Rimegepant for treating or preventing migraine

Part 1 Slides for public - ACIC information redacted

Technology appraisal committee D - 19th January 2023

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Company: Pfizer

Process: STA 2018

Rimegepant (VYDURA, Pfizer)

Marketing authorisation (MHRA)	Rimegepant is indicated for: • Preventive treatment of episodic migraine in adults who have at least four migraine attacks per month. • Acute treatment of migraine with or without aura in adults. **<u>Each indication will be considered separately</u>**
Mechanism of action	Rimegepant inhibits the action of calcitonin gene related peptide, which is believed to transmit signals that can cause severe pain.
Administration	Tablet, taken orally
Dose	Acute – 75mg, taken as needed, no more than once daily. Prevention – 75mg, taken every other day.
Price	List price per pack: £160 Acute (per attack): £20 Prevention (per month): £300 (assuming 15 tablets). No patient access scheme is currently available.

Abbreviations: MHRA, Medicines and Healthcare products Regulatory Agency

Background on migraines

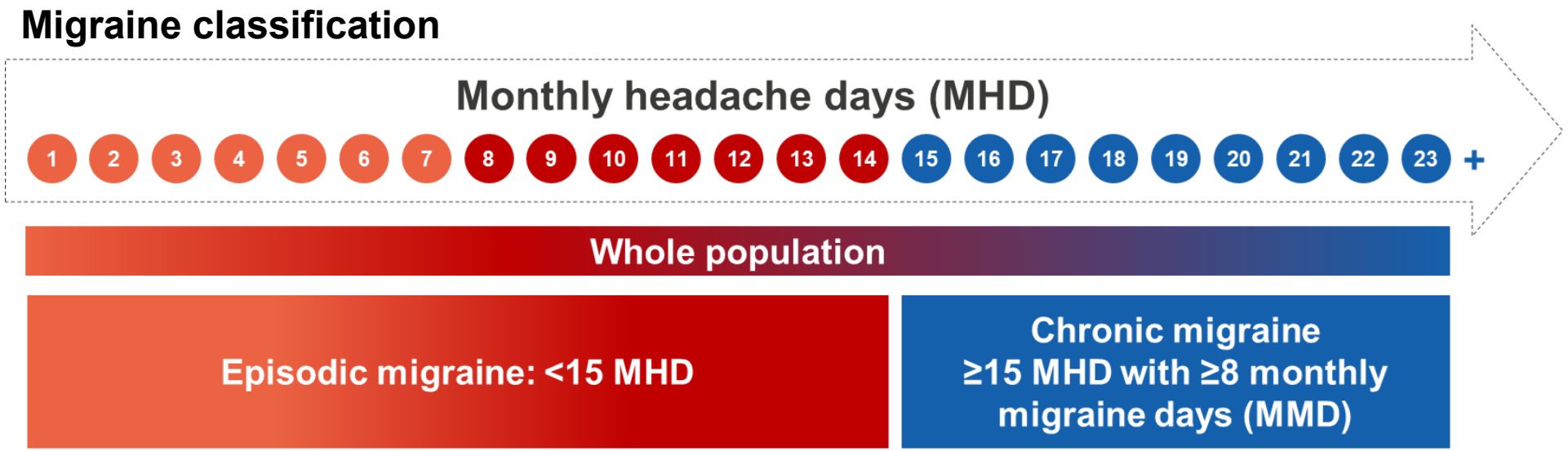
A migraine is a headache disorder with recurring attacks usually lasting 4–72 hours.

Symptoms: Migraines are usually more intense, painful and debilitating than headaches - often accompanied by nausea, vomiting, sensitivity to light/sound.

Causes: Factors triggering attacks can include stress, overtiredness, menstruation, caffeine/alcohol consumption.

Epidemiology: Approximately 190,000 migraine attacks every day in England. Prevalence 5-25% in women; 2-10% in men.

Classification: 1) With or without aura (warning sign of a migraine e.g., flashing lights), 2) episodic or chronic based on frequency.



