Atogepant for preventing migraine [ID5090]

Confidential information redacted

Technology appraisal committee D [8 Feb 2024]

Chair: Paul Arundel

Lead team: Martin Bradley, Rob Hodgson, Paul Caulfield

External assessment group: BMJ-TAG

Technical team: Kirsty Pitt, Caron Jones, Jasdeep Hayre

Company: AbbVie

Atogepant for preventing migraine

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Summary

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Background on migraine

Common condition with potentially debilitating symptoms

Causes

- Not fully understood but has been linked to genetic factors, environmental factors, certain comorbid conditions and stress

Epidemiology

- Affects around 1 in 7 people, estimated 10 million people affected in UK
- Costs to NHS of £150M per annum with 11.4 working days lost to sickness per work year

Diagnosis and classification

- There are no tests for migraine and diagnosis is by observation and exclusion of other causes
- Diagnosis typically in adulthood and 2-3 times more common in women
- Episodic migraine (EM) is <15 headache days per month and chronic migraine (CM) ≥15 days

Symptoms and prognosis

- Symptoms (lasting 4 hrs to 3 days) affect the whole body and can be severely debilitating and impact mental wellbeing and physical activities (e.g. light/sound sensitivity, nausea, dizziness)

Patient and clinical perspectives*

Atogepant could improve quality of life and accessibility of treatment

Patient group submission

- Effective treatment improves the quality of life and ability to function for people with migraine, with impact on work, education, family and social life
- Atogepant may be beneficial for people who cannot self-inject or tolerate multiple injections, are needle-phobic, or people who can't access specialist headache clinics
- Availability of treatment in primary care would enable more equitable access and reduce costs

"I have tried everything there is to try! Anti-depressants, anti-convulsants, HRT, etc. I experienced unpleasant side-effects to a greater or lesser extent from everything and no relief from migraine at all."

Professional group submissions

- Atogepant is easy to administer, and data suggests a favourable tolerability and safety profile
- Could be used in community-based clinics or primary care supported by specialist consultants
- Other oral preventative medications can cause side effects e.g. somnolence, weight gain, depression, hypotension
- Some inconsistencies with the sample used in ADVANCE trial (discussed later)

* See appendix –Patient perspectives and Clinical perspectives

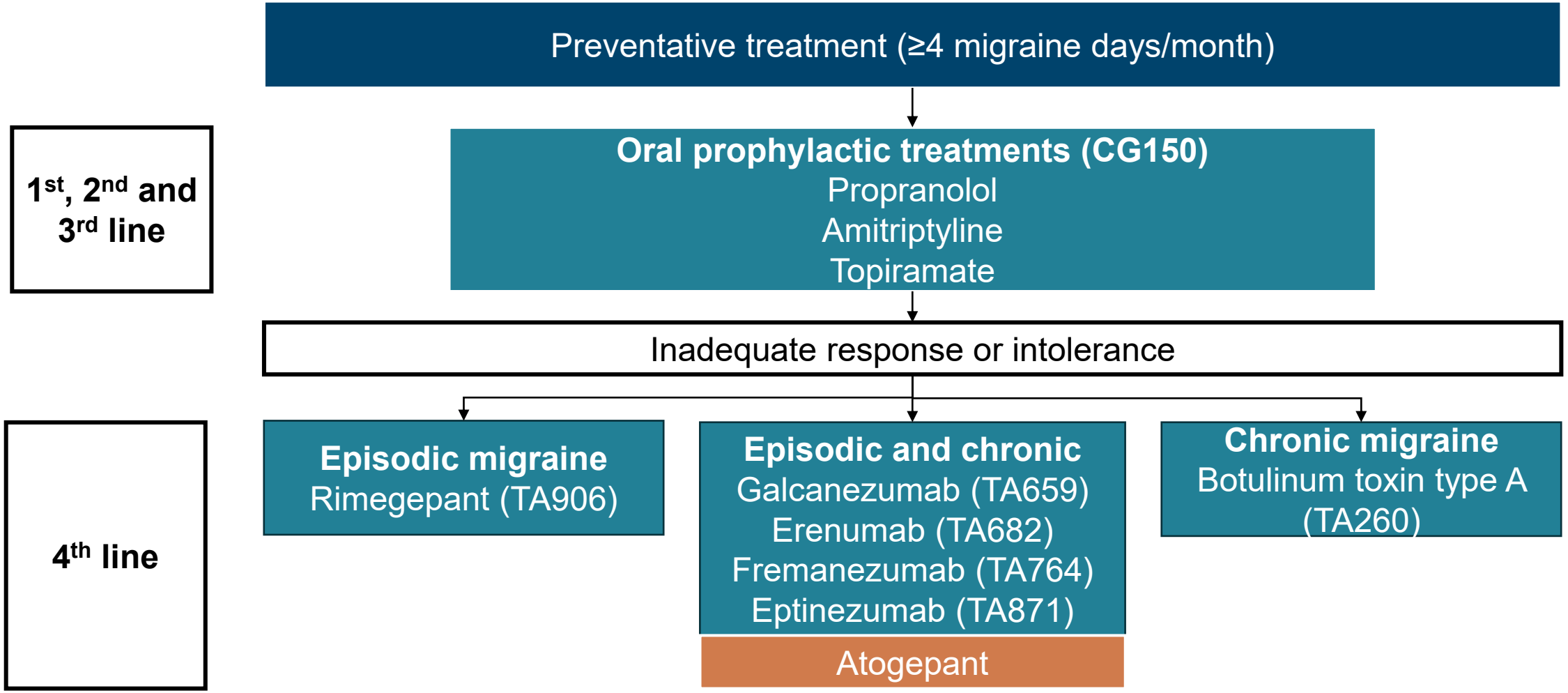
Equality considerations

- Migraine can be classified as a disability under Equality Act (2010)
- Healthcare professionals stated that migraine is more common in women (22%) compared to men (8%)
- Atogepant, which is administered orally, is unlikely to raise specific issues of inequality
- Oral treatments may help reduce inequity in access for those patients using subcutaneous or intravenous formulations at a hospital
- **Clinical expert**: Patients may not be under the care of a specialist so may not have access to atogepant
- **Patient expert**: A patient organisation stated that appropriate treatments need to be available for everyone including those who cannot self-administer due to physical, cognitive or other disability, are needle-phobic and who may have side effects

Are there any equality issues relevant to the potential recommendations?

