 2021. Available from: https://clinicaltrials.gov/study/NCT03700320. Date accessed: Oct 23.
30. National Institute for Health and Care Excellence (NICE). Headaches in over 12s: diagnosis and management. Clinical guideline [CG150]. Available from: https://www.nice.org.uk/guidance/cg150/chapter/Recommendations#management-2. Date accessed: Oct 23.
31. Detke HC, Goadsby PJ, Wang S, Friedman DI, Selzler KJ, Aurora SK. Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study. *Neurology* 2018; **91**: e2211-e21.
32. Tepper S, Ashina M, Reuter U, Brandes JL, Doležil D, Silberstein S, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Neurol* 2017; **16**: 425-34.
33. Aurora SK, Dodick DW, Turkel CC, DeGryse RE, Silberstein SD, Lipton RB, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. *Cephalalgia* 2010; **30**: 793-803.
34. Diener HC, Dodick DW, Aurora SK, Turkel CC, DeGryse RE, Lipton RB, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. *Cephalalgia* 2010; **30**: 804-14.
35. Ailani J, Lipton RB, Goadsby PJ, Guo H, Miceli R, Severt L, et al. Atogepant for the Preventive Treatment of Migraine. *The New England journal of medicine* 2021; **385**: 695-706.
36. AbbVie Data on File [CONFIDENTIAL]. Atogepant Migraine MAAP 304 study_combined priority 1 2 3 analysis. 2022.
37. AbbVie Data on File [CONFIDENTIAL]. Atogepant CM study 303 MAAP priority 1 to 3 analysis. 2022.
38. Cole JC, Lin P, Rupnow MF. Minimal important differences in the Migraine-Specific Quality of Life Questionnaire (MSQ) version. *Cephalalgia* 2009; **29**: 1180-7.

39. Coeytaux RR, Kaufman JS, Chao R, Mann JD, Devellis RF. Four methods of estimating the minimal important difference score were compared to establish a clinically significant change in Headache Impact Test. *Journal of clinical epidemiology* 2006; **59**: 374-80.
40. Smelt AF, Assendelft WJ, Terwee CB, Ferrari MD, Blom JW. What is a clinically relevant change on the HIT-6 questionnaire? An estimation in a primary-care population of migraine patients. *Cephalalgia* 2014; **34**: 29-36.
41. NICE Guidelines Technical Support Unit (TSU), University of Bristol. Frequently asked questions (FAQs) regarding evidence synthesis, 2019. Available from: https://www.bristol.ac.uk/media-library/sites/social-community-medicine/documents/mpes/TSU%20Frequently%20asked%20questions_Dec2019.pdf. Date accessed: Mar 23.
42. NICE Guidelines Technical Support Unit (TSU). Meta-analysis of Event Outcomes. Guidance Methodology Document 3, 2021. Available from: https://www.bristol.ac.uk/media-library/sites/social-community-medicine/documents/mpes/gmd-3-events-jan2021.pdf. Date accessed: Nov 23.
43. Stauffer VL, Dodick DW, Zhang Q, Carter JN, Ailani J, Conley RR. Evaluation of galcanezumab for the prevention of episodic migraine: the EVOLVE-1 randomized clinical trial. *JAMA Neurol* 2018; **75**: 1080-8.
44. Goadsby PJ, Reuter U, Hallström Y, Broessner G, Bonner JH, Zhang F, et al. A controlled trial of erenumab for episodic migraine. *New England Journal of Medicine* 2017; **377**: 2123-32.
45. Sakai F, Takeshima T, Tatsuoka Y, Hirata K, Lenz R, Wang Y, et al. A Randomized Phase 2 Study of Erenumab for the Prevention of Episodic Migraine in Japanese Adults. *Headache* 2019; **59**: 1731-42.
46. Wang SJ, Roxas AA, Jr., Saravia B, Kim BK, Chowdhury D, Riachi N, et al. Randomised, controlled trial of erenumab for the prevention of episodic migraine in patients from Asia, the Middle East, and Latin America: The EMPOwER study. *Cephalalgia* 2021; **41**: 1285-97.
47. Skljarevski V, Matharu M, Millen BA, Ossipov MH, Kim B-K, Yang JY. Efficacy and safety of galcanezumab for the prevention of episodic migraine: results of the EVOLVE-2 phase 3 randomized controlled clinical trial. *Cephalalgia* 2018; **38**: 1442-54.
48. Sakai F, et al. Efficacy and safety of galcanezumab for prevention of migraine headache in Japanese patients with episodic migraine: A phase 2 randomized controlled clinical trial. *Cephalalgia Reports* 2020; **1**: 1-10.
49. Hu B, Li G, Li X, Wu S, Yu T, Li X, et al. Galcanezumab in episodic migraine: the phase 3, randomized, double-blind, placebo-controlled PERSIST study. *J Headache Pain* 2022; **23**: 90.
50. Dodick DW, Silberstein SD, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Effect of fremanezumab compared with placebo for prevention of episodic migraine: a randomized clinical trial. *Jama* 2018; **319**: 1999-2008.
51. Sakai F, Suzuki N, Kim BK, Tatsuoka Y, Imai N, Ning X, et al. Efficacy and safety of fremanezumab for episodic migraine prevention: Multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in Japanese and Korean patients. *Headache* 2021; **61**: 1102-11.
52. Bigal ME, Dodick DW, Rapoport AM, Silberstein SD, Ma Y, Yang R, et al. Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of high-frequency episodic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. *The Lancet Neurology* 2015; **14**: 1081-90.
53. Ashina M, Saper J, Cady R, Schaeffler BA, Biondi DM, Hirman J, et al. Eptinezumab in episodic migraine: a randomized, double-blind, placebo-controlled study (PROMISE-1). *Cephalalgia* 2020; **40**: 241-54.