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Patient perspectives

Rimegepant offers patients a new dual therapy alternative.

Submissions from The Migraine Trust, including nominated patient experts

- Migraines greatly affect the day-to-day lives of people who live with the condition. In particular, it impacts people's wellbeing, relationships, education and employment.
- Common symptoms include headache, aura, sensitivity to light, sound and smells, nausea and dizziness.
- For many, migraines are a genetic condition, affecting 22% of women and 8% of men.
- The difficulty with migraine is that it is a very individual condition in terms of triggers and presentation. As a result, a 'one size fits all' account is difficult.
- Many people find the current acute and preventive migraine treatments available on the NHS unsuitable due to side-effects, contraindications and lack of efficacy in managing symptoms.
- Rimegepant offers potential benefits in terms of not causing medication overuse headache, which can be a significant issue for many people affected by migraine.

"Untreated, my attacks last for 3 days – most of that time in severe/unbearable pain"

"The distinction between chronic and episodic is not as clear cut as is made out and a patient can fluctuate between the two."

"I've been taking Rimegepant since 2021 and I get no side effects and do not experience MOH syndrome or rebound headaches."

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Abbreviations: MOH, medication overuse headache

Clinical perspectives

There is significant unmet need in the acute and preventative treatment of migraines.

Submissions from NHS GP with a special interest in headache, ABN and BASH

- Treatment aims to provide effective and sustained relief of headache and associated symptoms in an acute migraine episodes, and reduce the frequency and severity of migraines.
- There is currently a limited service, with only 15 specialist UK headache centres.
- There are structural differences between episodic and chronic migraines, with co-morbidity much higher in chronic patients.
- Rimegepant is the first treatment that works effectively for acute therapy and as a preventive option. It is also tolerable and safe, reduces A&E visits and requires no setup or training costs for specialist prescribers in primary and acute settings.
- Rimegepant is easy to use, although use of acute and prevention makes it very confusing for the prescriber and patient.
  - ↳ Can it be taken both acutely and preventatively simultaneously?
  - ↳ What happens on days when you have taken a preventer and need relief?

"Rimegepant is the first ever CGRP receptor antagonist that works both as abortive and preventive treatment option."

“Rimegepant could be a very useful addition but the key is to have it available to primary care if the burden of migraine is to be addressed.”

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Abbreviations: ABN, Association of British Neurologists BASH; British Association for the Study of Headaches

Other considerations

Equality considerations

- Frequent and severe migraine is classified as a disability under the 2010 Equality Act.
- Migraines are more common among women than men (5-25% vs 2-10%).
- Migraines are highly prevalent in people aged 18 to 45 years.

Innovation

- First dual indication treatment approved for both acute and preventive treatment of episodic migraine.
- First oral alternative to injectable preventative options, with potential for primary care prescription.
- Clinician noted that there is a need for an alternative oral formulation than currently available and rimegepant is a ‘step-change’ in the management of migraines.

Does the committee consider that there are any relevant equality or health inequality issues that it should consider in its decision making, and if so how?

Acute Migraine

People with or without aura.