Treatment pathway

Atogepant positioned as an option for people with ≥3 prior preventative treatments



Atogepant (Aquipta, AbbVie)

Marketing authorisation	Granted in August 2023 Indicated for prophylaxis of migraine in adults who have at least 4 migraine days per month • Company submission covers subset: when 3 or more preventative treatments have failed
Mechanism of action	CGRP receptor antagonist
Administration	Oral tablet, once daily
Price	• List price is £463.69 per 28-tablet pack • There is a confidential patient access scheme

Abbreviations: CGRP, calcitonin gene-related peptide

Key issues

Issue	ICER impact
Comparators – Should botulinum toxin A, rimegepant and eptinezumab be included as comparators?	Large
Network meta-analyses – Which population should be used for the NMAs in episodicand chronic migraine? Overall or 3+TF?	Large
Network meta-analyses – Which analyses are most appropriate for the NMAs?	Large
Monitoring costs - Should additional monitoring costs be included?	Small
Injection-related disutility - Should injection-related disutility be included for comparators administered subcutaneously?	Small
Mean MMDs – Should responder mean MMDs be restricted to 1 or 0?	Small
Long-term discontinuation - Which rate of long-term discontinuation is more appropriate? 3.59% (company) or 0.44% (EAG)?	Large
Uncertainty arising from lack of direct comparative evidence, and differences between studies used in the NMA, e.g. clinical and methodological differences	Unknown

Abbreviations: NMA, network meta-analysis; 3+TF, ≥3 prior preventive treatments have failed; MMD, monthly migraine days; ICER, incremental cost-effectiveness ratio

Key issue: Comparators

Company excluded botulinum toxin A, rimegepant and eptinezumab

Background

- Rimegepant (episodic migraine only, TA906) and eptinezumab (TA871) have been recently recommended
- Botulinum toxin A recommended in chronic migraine only (TA260)

Company

- Doesn't consider rimegepant and eptinezumab established practice in NHS
- Eptinezumab uptake expected to be slow as set up of services required for infusion in clinic – likely to be reserved for people with severe migraine attacks or unable to use subcutaneous treatments
- Extensive waiting lists and need to travel for botulinum toxin A means use is decreasing
  - Not considered comparator in eptinezumab appraisal (TA871)

EAG comments

- Clinical advice that botulinum toxin A still relevant and there can be waiting lists for mAbs too
- Clinical advice that rimegepant likely to become important comparator as it is another oral option, while there was less concern about eptinezumab as a comparator
- Has updated NMAs and economic model to include botulinum toxin A, rimegepant and eptinezumab

To note: Botulinum toxin A was included as comparator in appraisals for erenumab, fremenazumab and galcanezumab. Eptinezumab was appraised as a cost comparison.

Should botulinum toxin A, rimegepant and eptinezumab be included as comparators?

Abbreviations: mAbs, monoclonal antibodies; NMA, network meta-analysis

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Key clinical trials – results*

Clinical trial outcomes	Episodic migraine				Chronic migraine	
	CGP-MD-01 (n=355)	ADVANCE (n=436)	ELEVATE mITT ([redacted])	ELEVATE 3+TF ([redacted])	PROGRESS mITT (n=502)	PROGRESS 3+TF ([redacted])
CFB MMD, mean difference (95% CIs)	**-0.70** (-1.35 to -0.06) ¶**	**-1.7** (-2.3 to -1.2)**	[redacted]	[redacted]	**-1.82** (-2.89 to -0.75)**	[redacted]
Reduction in mean MMDs ≥30%, OR (95% CIs)	N/A	N/A	N/A	N/A	[redacted]	[redacted]
Reduction in mean MMDs ≥50%, OR (95% CIs)	1.42 (1.00 to 2.03)	**3.8** (2.6 to 5.7)**	[redacted]	[redacted]	**2.04** (1.38 to 3.00)**	[redacted]
CFB acute MUDs, mean difference (95% CIs)	**-1.11** (-1.68 to -0.54)**	**-1.5** (-2.0 to -1.0)**	[redacted]	[redacted]	**−2.13** (−3.13 to −1.13)**	[redacted]

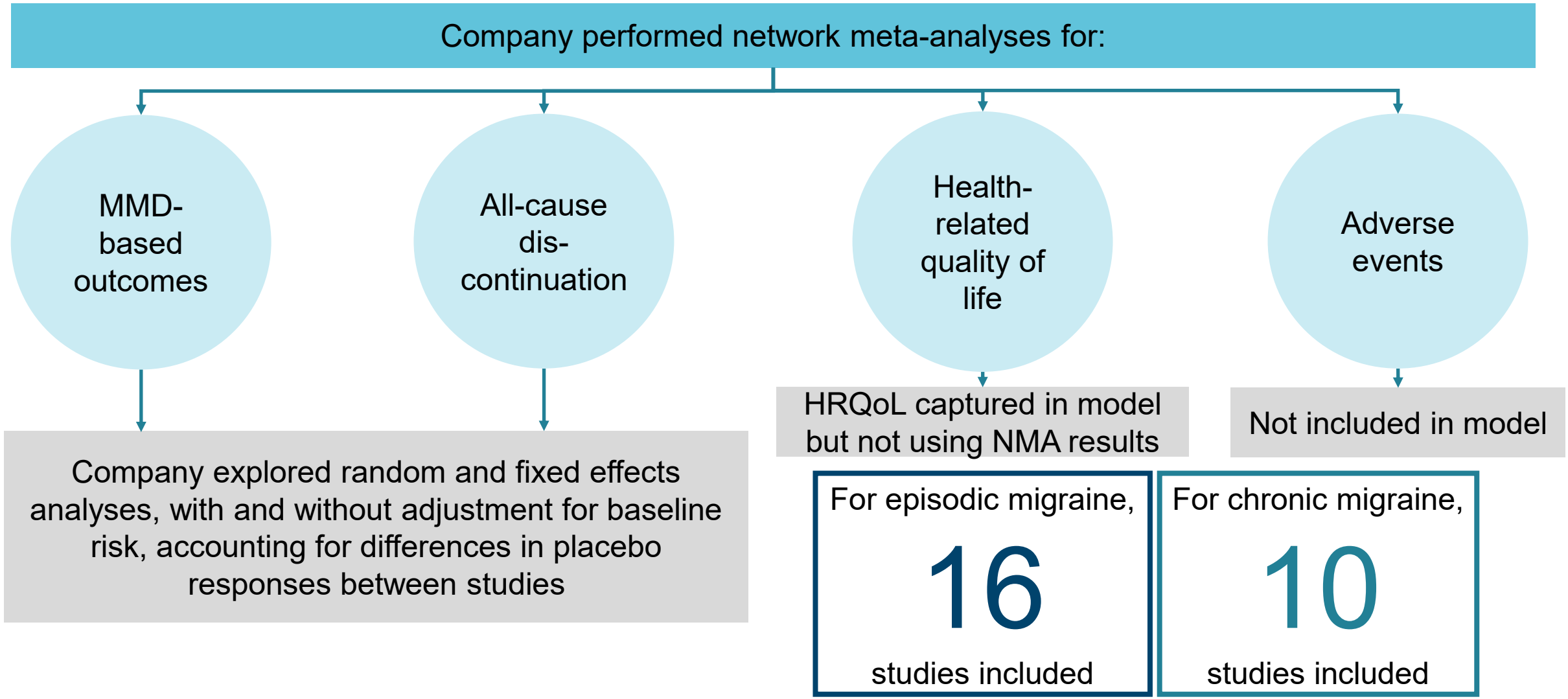
****indicates statistically significant results;** ¶P=0.0325