54. Silberstein SD, Dodick DW, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Fremanezumab for the preventive treatment of chronic migraine. *The New England journal of medicine* 2017; **377**: 2113-22.
55. Sakai F, Suzuki N, Kim BK, Igarashi H, Hirata K, Takeshima T, et al. Efficacy and safety of fremanezumab for chronic migraine prevention: Multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in Japanese and Korean patients. *Headache* 2021; **61**: 1092-101.
56. Bigal ME, Edvinsson L, Rapoport AM, Lipton RB, Spierings ELH, Diener HC, et al. Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine: A multicentre, randomised, double-blind, placebo-controlled, phase 2b study. *Lancet Neurol* 2015; **14**: 1091-100.
57. Lipton RB, Goadsby PJ, Smith J, Schaeffler BA, Biondi DM, Hirman J, et al. Efficacy and safety of eptinezumab in patients with chronic migraine: PROMISE-2. *Neurology* 2020; **94**: e1365-e77.
58. Dodick DW, Lipton RB, Silberstein S, Goadsby PJ, Biondi D, Hirman J, et al. Eptinezumab for prevention of chronic migraine: A randomized phase 2b clinical trial. *Cephalalgia* 2019; **39**: 1075-85.
59. Tassorelli C, Onishchenko K, Duan M, Hemstock M, Voller C, Gandhi P, et al. Comparative Efficacy, Quality of Life, and Safety/Tolerability of Atogepant and Rimegepant in Migraine Prevention: A Matching-Adjusted Indirect Comparison. *Presented at the 65th Annual Scientific Meeting of the American Headache Society; June 15–18, 2023; Austin, TX* 2023.
60. Gillard PJ, Devine B, Varon SF, Liu L, Sullivan SD. Mapping from disease-specific measures to health-state utility values in individuals with migraine. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2012; **15**: 485-94.
61. Bash. NATIONAL HEADACHE MANAGEMENT SYSTEM FOR ADULTS 2019, 2019. Available from: https://www.bash.org.uk/downloads/guidelines2019/01_BASHNationalHeadache_Management_SystemforAdults_2019_guideline_versi.pdf. Date accessed: Aug 2022.
62. Finance and NHS/Medicines PaIG. The Pharmaceutical Price Regulation Scheme 2014, 2013. Available from: https://assets.publishing.service.gov.uk/media/5a8203f440f0b6230269a61b/The_pharmaceutical_price_regulation_scheme_2014.pdf. Date accessed: Nov 23.
63. National Institute for H, Care E. Eptinezumab for preventing migraine [TA871]. Available at: https://www.nice.org.uk/guidance/TA871 [Last accessed: 22/03/2023]. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10677. Date accessed: 20 October 2022.
64. National Institute for H, Care E. Galcanezumab for preventing migraine [TA659]. Available at: https://www.nice.org.uk/guidance/TA659 [Last accessed: 20 October 2022]. Available from: https://www.nice.org.uk/guidance/TA659. Date accessed: 20 October 2022.
65. Vernieri F, Brunelli N, Messina R, Costa CM, Colombo B, Torelli P, et al. Discontinuing monoclonal antibodies targeting CGRP pathway after one-year treatment: an observational longitudinal cohort study. *J Headache Pain* 2021; **22**: 154.
66. Schiano di Cola F, Caratozzolo S, Venturelli E, Balducci U, Sidoti V, Pari E, et al. Erenumab Discontinuation After 12-Month Treatment: A Multicentric, Observational Real-Life Study. *Neurol Clin Pract* 2021; **11**: e834-e9.
67. Matza LS, Deger KA, Vo P, Maniyar F, Goadsby PJ. Health state utilities associated with attributes of migraine preventive treatments based on patient and general population preferences. *Qual Life Res* 2019; **28**: 2359-72.
68. Schürks M, Rist PM, Shapiro RE, Kurth T. Migraine and mortality: a systematic review and meta-analysis. *Cephalalgia* 2011; **31**: 1301-14.
69. Hernández Alava M, Pudney S, Wailoo A. Estimating EQ-5D by Age and Sex for the UK. NICE DSU Report. 2022.
70. Pssru. Unit costs of Health & Social Care 2022. Available at: https://www.pssru.ac.uk/unitcostsreport/ [Last accessed: 21/08/2023]. Date accessed.