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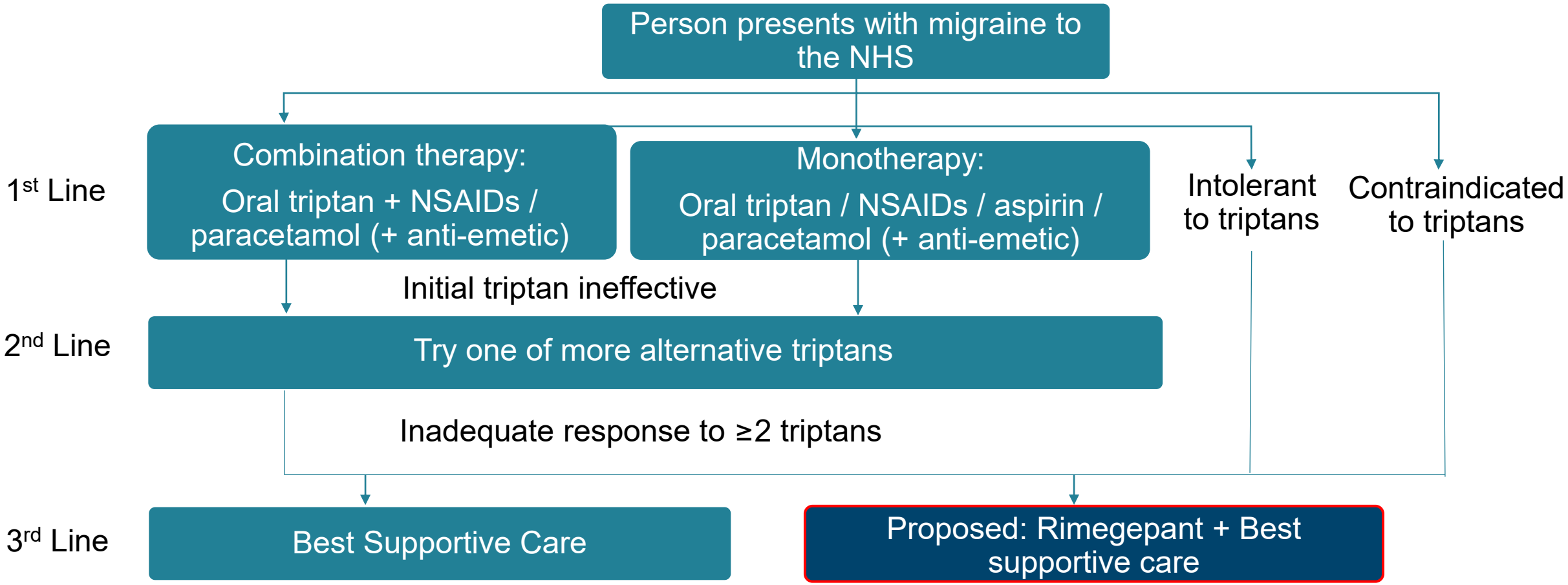
Treatment pathway: acute migraine

Rimegepant is proposed as 3rd line treatment for acute migraines



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Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs

Decision problem: acute migraine

	Final scope	Company	EAG
Population	Adults with Migraine	Adults who have had inadequate symptom relief after taking ≥2 triptans or in whom triptans are contraindicated or not tolerated.	Narrower population is reasonable.
Intervention	Rimegepant		N/A
Comparators	• Best supportive care With or without an anti-emetic: • Oral or non-oral triptan, with or without, paracetamol or NSAID	Best supportive care	Agree with company.
Outcomes	• Reduction in headache pain (including freedom from pain), nausea, vomiting and hypersensitivity • Speed of onset • Freedom from most bothersome symptom • Regain of normal functioning • Prevention of recurrence • Use of rescue medication • Adverse effects • Health-related quality of life		N/A

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drug; N/A, not applicable

Key issues for treating acute migraine

Key Issue	Resolved?	Reason	ICER impact
MMD reductions with rimegepant PRN	No	Different opinions	Large
Baseline MMD distribution	Partially	Different opinions	Small
Inclusion of BHV3000-310 study	Partially	Different opinions	Small
Modelling rimegepant response	No	Unresolvable due to data limitations	Unknown
Trial generalisability	No	Unresolvable due to data limitations	Unknown
Additional issues			
Rimegepant responders discontinuation trajectories	No	Different opinions	Small
Trial population	No	Different opinions	Small

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Abbreviations: MMDs, monthly migraine days; NMA, network meta-analysis; PRN, pro-re-nata