*Link to Key clinical trials - designs

Abbreviations: OR, odds ratio; CFB, change from baseline; MMD, monthly migraine days; MUD; medication use days; mITT, modified intention to treat population

Network meta-analysis

Company's NMA methods



Abbreviations: NMA, network meta-analysis; MMD, monthly migraine days

Key issue: Network meta-analyses – population*

For MMD-related outcomes in episodic migraine, company uses subgroup population

Company

- For NMAs of monthly migraine day (MMD)-related outcomes in **episodic** migraine (EM), company uses subgroup of trials: people for whom 3 previous treatments have failed (3+TF)
  - Relevant to decision problem and ELEVATE was stratified for this subgroup
- For **chronic** migraine, company uses overall population

EAG comments

- Although ELEVATE is stratified for the 3+TF subgroup, comparator trials are not and baseline characteristics for the subgroup are not well reported
- Scarce data in the subgroup – 1 study for each comparison and smaller sample sizes
- EAG received clinical advice that there are no concerning differences between subgroup and overall population of ELEVATE
- Note that adjusted NMA models did not converge in the 3+ TF subgroup for MMD-related outcomes
- Prefer to use overall population
- Some differences in cost-effectiveness results

Note: 3+TF subgroup used for decision-making in previous migraine appraisals, except rimegepant**

Which population should be used for the NMAs in episodic and chronic migraine?

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Abbreviations: NMA, network meta-analysis; MMD, monthly migraine days

** Updated after committee meeting

*Link to ELEVATE baseline characteristics

Key issue: Network meta-analyses – models*

Company prefers random effects unadjusted NMAs, EAG preferences differ

Background

- Company uses **random effects, unadjusted** NMAs for all outcomes
  - Company considers heterogeneity exists amongst studies, so RE analyses are appropriate
- Differing placebo effects were observed in the included trials, so company explored adjusting for this
  - However, considered that adjusting did not substantially improve model fit
- EAG prefer some alternative analyses described in table below - based on model fit, as well as impact on between-study standard deviation

Analysis	EAG preference	Reason
EM MMD-related outcomes	RE adjusted (overall population)	Between-study heterogeneity reduced with adjustment, or very little difference in between-study heterogeneity and other model fit statistics
EM treatment discontinuation	RE adjusted	As above
CM change from baseline in MMDs	RE adjusted	As above
CM ≥ 50% MMD reduction	RE adjusted	As above
CM ≥ 30% MMD reduction	FE unadjusted	Insufficient data to inform between-study heterogeneity in the RE analysis

Which analyses are most appropriate for the NMAs?

Abbreviations: NMA, network meta-analysis; MMD, monthly migraine days; RE, random effects; FE, fixed effects

*See appendix: Network meta-analysis methods

Network meta-analyses – results, episodic migraine (1)

Company and EAG prefer different models

Atogepant 60 mg once daily vs	Company-preferred NMA (unadjusted)	EAG-preferred NMA (adjusted, overall population)
CFB in MMD, mean difference (95% CrI) (negative results favour atogepant)		
Erenumab	[redacted]	[redacted]
Fremanezumab 225 mg	[redacted]	[redacted]
Fremanezumab 675 mg	[redacted]	[redacted]
Galcanezumab	[redacted]	[redacted]
Rimegepant	-	[redacted]
Eptinezumab 100 mg	-	[redacted]
Eptinezumab 300 mg	-	[redacted]
≥50% reduction in MMDs, odds ratio (95% CrI) (results above 1 favour atogepant)		
Erenumab	[redacted]	[redacted]
Fremanezumab 225 mg	[redacted]	[redacted]
Fremanezumab 675 mg	[redacted]	[redacted]
Galcanezumab	[redacted]	[redacted]
Rimegepant	-	[redacted]
Eptinezumab 100 mg	-	[redacted]
Eptinezumab 300 mg	-	[redacted]

Abbreviations: CFB, change from baseline; MMD, monthly migraine day; NMA, network meta-analysis

Network meta-analyses – results, episodic migraine (2)

Company and EAG prefer different models

Atogepant 60 mg once daily vs	Company-preferred NMA (unadjusted)	EAG-preferred NMA (adjusted, overall population)
CFB in acute MUDs, mean difference (95% CrI) (negative results favour atogepant)		
Erenumab	-	[redacted]
Fremanezumab 225 mg	[redacted]	[redacted]
Fremanezumab 675 mg	[redacted]	[redacted]
Galcanezumab	[redacted]	[redacted]
Rimegepant	-	-
Eptinezumab 100 mg	-	[redacted]
Eptinezumab 300 mg	-	[redacted]

****indicates that the 95% credible intervals do not include the null effect**

Abbreviations: CFB, change from baseline; MUDs, medication use days; NMA, network meta-analysis

Network meta-analyses – results, chronic migraine (1)

Company and EAG prefer different models

Atogepant 60 mg once daily vs	Company-preferred NMA (unadjusted)	EAG-preferred NMA (adjusted except when specified)
CFB in MMD, mean difference (95% CrI) (negative results favour atogepant)		
Erenumab	[redacted]	[redacted]
Fremanezumab 225 mg	[redacted]	[redacted]
Fremanezumab 675 mg	[redacted]	[redacted]
Galcanezumab	[redacted]	[redacted]
Botulinum toxin type A	[redacted]	[redacted]
Eptinezumab 100 mg	-	[redacted]
Eptinezumab 300 mg	-	[redacted]
≥30% reduction in MMDs, odds ratio (95% CrI) (results above 1 favour atogepant)		
Erenumab	-	-
Fremanezumab	[redacted]	[redacted]
Fremanezumab	[redacted]	[redacted]
Galcanezumab	[redacted]	[redacted]
Botulinum toxin type A	-	-
Eptinezumab 100 mg	-	-
Eptinezumab 300 mg	-	-

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Abbreviations: CFB, change from baseline; MMDs, monthly migraine days; NMA, network meta-analysis

*Unadjusted analyses

Network meta-analyses – results, chronic migraine (2)