71. Nhs. NHS reference costs 2021-2022: the main schedule. Available from: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/ [Last accessed: 21/08/2023]. Date accessed.
72. Vo P, Fang J, Bilitou A, Laflamme AK, Gupta S. 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**: 1-11.
73. British National F. British National Formulary. Available at: http://www.bnf.org [Last accessed: 25/08/2023].

8 Appendices

8.1 Meta-analyses of atogepant RCTs in episodic migraine

In the company submission for episodic migraine (EM), the company focused on the subgroup from ELEVATE with ≥3 prior oral preventive treatment failures (3+ TF) given this is most aligned with the decision problem and it was stratified for at randomisation in this randomised controlled trial (RCT). The EAG considers this to be reasonable but, given the External Assessment Group (EAG)'s preference for network meta-analysis (NMAs) within the EM population is the overall migraine population analyses (see Section 3.4.1), the EAG presents meta-analyses of the three atogepant RCTs in EM here, including the overall modified intention to treat (mITT) populations from each (ELEVATE, ADVANCE and CGP-MD-01).

Random effects analyses have been used for all analyses, as indicated in the Forest plots below. This is because there was reason to suspect clinical heterogeneity across the studies given ELEVATE differs to ADVANCE and CGP-MD-01 in that it is specific to patients with EM and 2-4 prior treatment failures. This assumption appears to be supported by meta-analysed results for most outcomes based on statistically significant heterogeneity and or high (>60) I^2 values, or a notable difference in the direction of the point estimates, but results for change from baseline (CFB) in the emotional function subdomain of the migraine-specific quality of life questionnaire (MSQ-EF) are not supportive of this. As discussed in Section 3.3, the three RCTs are [redacted] for atogepant based on point estimates (apart from discontinuation and treatment-emergent adverse events [TEAEs]), but the results from ADVANCE and/or CGP-MD-01 indicate treatment differences that [redacted] (and for CGP-MD-01 are often [redacted]). Pooled results suggest [redacted] benefits for atogepant 60 mg once daily vs placebo for all outcomes (apart from discontinuation and TEAEs where rates are [redacted] for atogepant but [redacted]), although these are [redacted] compared with when the ELEVATE mITT population is considered alone.

Figure 12. CFB in MMD – meta-analysis of three EM RCTs

Abbreviations: atog, atogepant 60 mg; CFB, change from baseline; CI, confidence interval; EM, episodic migraine; IV, inverse variance; MMD, monthly migraine days; RCT, randomised controlled trial; SD, standard deviation.

Figure 13. ≥50% reduction in MMDs from baseline – meta-analysis of three EM RCTs

Abbreviations: atog, atogepant 60 mg; CI, confidence interval; EM, episodic migraine; M-H, Mantel–Haenszel; MMD, monthly migraine days; RCT, randomised controlled trial.

Figure 14. CFB in acute MUDs – meta-analysis of three EM RCTs

Abbreviations: atog, atogepant 60 mg; CFB, change from baseline; CI, confidence interval; EM, episodic migraine; IV, inverse variance; MUD, medication use days; RCT, randomised controlled trial; SD, standard deviation.

Figure 15. All-cause discontinuation – meta-analysis of three EM RCTs

Abbreviations: atog, atogepant 60 mg; CI, confidence interval; EM, episodic migraine; M-H, Mantel–Haenszel; RCT, randomised controlled trial.