Clinical effectiveness

Acute Migraine

NICE National Institute for Health and Care Excellence

Key clinical trials and outcomes: acute migraine

There are 3 key clinical trials that compare rimegepant to placebo

	BHV3000-301 (n = 1,084)	BHV3000-302 (n = 1,072)	BHV3000-303 (n = 1,351)
Design	Multicentre, randomised, double-blind, placebo-controlled, Phase 3 trial.		
Population	• Adults • 2-8 moderate-to-severe migraine attacks per month • Less than 15 MMD		
Intervention	Rimegepant 75mg		
Comparator	Placebo		
Duration	11 weeks		
Formulation	Tablet	Tablet	Oral dispersible tablet
Primary outcome	• Freedom from pain at 2 hours • Freedom from most bothersome symptom at 2 hours		
Key secondary outcomes	• Reduction in headache pain • Pain relief at 2 hours		
Location	United States		
Used in model?	Yes	Yes	Yes

Abbreviations: MMD, monthly migraine days

Additional clinical trials: acute migraine

There are 2 additional trials that compare rimegepant to placebo

	BHV3000-310 (Asian population) (n = 1,340)	BHV3000-201 (long-term study) (n= 1197)
Design	Multicentre, randomised, double-blind, Phase 3 trial.	Multicentre, open-label, single arm, Phase 2/3 trial
Population	• Adults • 2-8 moderate-to-severe monthly migraine attacks • Less than 15 MMD	• Adults • 2-14 moderate-to-severe monthly migraine attacks
Intervention	Rimegepant 75mg	Rimegepant 75mg
Comparator	Placebo	None
Duration	11 weeks	58 weeks
Formulation	Oral dispersible tablet	Tablet
Primary outcome	• Freedom from pain at 2 hours • Freedom from most bothersome symptom at 2 hours	Safety and tolerability
Key secondary outcomes	• Reduction in headache pain • Pain relief at 2 hours	Post-hoc: change from baseline in mean MMD
Location	Asia	United States
Used in model?	EAG – Yes, Company - No	Yes (long-term parameters)

Additional issue: Trial population

Background

- Decision problem: Adults who had inadequate symptom relief after ≥2 triptans or in whom triptans are contraindicated or not tolerated.
  - ↳ Only 9.3% of people in the 3 pooled RCTs discontinued ≥2 triptans.
- There is a mixed opinion over which trial population should be used in the model.

Company

- Prefer to use subgroup of people who have not responded to ≥2 prior triptans.

EAG

- Prefer full trial population (mITT) despite concerns of generalisability to decision problem population.
  - ↳ More relevant, larger sample and includes contraindicated people.
  - ↳ [redacted] in results between populations.
- Subgroup analysis limitations:
  - Not stratified at randomisation and was amended post-hoc = broke randomisation.
  - Few baseline characteristics imbalances - aura and severe migraine.

Other considerations

- Majority of trial population do not meet proposed population.
- Clinician: clinical trial not exactly reflective of current UK clinical practice.

NICE Which trial population should be used in the model - mITT or subgroup with ≥2 triptan failures?

Clinical trial results: acute migraines

Rimegepant is more effective at providing pain relief at 2 hours than placebo

	EAG's preferred analysis (4 RCTs*, mITT population)	Company's preferred analysis (3 RCTs, subgroup with ≥2 triptan failures)
Outcome	Risk difference between rimegepant and placebo (95% CI; p-value)	Risk difference between rimegepant and placebo (95% CI; p-value)
Pain relief at 2 hours**	[redacted]	[redacted]
Pain freedom at 2 hours	[redacted]	[redacted]

*Includes BHV3000-310 trial based on Asian population

** Not a primary outcome but used to inform response in economic model

Adverse events are considered mild to moderate, with only low rates of severe/serious events.

- [redacted] recorded in long-term study.
- Not included in the model.

Abbreviations: CI, confidence interval; CS, company submission; EAG, External Assessment Group; mITT, modified intention to treat; RCTs, randomised controlled trials.

Key issue: Trial generalisability (1/2)

Clinical trials exclude people with chronic migraines.

Background

- Indication = acute migraines with or without aura (episodic and chronic).
- Clinical trials exclude people with chronic migraines → uncertain if episodic migraine efficacy is similar.

↳ Concern: chronic migraines harder to treat due to increased risk of medication overuse headache (MOH).