Company and EAG prefer different models

Atogepant 60 mg once daily vs	Company-preferred NMA (unadjusted)	EAG-preferred NMA (adjusted except when specified)
≥50% reduction in MMDs, odds ratio (95% CrI) (results above 1 favour atogepant)		
Erenumab	[redacted]	[redacted]
Fremanezumab 225 mg	[redacted]	[redacted]
Fremanezumab 675 mg	[redacted]	[redacted]
Galcanezumab	[redacted]	[redacted]
Botulinum toxin type A	[redacted]	[redacted]
Eptinezumab 100 mg	-	[redacted]
Eptinezumab 300 mg	-	[redacted]
CFB in acute MUDs, mean difference (95% CrI) (negative results favour atogepant)		
Erenumab	[redacted]	[redacted]
Fremanezumab 225 mg	[redacted]	[redacted]
Fremanezumab 675 mg	[redacted]	[redacted]
Galcanezumab	[redacted]	[redacted]
Botulinum toxin type A	[redacted]	[redacted]
Eptinezumab 100 mg	-	[redacted]
Eptinezumab 300 mg	-	[redacted]

NICE

Abbreviations: MMDs, monthly migraine days; MUDs, medication use days

*Unadjusted analyses

Key issue: Uncertainty in evidence

No direct evidence and issues with NMAs

Background

- There is no direct evidence comparing atogepant with any of the comparators
- Company performed network meta-analyses to compare the treatments
- Differences between trials included in the NMA lead to uncertainty

EAG comments on differences between trials

Study populations and concomitant treatments

- Some focused on patients with 2-4 prior treatment failures, others did not require prior treatment failures
- Some allowed concomitant preventive treatments, some did not
- Some difference between baseline MMDs although EAG unsure whether this would impact NMAs

Outcome definitions and time-points

- Data for MMD-related and HRQoL outcomes most reported at 12 weeks or average across weeks 1-12, but some followed up until 24/26 weeks or reported an average across wks 9-12
- Variation in definition of endpoints across trials e.g. length of time required for a migraine day to be confirmed
- Most studies used mean values from least squares regression for change from baseline outcomes, but some did not
- Some differences in approach to missing data

Placebo rate

- Differences an issue particularly for MMD-related outcomes
- EAG's preference in most cases for random effects analyses adjusted for baseline risk should reduce impact of differences

Abbreviations: NMA, network meta-analysis; MMD, monthly-migraine days; HRQoL, health-related quality of life

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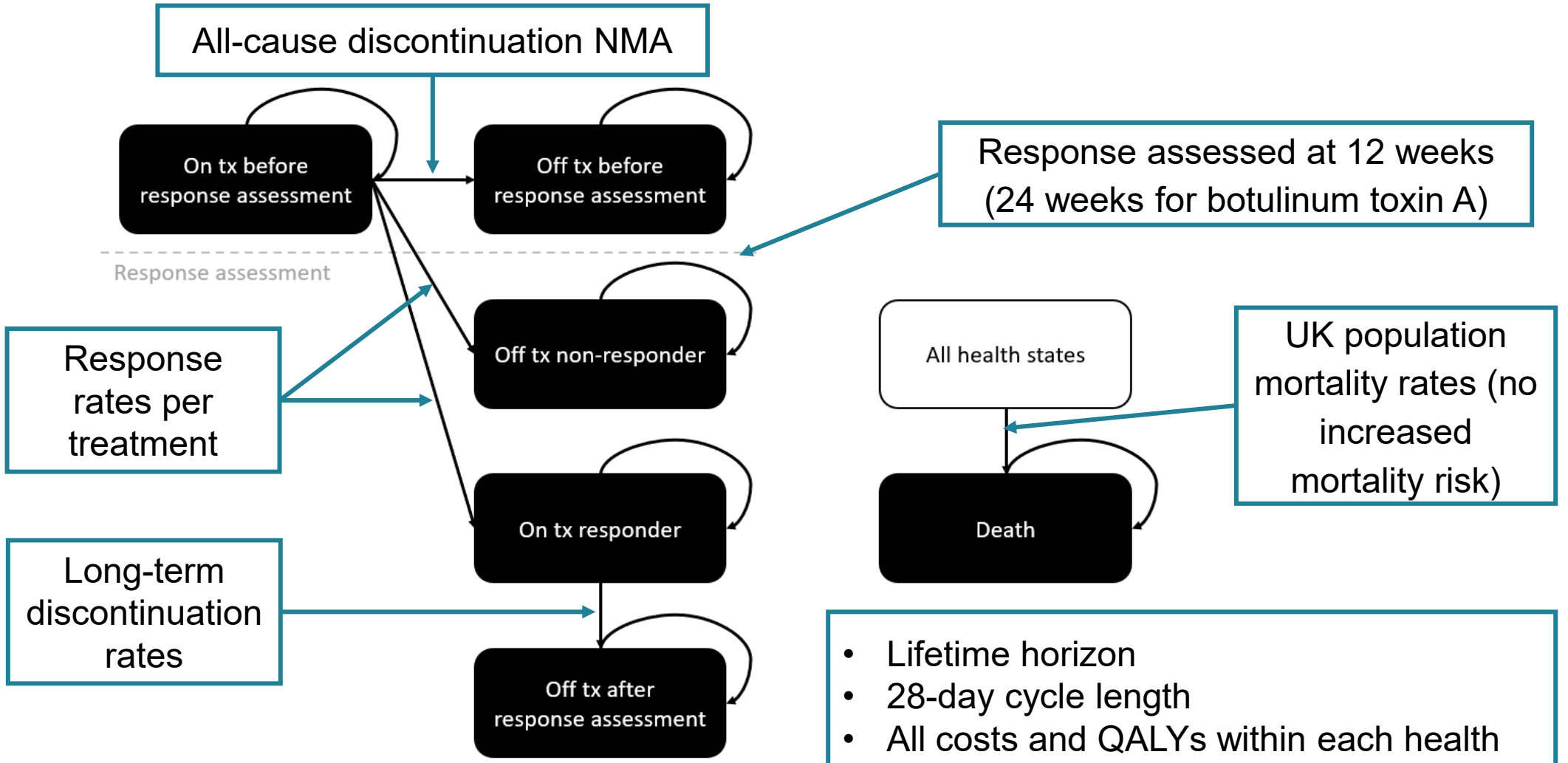
Model structure*

Company's semi-Markov state transition model



Abbreviations: Tx, treatment; NMA, network meta-analysis; QALY, quality-adjusted life year; MMD, monthly migraine days

*Link to Company's model overview

Key issue: Additional monitoring costs*

EAG considers monitoring costs are duplicated in model

Company

- Healthcare resource use based on MMDs, sourced from National Health and Wellness Survey
  - Includes neurologist and GP visits
- In base case CGRP mABs and atogepant were assumed to be initiated in secondary care
- Additional costs above those included in healthcare resource use:
  - 100% headache specialist for CGRP mAbs
  - 50:50 split of headache specialist/general neurologist for atogepant
  - Clinical follow-ups are assumed to be conducted by a GP for atogepant and a headache specialist for CGRP mAbs

EAG comments

- Removes additional costs as considers to be double counting
- Additional monitoring costs were not included in the committee's preferred model for previous migraine appraisals

Should additional monitoring costs be included?