Figure 16. CFB in MSQ-RFR – meta-analysis of three EM RCTs

Abbreviations: atog, atogepant 60 mg; CFB, change from baseline; CI, confidence interval; EM, episodic migraine; IV, inverse variance; MSQ-RFR, role function-restrictive subdomain of migraine-specific quality of life questionnaire; RCT, randomised controlled trial; SD, standard deviation.

Figure 17. CFB in MSQ-RFP – meta-analysis of three EM RCTs

Abbreviations: atog, atogepant 60 mg; CFB, change from baseline; CI, confidence interval; EM, episodic migraine; IV, inverse variance; MSQ-RFR, role function-preventive subdomain of migraine-specific quality of life questionnaire; RCT, randomised controlled trial; SD, standard deviation.

Figure 18. CFB in MSQ-EF – meta-analysis of three EM RCTs

Abbreviations: atog, atogepant 60 mg; CFB, change from baseline; CI, confidence interval; EM, episodic migraine; IV, inverse variance; MSQ-RFR, emotional function subdomain of migraine-specific quality of life questionnaire; RCT, randomised controlled trial; SD, standard deviation.

Figure 19. CFB in HIT-6 – meta-analysis of three EM RCTs

Abbreviations: atog, atogepant 60 mg; CFB, change from baseline; CI, confidence interval; EM, episodic migraine; HIT-6, Headache Impact Test-6; IV, inverse variance; RCT, randomised controlled trial; SD, standard deviation.

Figure 20. TEAEs – meta-analysis of three EM RCTs

Abbreviations: atog, atogepant 60 mg; CI, confidence interval; EM, episodic migraine; M-H, Mantel–Haenszel; RCT, randomised controlled trial; TEAEs, treatment-emergent adverse events.

8.2 Additional EAG NMA results

8.2.1 Episodic migraine – MMD-related outcomes in the overall migraine population

Results from the unadjusted random effects(RE) NMAs within the overall migraine population performed by the EAG for these outcomes are presented below in Table 64. The EAG notes that

these are very similar to the results presented by the company in Table 27 of the company submission (CS) for the RE unadjusted analyses in the overall migraine population for EM.

Table 64. Relative effect of atogepant 60 mg once daily vs comparators in EM for MMD outcomes – RE unadjusted analyses

Atogepant 60 mg once daily vs	RE unadjusted NMA results - EAG
CFB in MMD, MD (95% CrI)	
Erenumab 140 mg once monthly	[redacted]
Fremanezumab 225 mg once monthly	[redacted]
Fremanezumab 675 mg once every three months	[redacted]
Galcanezumab 120 mg once monthly	[redacted]
Rimegepant 75 mg every other day	[redacted]
Eptinezumab 100 mg once every three months	[redacted]
Eptinezumab 300 mg once every three months	[redacted]
≥50% reduction in MMDs, OR (95% CrI)	
Erenumab 140 mg once monthly	[redacted]
Fremanezumab 225 mg once monthly	[redacted]
Fremanezumab 675 mg once every three months	[redacted]
Galcanezumab 120 mg once monthly	[redacted]
Rimegepant 75 mg every other day	[redacted]
Eptinezumab 100 mg once every three months	[redacted]
Eptinezumab 300 mg once every three months	[redacted]
CFB in acute MUDs, MD (95% CrI)	
Erenumab 140 mg once monthly	[redacted]
Fremanezumab 225 mg once monthly	[redacted]
Fremanezumab 675 mg once every three months	[redacted]
Galcanezumab 120 mg once monthly	[redacted]
Rimegepant 75 mg every other day*	-

Eptinezumab 100 mg once every three months	[redacted]
Eptinezumab 300 mg once every three months	[redacted]

*rimegepant could not be included in the NMA for CFB in acute MUDs when rerun by the EAG given this outcome was not reported for the only available rimegepant study.

Outputs from the NMAs are means for the CFB outcome and median OR for the proportion with ≥50% reduction in MMD from baseline. Bold values indicate statistically significant differences.

Abbreviations: CFB, change from baseline; CrI, credible interval; EAG, External Assessment Group; EM, episodic migraine; MD, mean difference; MMD, monthly migraine days; MUDs, medication use days; NMA, network meta-analysis; OR, odds ratio; RE, random effects.