Company

- No further evidence to assess differences in effectiveness between episodic and chronic migraines.
- Do not expect any difference between chronic and episodic migraines.
- [redacted] MOH [redacted] in long-term study → chronic MOH concerns ≠ higher ICER.

EAG

- Unresolvable uncertainty remains in the absence of comparative evidence.
- Increased likelihood of baseline MOH in chronic patients due to other treatments = more complex to treat.
- Clinicians - do not expect a large difference in efficacy between populations.
  ↳ MOH bigger problem in chronic patients = acute attacks harder to treat = higher ICER.

Abbreviations: ICER, incremental cost-effectiveness ratio; MOH, medication overuse headache

Key issue: Trial generalisability (2/2)

Mixed opinion on extrapolating trial data for episodic migraines to chronic migraines.

Other considerations

- Possible to extrapolate as attacks are similar but chronic migraines have greater negative impact.
- Patient expert: people can fluctuate between episodic and chronic migraines → how to interpret results when people could start the trial eligible and become 'ineligible' due to escalations of attacks.
- Structural, comorbidity and burden differences between groups mean efficacy not necessarily similar.
  - Around 60-80% patients with chronic migraine have medication overuse headache.
- Chronic migraines are more refractory and there is no reliable evidence to show size of benefit within chronic population → extrapolating evidence from episodic to chronic migraines may overestimate benefit.

Can the efficacy of rimegepant for episodic migraines be extrapolated to chronic migraines?

Cost effectiveness

Acute Migraine

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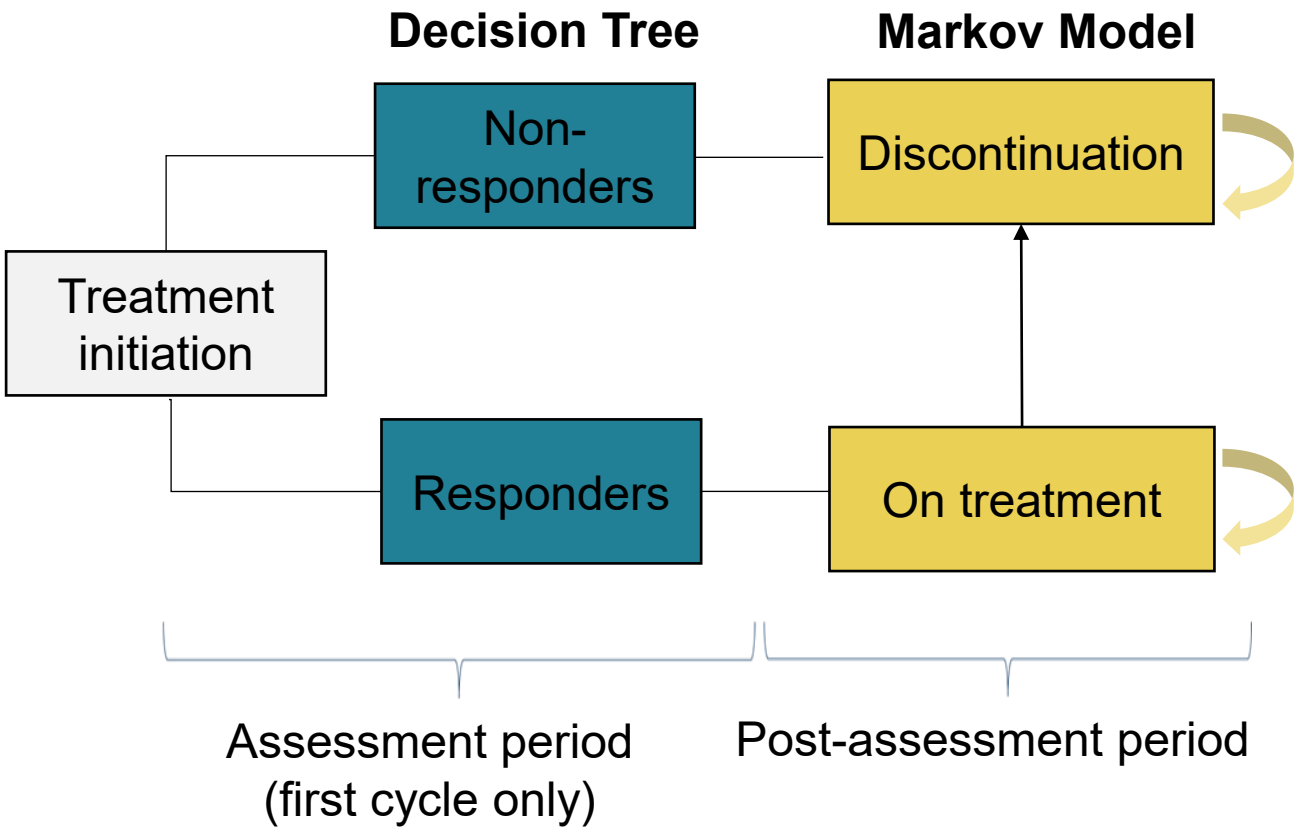
Company's model overview: acute migraine