*Link to Health state resource use

Abbreviations: CGRP, calcitonin gene-receptor peptide; mAbs, monoclonal antibodies; MMD, monthly migraine days

Key issue: Injection-related disutility

EAG considers source of injection-related utility is unreliable

Company

- Includes disutility for subcutaneous injections for comparators

EAG comments

- Source paper does not show the injection-related disutility to be statistically significant for subcutaneous injections and the utility values are not based on EQ-5D
- EAG removes injection-related disutility in its base case results
- Not included in previous migraine evaluations

Should injection-related disutility be included for comparators administered subcutaneously?

Key issue: Treatment effectiveness in economic model*

EAG amends mean MMD restriction and uses alternative source for long-term discontinuation

Mean MMDs

Company

- Health-state related quality of life determined by MMDs
- **Mean MMDs** applied to the start and end of a transition to each health state
- Treatment-specific non-responder MMDs assumed equal across active treatments
- Treatment-specific CFB values derived from NMA and used to obtain treatment-specific MMDs for comparator treatments

EAG comments

- To prevent clinically implausible MMD results from NMA, company restricted mean MMDs for responders from falling below 1
- EAG agreed negative values are implausible but considers restriction should be 0 (only affects EM)

*Link to Treatment effectiveness – monthly migraine days

Long-term discontinuation

Company

- **Discontinuation rate** for all active treatments of 3.59% per cycle, based on LTS-302 study – long-term safety and tolerability study of atogepant in episodic migraine
- Calculation assumes around 173/546 patients discontinue every 291.6 days: 3.59% per cycle

EAG comments

- 173 is the total number of patients who discontinue, and 291.6 is mean time to discontinuation, so company's method is implausible and will significantly over-estimate long-term discontinuation
- EAG use long-term discontinuation rate from galcanezumab evaluation (TA659 - 0.44%)
- NB. 2.38% used in erenumab evaluation

Should responder mean MMDs be restricted to 1 or 0?
Which rate of long-term discontinuation is more appropriate? 3.59% (company) or 0.44% (EAG)?

Abbreviations: MMD, monthly migraine day; CFB, change from baseline; NMA, network meta-analysis; EM, episodic migraine

Summary of company and EAG base case assumptions

Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
NMA	Excluded rimegepant and eptinezumab. Used 3+TF population for EM. Used random effects, unadjusted NMAs for all outcomes.	Included rimegepant and eptinezumab. Used mITT population for EM. Alternative uses of random/fixed effects and adjusted/unadjusted models.
Responder MMD	Added restriction so that mean MMD figures resulting from NMAs could not be below 1	Responder MMD restricted to 0 (only impacts EM)
Long-term discontinuation	3.59% (rate per cycle), calculated from LTS-302 study	0.44%, taken from TA659
Monitoring costs	Additional costs included	Additional costs excluded
Acute medication costs	Sourced from eMIT (older version)	Updated with July-Dec 22 eMIT costs
Injection-related disutility	Included	Excluded

EAG also corrected an error in life tables used by company - sourced from ONS.

Abbreviations: NMA, network meta-analysis; EM, episodic migaine; 3+TF, ≥3 prior preventive treatments have failed; mITT, modified intention to treat; MMD, monthly migraine days; eMIT, electronic market information tool

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

Notes on the cost-effectiveness results

- Incremental QALYs are small
- When ICERs are calculated, some results show atogepant to be better, some show atogepant to be worse than comparators
- A summary of net health benefits is presented on the following slides (assuming **all confidential discounts** are applied)

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Episodic migraine – company base case and EAG scenarios

Individual scenarios have little impact on cost-effectiveness

Impact of EAG scenario analyses

		Net health benefit at £20,000 (QALYs)					
No	**Scenario (applied to company base case)**	**Galcanezumab**	**Erenumab**	**Fremanezumab 225**	**Fremanezumab 675**	**Rimegepant**	**Eptinezumab**
	Company base case (corrected)	**+**	**+**	**+**	**+**	**N/A**	**N/A**
1	Remove monitoring costs	+	+	+	+	N/A	N/A
2	Remove injection-related disutility	+	+	+	+	N/A	N/A
3	Alternative long-term discontinuation	+	+	+	+	N/A	N/A
4	Restrict MMD to 0	+	+	+	+	N/A	N/A
5	Updates to the NMA	+	+	+	+	+	+
1-5	**EAG base case**	**+**	**-**	**-**	**+**	**-**	**-**

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; MMD, monthly migraine days; NMA, network meta-analysis; SW, south-west quadrant

Chronic migraine – company base case and EAG scenarios

Individual scenarios have some impact on cost-effectiveness

Impact of EAG scenario analyses

		Net health benefit at £20,000 (QALYs)					
No	**Scenario (applied to company base case)**	**Galcanezumab**	**Erenumab**	**Fremanezumab 225**	**Fremanezumab 675**	**Botulinum toxin A**	**Eptinezumab**
	Company base case (corrected)	**+**	**+**	**+**	**+**	**+**	**N/A**
1	Remove monitoring costs	+	-	+	+	+	N/A
2	Remove injection-related disutility	+	+	+	+	-	N/A
3	Alternative long-term discontinuation	+	-	+	+	-	N/A
4	Updates to the NMA	+	+	+	+	+	+
1-4	**EAG base case**	**+**	**-**	**+**	**+**	**-**	**-**

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; MMD, monthly migraine days; NMA, network meta-analysis

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Mean MMDs – Should responder mean MMDs be restricted to 1 or 0?	Small
Long-term discontinuation - Which rate of long-term discontinuation is more appropriate? 3.59% (company) or 0.44% (EAG)?	Large
Uncertainty arising from lack of direct comparative evidence, and differences between studies used in the NMA, e.g. clinical and methodological differences	Unknown

Abbreviations: NMA, network meta-analysis; 3+TF, ≥3 prior preventive treatments have failed; MMD, monthly migraine days; ICER, incremental cost-effectiveness ratio

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Thank you.