Some minor edits to NMA input data were made by the EAG for these outcomes, as outlined below in Table 65, but the EAG considers these have not had a large impact on the results of the NMAs given how similar the results are to the original results presented by the company. The most notable difference is for the comparison against fremanezumab 225 mg once monthly CFB in acute medication use days (MUDs), where the point estimate in the EAG-corrected NMAs is slightly smaller than that in Table 27 of the CS appendices.

Table 65. EAG corrections to NMA input data – MMD-related outcomes in EM overall migraine analyses

Study (arm; value corrected)	Value in company analysis	Correction made in EAG analysis
CFB in MMDs		
ADVANCE (placebo, mean [SE])	-2.50 (0.20)	-2.48 (0.21)
ADVANCE (atogepant 60 mg, SE)	0.20	0.206
ELEVATE (placebo, SE)	[redacted]	[redacted]
ELEVATE (atogepant 60 mg, SE)	[redacted]	[redacted]
≥50% reduction in MMDs		
EMPOwER (placebo, number of events)	149/330	148/330
CFB in acute MUDs		
CGP-MD-01 (atogepant 60 mg, SE)	[redacted]	[redacted]

ADVANCE (placebo, mean [SE])	-2.40 (0.2)	-2.35 (0.184)
ADVANCE (atogepant 60 mg, SE)	-3.90 (0.2)	-3.85 (0.180)
ELEVATE (placebo, SE)	[redacted]	[redacted]
ELEVATE (atogepant 60 mg, SE)	[redacted]	[redacted]
HALO EM (placebo, SE)	0.21	0.22
HALO EM (fremanezumab 225 mg, SE)	0.64	0.22

Abbreviations: CFB, change from baseline; EAG, External Assessment Group; EM, episodic migraine; MMD, monthly migraine days; MUDs, medication use days; NMA, network meta-analysis; SE, standard error.

8.2.2 *Chronic migraine – MMD-related outcomes in the overall migraine population*

Results from the unadjusted RE NMAs within the overall migraine population performed by the EAG for these outcomes in chronic migraine (CM) are presented below in Table 66. The EAG notes that these are very similar to the results presented by the company in Tables 30 and 116 of the CS appendices for the RE unadjusted analyses in the overall migraine population for CM.

Table 66. Relative effect of atogepant 60 mg once daily vs comparators in CM for MMD outcomes – RE unadjusted analyses

Atogepant 60 mg once daily vs	RE unadjusted NMA results - EAG
CFB in MMD, MD (95% CrI)	
Erenumab 140 mg once monthly	[redacted]
Fremanezumab 225 mg once monthly	[redacted]
Fremanezumab 675 mg once every three months	[redacted]
Galcanezumab 120 mg once monthly	[redacted]
BoNT/A	[redacted]
Eptinezumab 100 mg once every three months	[redacted]
Eptinezumab 300 mg once every three months	[redacted]

≥50% reduction in MMDs, OR (95% CrI)	
Erenumab 140 mg once monthly	[redacted]
Fremanezumab 225 mg once monthly	[redacted]
Fremanezumab 675 mg once every three months	[redacted]
Galcanezumab 120 mg once monthly	[redacted]
BoNT/A	[redacted]
Eptinezumab 100 mg once every three months	[redacted]
Eptinezumab 300 mg once every three months	[redacted]

Outputs from the NMAs are means for the CFB outcome and median OR for the proportion with ≥50% reduction in MMD from baseline. Bold values indicate statistically significant differences.

Abbreviations: BoNT/A, botulinum toxin type A; CFB, change from baseline; CM, chronic migraine; CrI, credible interval; EAG, External Assessment Group; MD, mean difference; MMD, monthly migraine days; NMA, network meta-analysis; OR, odds ratio; RE, random effects.

Some minor edits to NMA input data were made by the EAG for these outcomes, as outlined below in Table 67 below.

Table 67. EAG corrections to NMA input data – MMD-related outcomes in CM overall migraine analyses

Study (arm; value corrected)	Value in company analysis	Correction made in EAG analysis
CFB in MMDs		
N/A		
≥30% reduction in MMDs		
FOCUS (placebo, number of events)	32/167	27/167
FOCUS (fremanezumab 225 mg, number of events)	93/173	91/173
≥50% reduction in MMDs		
HALO CM data was initially said not to be available for this outcome but the EAG identified this and included it in the NMA. Included data were 67/371, 153/375 and 144/366 for placebo, fremanezumab 225 mg and fremanezumab 675 mg groups, respectively.		
CFB in acute MUDs		
CONQUER (galcanezumab 120 mg, mean difference vs placebo [SE])	-4.0 (0.714286)	-3.9 (0.73979592)

Abbreviations: CFB, change from baseline; CM, chronic migraine; EAG, External Assessment Group; NMA, network meta-analysis; MMD, monthly migraine days; MUDs, medication use days; N/A, not applicable; SE, standard error.