Technology affects **costs** by:

- Higher unit price compared to BSC.
- Reducing the number of severe migraines that incur healthcare costs compared to BSC.

Technology affects **QALYs** by:

- Reducing the number of MMDs compared to BSC.
- Reducing the severity of migraines (pain relief) compared to BSC.

Assumptions with greatest **ICER** effect:

- Assuming rimegepant pro-re-nata (PRN) can result in reductions in MMDs;
- Time horizon;
- Quality-adjusted life hour outcomes;
- Baseline number of MMDs.

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Abbreviations: BSC, best supportive care; MMD, monthly migraine days; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio

Key issue: Inclusion of BHV3000-310 study

Background

- Marketing authorisation based on oral dispersible tablet (ODT).
- 1/3 trials in company's analysis use tablet formulation.
  - ↳ Company excluded additional study that uses ODT (study BHV3000-310, solely Asian population).
- Studies solely in Asian population included for the migraine prevention network meta-analysis.

Company

- BHV3000-310 is not reflective of the UK population.
  - ↳ Cultural differences in pain reporting, e.g., baseline severe pain experienced (key RCTs: 30.9%, 35%, 29.7% vs BHV3000-310: 18%)
- EMA, MHRA and EPAR conclude bioequivalence between the rimegepant formulations ODT and tablets.

EAG

- Severe pain at baseline same ([redacted]) for BHV3000-310 and pooled RCTS (subgroup population).
- Key trials based in USA – potential cultural differences in reporting pain compared to UK.
- If mITT population used, include BHV3000-310 trial (triptan discontinuation subgroup not recorded).

Should study BHV3000-310 be included in the model?

Abbreviations: ODT, oral dispersible tablet; EMA, European medicines agency; MHRA, Medicines and Healthcare products Regulatory Agency; EPAR, European public assessment report.

Key issue: Modelling rimegepant response

Background

- Model assumption: no response to first rimegepant treatment = no response to subsequent treatments.
- The response to the first migraine attack when treated with rimegepant informs the economic modelling.
- No stopping rule for acute treatment in summary of product characteristics.

Company

- No long-term data to inform how response to a single attack may predict response on future migraines.

EAG

- Unresolvable uncertainty as there is no long-term data to support assumption.

Other considerations

- Response to treatment may vary considerably between attacks.
- General recommendation in clinical practice, no response after 3 attacks = treatment ineffective.
- Single administration is being used to drive efficacy results over 20-year time horizon = highly uncertain.

Should the model assume the first response to treatment reflects subsequent responses?

Key issue: Baseline MMD distribution

Distribution preference for baseline MMD differs between the EAG and company.

Background

- Study BHV3000-201 = source of baseline MMD distribution.
  - ↳ Includes people with 2-14 migraines per month.

Company

- Study BHV3000-201 provides natural distribution of the full range of MMDs seen in the UK population.
- Prefer to model baseline MMD distribution with observed data.

EAG

- Agree BHV3000-201 baseline MMDs are representative of UK.
- Prefer Poisson distribution to model baseline MMD.
- Observed data is sporadic.
- Poisson aligns with the distribution observed for migraine prevention and the expected distribution for acute treatment.