Atogepant for preventing migraine [ID5090]

Supplementary appendix

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Patient perspectives

Patients value an effective, accessible treatment

Submission from The Migraine Trust

- Patients want treatment that specifically targets migraine symptoms with minimal side effects
- Effective treatment improves the quality of life and ability to function for people with migraine, with impact on work, education, family and social life
- A well tolerated preventive treatment could reduce reliance on acute and over-the-counter medicines
- Preventive treatments such as mAbs and Botox have been helpful for many but access has been inadequate and unequal across country
- Atogepant may be beneficial for people who cannot self-inject or tolerate multiple injections, are needle-phobic, or people who can't access specialist headache clinics
- Availability of treatment in primary care would enable more equitable access and reduce costs – access to treatment from any headache specialist clinician should be considered

Link to Patient and clinical perspectives

Clinical perspectives

Atogepant could provide advantages but is difficult to compare to current treatments

Submissions from Association of British Neurologists and British Society for the Study of Headache

- Comparison between atogepant and other treatments is difficult due to differences in study design and placebo rates
- Patients were excluded from ADVANCE atogepant trial if previously had more than 4 other preventive treatments from 2 other classes – this is the group of patients in whom a new treatment is likely to be used
- Atogepant is easy to administer, and data suggests a favourable tolerability and safety profile
- Could be used in community-based clinics supported by specialist consultants

Link to Patient and clinical perspectives

Recent NICE appraisals for preventing migraine

Technology appraisal	Drug	Recommendation
TA906 (July 2023)	Rimegepant	Recommended for adults with at least 4 and fewer than 15 migraine attacks per month (episodic migraine) when at least 3 preventive drug treatments have failed. Stopping rule after 12 weeks.
TA871 (March 2023)	Eptinezumab	Recommended for adults with 4 or more migraine days a month when at least 3 preventive drug treatments have failed. Stopping rule after 12 weeks.
TA764 (February 2022)	Fremanezumab	Recommended for adults with 4 or more migraine days a month when at least 3 preventive drug treatments have failed. Stopping rule after 12 weeks.
TA682 (March 2021)	Erenumab	Recommended for adults with 4 or more migraine days a month when at least 3 preventive drug treatments have failed. Stopping rule after 12 weeks.
TA659 (Nov 2020)	Galcanezumab	Recommended for adults with 4 or more migraine days a month when at least 3 preventive drug treatments have failed. Stopping rule after 12 weeks.
TA260 (June 2012)	Botulinum toxin type A	Recommended for chronic migraine. Stopping rule based on response to treatment.

Decision problem (1)

Some differences between NICE scope and company submission

Population, intervention and comparators from the scope

	Final scope	Company	EAG comments
Population	Adults with migraine who have 4 or more migraine days a month, in whom at least 3 preventive drug treatments have failed	In line with final scope	Note: narrower than marketing authorisation.
Intervention	Atogepant 60 mg	In line with final scope	No issues.
Comparators	•Botulinum toxin type A (CM only) •Galcanezumab •Erenumab •Fremanezumab •Eptinezumab (subject to NICE evaluation) •Rimegepant (subject to NICE evaluation)	Botulinum toxin type A not included due to NHS capacity issues and waiting lists meaning most patients are initiated on CGRP mAbs. Rimegepant and eptinezumab not included as recent TA recommendations mean market share is low.	EAG included all treatments in scope.

Abbreviations: CM, chronic migraine; CGRP, calcitonin gene-related peptide; mAbs, monoclonal antibodies

Decision problem (2)

Some differences between NICE scope and company submission

Outcomes from the scope

	Final scope	Company	EAG comments
Outcomes	• Change in frequency of migraine days per month • Change in frequency of headache days per month • Change in severity of headaches and migraines • Change in number of cumulative hours of headache or migraine on headache or migraine days • Changes in acute pharmacological medication given • Adverse effects of treatment • Health-related quality of life	In line with final scope.	No issues.

Key clinical trials - designs

Clinical trial designs

	CGP-MD-01 (n=795*)	ADVANCE (n=873*)	ELEVATE ([redacted]	PROGRESS (n=755*)
Design	Phase 2b/3 RCT	Phase 3 RCT	Phase 3 RCT	Phase 3 RCT
Population	Adults with episodic migraine, when up to 2 preventive treatments failed	Adults with episodic migraine, when up to 4* preventive treatments failed	Adults with episodic migraine when 2-4 preventive treatments failed, including pre-specified subgroup when ≥3 treatments have failed (3+TF)	Adults with chronic migraine, up to 4 prior preventive treatments permitted
Arms	Atogepant v placebo	Atogepant v placebo	Atogepant v placebo	Atogepant v placebo
Used in model?	Company: no EAG: yes	Company: no EAG: yes	Yes	Yes

*corrected after committee meeting

Link to Key clinical trials – results

Abbreviations: RCT, randomised controlled trial; *mITT, modified intention to treat population

ELEVATE baseline characteristics

Similar between overall mITT population and 3+TF subgroup

Baseline characteristics – comparing overall population with 3+TF subgroup

	Overall mITT population		3+TF subgroup	
Demographics	**Atogepant (N=[redacted])**	**Placebo (N=[redacted])**	**Atogepant (N=[redacted])**	**Placebo (N=[redacted])**
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Female, %	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Race group, %				
White	[redacted]	[redacted]	[redacted]	[redacted]
All other races	[redacted]	[redacted]	[redacted]	[redacted]
Region, %				
North America	[redacted]	[redacted]	[redacted]	[redacted]
Europe	[redacted]	[redacted]	[redacted]	[redacted]
Migraine History				
MMDs, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
MHDs, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Monthly acute MUDs, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
MSQ-RFR, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SD, standard deviation; MMDs, monthly migraine days; MHDs, monthly headache days; MUDs, monthly medication days; MSQ-RFR, Migraine-specific quality of life role function – restrictive domain score; mITT, modified intention-to-treat

*Link to Key issue: Network meta-analyses – population

Network meta-analysis methods (1)

Company used random effects unadjusted models for all outcomes

Outcome	Model	DIC - Episodic migraine, 3+ TF subgroup	DIC – Episodic migraine, overall mITT population (EAG NMAs with rimegepant and eptinezumab included)
Change from baseline in monthly migraine days (MMD)	Fixed effects (FE)	[redacted]	[redacted]
	Random effects (RE)	[redacted]	[redacted]
	FE adjusted	Did not converge	[redacted]
	RE adjusted	Did not converge	[redacted]
≥50% reduction in MMDs	FE	[redacted]	[redacted]
	RE	[redacted]	[redacted]
	FE adjusted	Did not converge	[redacted]
	RE adjusted	Did not converge	[redacted]
Change from baseline in monthly acute medication use days	FE	[redacted]	[redacted]
	RE	[redacted]	[redacted]
	FE adjusted	Did not converge	[redacted]
	RE adjusted	Did not converge	[redacted]

NICE *Company-preferred model, ^EAG-preferred model – link to Key issue: Network meta-analyses - models

Abbreviations: DIC, deviance information criterion; mITT, modified intention-to-treat; 3+TF, ≥3 prior preventive treatments have failed