8.2.3 *Episodic and chronic migraine – discontinuation*

Alternative RE results from the EAG's analyses for the discontinuation outcome in each population (RE unadjusted for EM, RE adjusted for CM) are presented in Table 68 below. The EAG's results for the RE unadjusted discontinuation NMA in EM are very similar to those preferred by the company in Section 3.4.3.2. The adjusted RE results for CM are very similar to those obtained by the EAG (and company) for the RE unadjusted analysis. The EAG did not make any changes to data analysed for the discontinuation NMAs, other than to add eptinezumab and rimegepant as comparators where applicable.

Table 68. Relative effect of atogepant 60 mg once daily vs comparators in EM and CM for discontinuation (cloglog analyses) – alternative analyses

Atogepant 60 mg once daily vs	Alternative analysis (RE unadjusted for EM, RE adjusted for CM)
EM, HR (95% CrIs)	
Erenumab 140 mg once monthly	[redacted]
Fremanezumab 225 mg once monthly	[redacted]
Fremanezumab 675 mg once every three months	[redacted]
Galcanezumab 120 mg once monthly	[redacted]
Rimegepant 75 mg every other day	[redacted]
Eptinezumab 100 mg once every three months	[redacted]
Eptinezumab 300 mg once every three months	[redacted]
CM, HR (95% CrIs)	
Erenumab 140 mg once monthly	[redacted]
Fremanezumab 225 mg once monthly	[redacted]
Fremanezumab 675 mg once every three months	[redacted]
Galcanezumab 120 mg once monthly	[redacted]
BoNT/A	[redacted]
Eptinezumab 100 mg once every three months	[redacted]
Eptinezumab 300 mg once every three months	[redacted]

Outputs from these NMAs are mean HRs. Bold values indicate statistically significant differences.

Abbreviations: BoNT/A, botulinum toxin type A; CM, chronic migraine; CrI, credible interval; EM, episodic migraine; HR, hazard ratio; RE, random effects.

8.3 Company's quality assessment of comparator studies

Table 69. Company's risk of bias assessment of comparator studies included in the NMAs – adapted from Tables 33 and 34 of the CS appendices

Study name Author (reference)	Was randomisation adequate?	Was allocation adequately concealed?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there unexpected imbalances in dropouts between groups?	Were any outcomes measured but not reported?	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
EM							
PERSIST (Hu 2022)	Yes	Yes	Yes	Yes	No	No	Yes
Sakai 2021	Yes	Yes	Yes	Yes	No	No	Yes
EMPOwER (Wang 2021)	Yes	Yes	Yes	Yes	No	No	Yes
BHV3000-305 (Croop 2021)	Yes	Yes	Yes	Yes	No	No	Yes
Sakai 2020	Yes	Yes	Yes	Yes	No	No	Yes
Sakai 2019	Yes	Yes	Yes	Yes	No	No	Yes
PROMISE-1 (Ashina 2020)	Yes	Unclear	Yes	Yes	No	No	Yes
CONQUER (Mulleners 2020)	Yes	Yes	Yes	Yes	No	No	Yes

FOCUS (Ferrari 2019)	Yes	Yes	Yes	Yes	No	No	Yes
LIBERTY (Reuter 2018)	Yes	Yes	Yes	Yes	No	No	Yes
HALO EM (Dodick 2018)	Yes	Yes	Yes	Yes	No	No	Yes
EVOLVE-2 (Skljarevski 2018)	Yes	Yes	Yes	Yes	No	No	Yes
EVOLVE-1 (Stauffer 2018)	Yes	Yes	Yes	Yes	No	No	No
STRIVE (Goadsby 2017)	Yes	Yes	Yes	Yes	No	No	Yes
Bigal 2015	Yes	Yes	Yes	Yes	No	No	Yes
CM							
Sakai 2021	Yes	Yes	Yes	Yes	No	No	Yes
PROMISE-2 (Lipton 2020)	Yes	Yes	Yes	Yes	No	No	Yes
CONQUER (Mulleners 2020)	Yes	Yes	Yes	Yes	No	No	Yes
Dodick 2019	Yes	Yes	Yes	Yes	No	No	Yes
FOCUS (Ferrari 2019)	Yes	Yes	Yes	Yes	No	No	Yes
REGAIN (Detke 2018)	Yes	Yes	Yes	Yes	No	No	Yes
HALO-CM (Silberstein 2017)	Yes	Yes	Yes	Yes	No	No	Yes
Tepper 2017	Yes	Yes	Yes	Yes	No	No	Yes
Bigal 2015	Yes	Yes	Yes	Yes	No	No	Yes