NMA methods (2)

Abbreviations: DIC, deviance information criterion; mITT, modified intention-to-treat

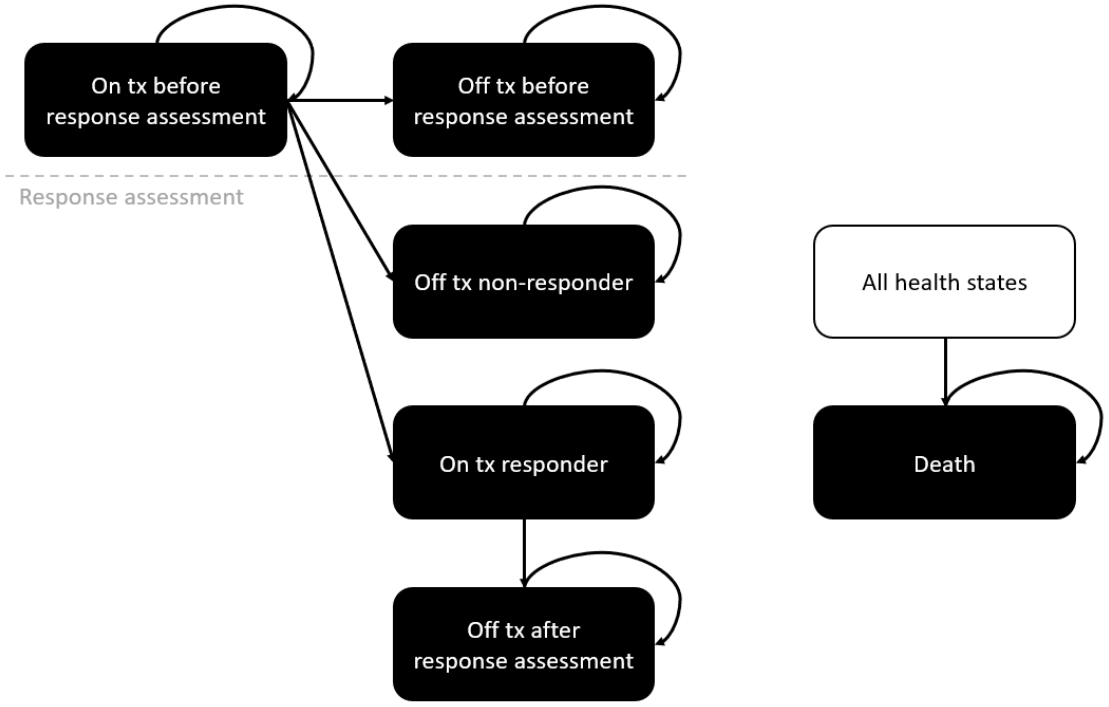
Company used random effects unadjusted models for all outcomes

Outcome	Model	DIC - Chronic migraine: overall mITT population	DIC – Chronic migraine: overall mITT population, with eptinezumab studies included
Change from baseline in monthly migraine days (MMD)	Fixed effects (FE)	[redacted]	[redacted]
	Random effects (RE)	[redacted]	[redacted]
	FE adjusted	[redacted]	[redacted]
	RE adjusted	[redacted]	[redacted]
≥30% reduction in MMDs	FE	[redacted]	[redacted]
	RE	[redacted]	[redacted]
	FE adjusted	[redacted]	[redacted]
	RE adjusted	[redacted]	[redacted]
≥50% reduction in MMDs	FE	[redacted]	[redacted]
	RE	[redacted]	[redacted]
	FE adjusted	[redacted]	[redacted]
	RE adjusted	[redacted]	[redacted]
Change from baseline in monthly acute medication use days	FE	[redacted]	[redacted]
	RE	[redacted]	[redacted]
	FE adjusted	[redacted]	[redacted]
	RE adjusted	[redacted]	[redacted]

*Company-preferred model, ^EAG-preferred model – link to Key issue: Network meta-analyses - models

Company's model overview

Model structure



- Technology affects **costs** by:
  - Reducing number of MMDs, which reduces healthcare costs
  - Discontinuation rules
  - Different unit price
  - Administration – no additional costs for oral tablet
- Technology affects **QALYs** by:
  - Reducing number of MMDs (mAbs are similarly effective so resulting QALYs are similar)
- Assumptions with greatest ICER effect:
  - Unit drug cost
  - Response
  - Long-term discontinuation

Link to Model structure

Abbreviations: MMDs, monthly migraine days; mAbs, monoclonal antibodies; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio

How company incorporated evidence into model

Input and evidence sources

Input	Assumption and source
Baseline characteristics	Age, sex, baseline MMDs and monthly acute MUDs from ADVANCE and ELEVATE for EM, and PROGRESS for CM.
Treatment effect	Proportion of patients with 50% reduction from baseline in MMD for EM (NMA) Proportion of patients with 30% reduction from baseline in MMD for CM (NMA)
Utilities	Response-specific utility values applied per MMD, derived by mapping MSQ v2.1 values from ELEVATE and PROGRESS to EQ-5D. Age-related utility decrements included from Health Survey for England.
Costs	Medication costs from MIMS/eMIT Administration costs for injectable drugs from PSSRU Drug monitoring and disease management costs from PSSRU MUD outcomes from NMAs
Resource use	Resource use per MMD based on NHWS data.

Abbreviations, EM, episodic migraine; CM, chronic migraine; MMD, monthly migraine days; NMA, network meta-analysis; MIMS, Monthly Index of Medical Specialties; eMIT, electronic market information tool; PSSRU, Personal Social Services Research Unit; MUD, medication use days; NHWS, National Health and Wellness Survey

Health state resource use

Healthcare resource use sourced from national survey and based on MMDs

- Health care resource use costs calculated for each health state by multiplying distribution of patients across MMDs by resource use per MMD value (see table) and associated unit costs (sourced from PSSRU)

Healthcare resource use values by MMDs, sourced from National Health and Wellness Survey

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

Link to Key issue: Additional costs and utilities in model

Abbreviations: MMD, monthly migraine days

Treatment effectiveness – monthly migraine days

MMD assumptions made per health state in the company's model

Health state	Base case MMD assumptions	
	Start (as pt enters health state)	End (pt transitions to the below)
On Tx before response assessment	Pooled baseline MMDs	Pooled baseline MMDs
Off Tx before response assessment	Tx-specific non-responder MMDs	Pooled baseline MMDs
Off Tx non-responder	Tx-specific non-responder MMDs	Pooled baseline MMDs
On Tx responder	Tx-specific responder MMDs	Tx-specific responder MMDs
Off Tx after response assessment	Tx-specific responder MMDs	Pooled baseline MMDs
Death	None	

Change from baseline in mean MMDs across the 12-week treatment period

	EM (RE)		CM (RE)	
	Median CFB (95% CrI)	Mean MMDs	Median CFB (95% CrI)	Mean MMDs
Atogepant (reference)	[redacted]	[redacted]	[redacted]	[redacted]
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 225 mg	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 675 mg	[redacted]	[redacted]	[redacted]	[redacted]

- Each MMD frequency incurs a specific utility value and healthcare resource use cost
- Poisson distributions fitted to mean MMD value

Abbreviations: MMD, monthly migraine days; Tx, treatment; EM, episodic migraine; CM, chronic migraine; RE, random effects; CFB, change from baseline; CrI, credible intervals

*Link to Key issue: Treatment effectiveness in economic model

What is the model assuming about the relative treatment effect throughout the time horizon?

Treatment effect persists beyond observed period
(no treatment effect waning)

Treatment effect wanes after observed period, either by:
- choice of extrapolation, OR
- introduction of explicit waning assumption

Is the assumption plausible?

Consider:

1. Is the modelled treatment effect consistent with the observed data?
2. Is clinical trial follow-up long enough to provide estimate of treatment effect waning (also consider observational and real-world data)?
3. Is there evidence to support a sustained treatment effect or effect waning from another technology with same or similar mechanism of action?
4. Does a stopping rule apply? Is treatment effect likely to continue following treatment discontinuation?
5. Are the hazard rates of key clinical inputs plausible? Consider the plots of smoothed empirical time-varying hazard ratios from pivotal trial or MAIC.
6. Are the model outputs plausible? Are they supported by clinical expert opinion?
7. What impact do scenarios of different treatment effect waning assumptions have?

Do not consider:

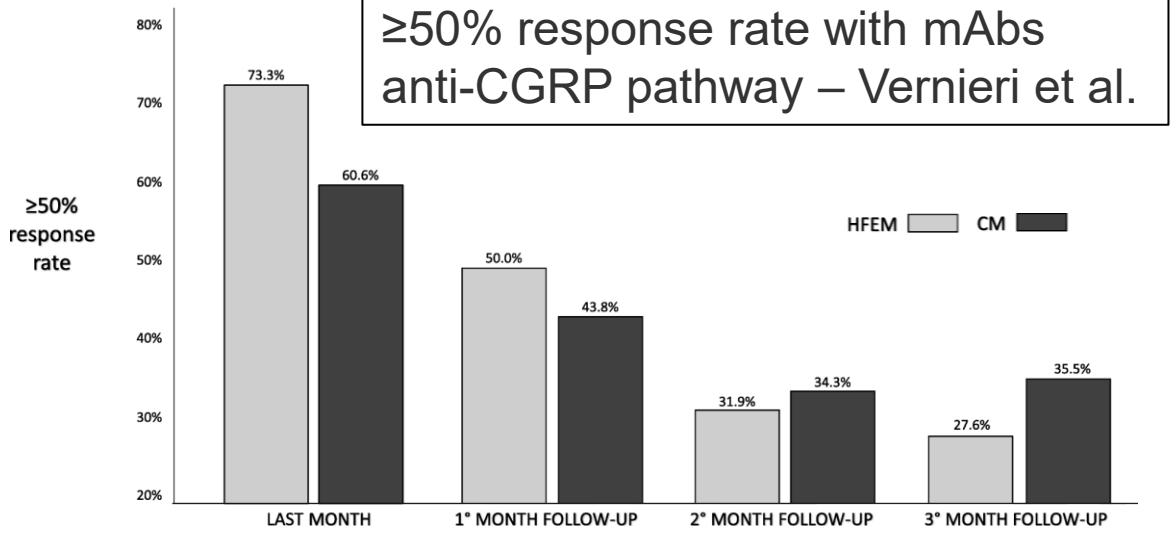
Committee's preferred assumptions from previous appraisals (evidence base varies between each evaluation – consistency with precedent is not required)

Treatment waning in the model

No treatment waning included in company base case

- In the model, when treatment is stopped, there is an immediate return to baseline MMDs i.e. loss of treatment effect
- For people remaining on treatment, the treatment effect is maintained until they stop treatment
- Company states no evidence for treatment effect continuing after discontinuation
- Vernieri et al. 2021 paper suggests benefits from discontinuing CGRP (erenumab and galcanezumab) treatments are lost relatively quickly
- An observational study of erenumab reaffirms this conclusion (Schiano di Cola et.a., 2021)
- A stopping rule applied at 12 weeks for previous evaluations

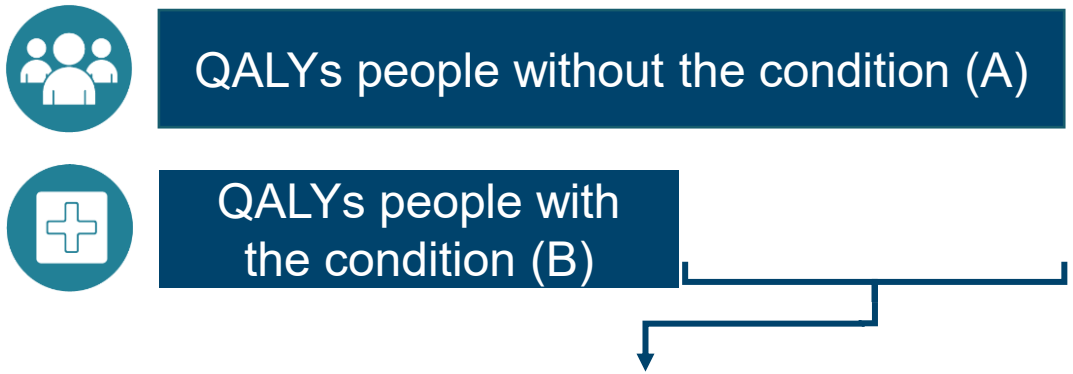
The frequencies of patients with ≥50% response rate with mAbs anti-CGRP pathway – Vernieri et al.



Abbreviations: MMD, monthly migraine day; CGRP, calcitonin gene-related peptide

QALY weightings for severity (1/2)

Severity modifier calculations and components:



Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A
- *Note: The QALY weightings for severity are applied based on **whichever of absolute or proportional shortfall implies the greater severity**. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

Abbreviations: QALY, quality-adjusted life year

QALY weightings for severity (2/2)

Company base case	QALYs of people without condition (based on trial population characteristics)	QALYs with the condition on current treatment	Absolute QALY shortfall (has to be >12)	Proportional QALY shortfall (has to be >0.85)
Episodic migraine				
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]
Chronic migraine				
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]

No severity modifier included by company and nothing further from EAG

NICE

Abbreviations: QALY, quality-adjusted life year