PREEMPT-1 (Aurora 2010)	Yes	Yes	Yes	Yes	No	No	Yes
PREEMPT-2 (Diener 2010)	Yes	Yes	Yes	Yes	No	No	Yes

Abbreviations: CM, chronic migraine; CS, company submission; EM, episodic migraine; ITT, intention to treat; NMA, network meta-analysis.

8.4 Data extraction tables for rimegepant and eptinezumab

The data extracted and included in relevant NMAs for rimegepant and eptinezumab comparators are presented below. A full systematic literature review (SLR) was not performed by the EAG to identify relevant rimegepant and eptinezumab studies given time constraints, but the EAG reviewed the relevant NICE appraisals for included studies (TA906 and TA871) and also the excluded studies lists provided within the CS and in response to clarification question A10, as the company's SLR covered rimegepant and eptinezumab. To identify secondary publications for each study, the EAG reviewed ClinicalTrials.gov using the clinical trial number. In some cases, data for an outcome was identified and extracted from ClinicalTrials.gov.

8.4.1 *Episodic migraine*

Table 70. Data extraction table for rimegepant and eptinezumab in EM – efficacy outcomes

Study name	Treatments	Time-point (weeks)	CFB in MMDs		CFB in MUDs		≥50% reduction in MMDs	
			N	Mean (SE)	N	Mean (SE)	n	N
PROMISE-1 (eptinezumab once every three months)[53]	Placebo	1-12	222	-3.2 (0.21)	222	-0.4 (0.09)	83 (37.4%)	222
	Eptinezumab 100 mg		221	-3.9 (0.21); difference vs placebo: -0.69 (-1.25 to -0.12)	221	-0.9 (0.13)	110 (49.8%)	221
	Eptinezumab 300 mg		222	-4.3 (0.20); difference vs placebo: -1.11 (-1.68 to -0.54)	222	-0.8 (0.12)	125 (56.3%)	222
BHV3000-305 (rimegepant every other day)[17]	Placebo	1-12 and 9-12 (1-12 used in NMA)	347	1-12: -2.7 (0.20); 9-12: -3.5 (0.26)	NR		144 (41.0%)	347
	Rimegepant 75 mg		348	1-12: -3.6 (0.20); 9-12: -4.3 (0.23)			171 (49.0%)	348

Abbreviations: CFB, change from baseline; EM, episodic migraine; MMD, monthly migraine days; MUDs, medication use days; NMA, network meta-analysis; NR, not reported; SE, standard error.

Table 71. Data extraction table for rimegepant and eptinezumab in EM – HRQoL outcomes

Study name	Treatments	Time-point (weeks)	CFB in MSQ-RFR		CFB in MSQ-RFP		CFB in MSQ-EF		CFB in HIT-6	
			N	Difference (SE) vs placebo	N	Difference (SE) vs placebo	N	Difference (SE) vs placebo	N	Difference (SE) vs placebo
	Placebo	N/A	NR		NR		NR		NR	

PROMISE-1 (eptinezumab once every three months)[53]	Eptinezumab 100 mg						
	Eptinezumab 300 mg						
BHV3000-305 (rimegepant every other day)[17]	Placebo	12 weeks	266	-	NR	NR	NR
	Rimegepant 75 mg		269	3.5 (0.2 to 6.7, SE 1.66), p=0.036			

Abbreviations: CFB, change from baseline; EM, episodic migraine; HIT-6, Headache Impact Test-6; HRQoL, health-related quality of life; MSQ, migraine-specific quality of life questionnaire; MSQ-EF, emotional function subdomain of MSQ; MSQ-RFP, role function-preventive subdomain of MSQ; MSQ-RFR, role function-restrictive subdomain of MSQ; N/A, not applicable; NR, not reported; SE, standard error.

Table 72. Data extraction table for rimegepant and eptinezumab in EM – discontinuation and TEAEs

Study name	Treatments	Time-point (weeks)	All-cause discontinuation	TEAEs
PROMISE-1 (eptinezumab once every three months)[53]	Placebo	12 weeks	20/225	132/222
	Eptinezumab 100 mg		13/225	141/223
	Eptinezumab 300 mg		11/224	129/224
BHV3000-305 (rimegepant every other day)[17]	Placebo	12 weeks	64/374	133/371
	Rimegepant 75 mg		57/373	133/370

Abbreviations: EM, episodic migraine; TEAEs, treatment-emergent adverse events.

8.4.2 *Chronic migraine*

Table 73. Data extraction table for eptinezumab in CM – efficacy outcomes

Study name	Treatments	Time-point (weeks)	CFB in MMDs		CFB in MUDs		≥30% reduction in MMDs		≥50% reduction in MMDs	
			N	Mean (SE)	N	Mean (SE)	n	N	n	N
PROMISE-2 (eptinezumab once every three months)[57]	Placebo	1-12	366	-5.6 (NR)	366	-1.9 (0.22)	NR		144 (39.3%)	366
	Eptinezumab 100 mg		356	-7.7 (NR); difference vs placebo: -2.0 (-2.9 to -1.2, SE 0.43)	356	-3.3 (0.26); difference vs placebo: -1.2 (-1.7 to -0.6, SE 0.28)			205 (57.6%)	356
	Eptinezumab 300 mg		350	-8.2 (NR); difference vs placebo: -2.6 (-3.4 to -1.7, SE 0.43)	350	-3.5 (0.25); difference vs placebo: -1.4 (-1.9 to -0.9, SE 0.26)			215 (61.4%)	350
Dodick 2019 (NCT02275117; eptinezumab once every three months)[58]	Placebo	1-12	116	-5.6 (0.61)	NR		NR		47 (40.5%)	116
	Eptinezumab 100 mg		118	-7.7 (0.64)					65 (55.1%)	118
	Eptinezumab 300 mg		114	-8.2 (0.66)					65 (57.0%)	114

Abbreviations: CFB, change from baseline; CM, chronic migraine; MMD, monthly migraine days; MUDs, medication use days; NR, not reported; SE, standard error.

Table 74. Data extraction table for eptinezumab in CM – HRQoL outcomes

Study name	Treatments	Time-point (weeks)	CFB in MSQ-RFR		CFB in MSQ-RFP		CFB in MSQ-EF		CFB in HIT-6	
			N	Difference (SE) vs placebo	N	Difference (SE) vs placebo	N	Difference (SE) vs placebo	N	Difference (SE) vs placebo
PROMISE-2 (eptinezumab once every three months)[57]	Placebo	12 weeks	NR		NR		NR		366	-4.6 (NR) for arm
	Eptinezumab 100 mg								356	-1.7 (-2.8 to -0.7, SE 0.54); -6.9 (NR) for arm
	Eptinezumab 300 mg								350	-2.9 (-3.9 to -1.8, SE 0.56); -8.6 (NR) for arm
Dodick 2019 (NCT02275117; eptinezumab once every three months)[58]	Placebo	12 weeks	NR		NR		NR		110	-5.8 (0.71) for arm
	Eptinezumab 100 mg								107	-1.1 (1.01); -6.9 (0.72) for arm
	Eptinezumab 300 mg								106	-4.2 (1.08); -10.0 (0.82) for arm

Abbreviations: CFB, change from baseline; CM, chronic migraine; HIT-6, Headache Impact Test-6; HRQoL, health-related quality of life; MSQ, migraine-specific quality of life questionnaire; MSQ-EF, emotional function subdomain of MSQ; MSQ-RFP, role function-preventive subdomain of MSQ; MSQ-RFR, role function-restrictive subdomain of MSQ; NR, not reported; SE, standard error.

Table 75. Data extraction table for eptinezumab in CM – discontinuation and TEAEs

Study name	Treatments	Time-point (weeks)	All-cause discontinuation	TEAEs
PROMISE-2 (eptinezumab once every three months)[57]	Placebo	12 weeks discontinuation; 32 weeks TEAEs	19/375	171/366
	Eptinezumab 100 mg		23/372	155/356
	Eptinezumab 300 mg		30/374	182/350

Dodick 2019 (NCT02275117; eptinezumab once every three months)[58]	Placebo	12 weeks discontinuation; 49 weeks TEAEs	4/121	68/121
	Eptinezumab 100 mg		4/122	70/122
	Eptinezumab 300 mg		2/121	77/121

Abbreviations: CM, chronic migraine; TEAEs, treatment-emergent adverse events.