Baseline MMD distribution in subgroup with no response to ≥2 triptan

NICE Which distribution should be used to model baseline MMDs – Poisson or observed data?

Abbreviations: MMD, monthly migraine days; ICER, incremental cost-effectiveness ratio

Key issue: MMD reductions with rimegepant PRN (1/2)

Possible MMD reductions for people receiving acute rimegepant treatment due to preventative properties.

Background

- Assumption: there are long-term reductions in MMD when using rimegepant PRN (as needed).
  - ↳ Results from BHV3000-201 post hoc analysis = highly uncertain and may suffer from confounding.
- MMD reductions modelled over 20-year time horizon, but based on 1 year follow-up data.

Company

- Disagree PRN MMD reductions highly uncertain:
  - MMD reduction among high frequency rimegepant PRN users observed in BHV3000-201.
  - Dual indication (acute and prevention) = biologically plausible to benefit from preventative properties.
    - ↳ NICE advisory board found UK clinicians accepted this concept.
- 2 year time horizon not appropriate:
  - Inadequate to capture the benefits of taking acute treatment in terms of decreasing MMD.
  - Neurologists: no justified reason that the effect will stop or wane in the data, and there is no evidence the benefit disappears over time.

Abbreviations: MMD, monthly migraine days; PRN, pro-ne-rata

Key issue: MMD reductions with rimegepant PRN (2/2)

A 2-year time horizon will be sufficient to capture immediate costs and benefits.

EAG

- Absence of long-term comparative data → appropriate to remove reduction in MMD by PRN.
- MMD reduction assumption produces questionable HRQoL data = there may be double counting of utility for people benefitting from the increased time between migraines and for having fewer migraines.
- Inclusion/exclusion of MMDs reduction by PRN rimegepant to impact the appropriate time horizon.
  ↳ If MMD reductions included, use 2 year time horizon.

Other considerations

- Reasonable to assume that frequent rimegepant use for acute treatment will have some preventive effect and will reduce MMDs → not based on a robust long term data.
- Evidence excludes people with chronic migraine = not representative of full UK migraine population = adds uncertainty to analysis.
- 2-year time horizon appropriate as costs and benefits are observed immediately.
- Single attack evidence used to inform model = limit time horizon to reduce long-term uncertainties

NICE Should reductions in MMD from PRN rimegepant be included or excluded? And what time horizon should be used in the model, 2 or 20 years?

Abbreviations: MMD, monthly migraine days; ICER, incremental cost-effectiveness ratio

Additional issue: Rimegepant responder discontinuation trajectory

Background

- Company base case: people who initially respond to rimegepant, then discontinue, respond to BSC for 12-months.
- Scenario: those who discontinue rimegepant follow BSC all-comers (mix of responders and non-responders) pain trajectory for 12-months.
- Mixed opinion over which trajectory discontinued rimegepant responders should follow.

Company

- Maintained BSC-responder trajectory in base case.

EAG

- Prefer BSC all-comer trajectory → more realistic.
- Conservative to apply to only responders, as non-responders may also respond to BSC.
- Clinical advice = small proportion of people will respond to BSC when they discontinue rimegepant.

Other considerations

- Comparator company: BSC non-responder pain trajectories the only logical option to ensure that an incorrect placebo benefit is not included within the modelling of rimegepant.

NICE Should discontinued rimegepant responders in the model follow BSC responders, BSC non-responders or BSC all-comers pain trajectories?

Abbreviations: BSC, best supportive care

Comparison of assumptions

The company and EAG differ on 6 key assumptions

Assumption	Company	EAG
Population	Subgroup with at least 2 triptan failures	mITT
Study BHV3000-310	Excluded	Included
Baseline distribution of MMDs	Observed data	Parametric distribution (Poisson)
Trajectories of rimegepant responders after discontinuation	BSC responders	BSC all-comers
Assuming rimegepant PRN can result in reductions in MMDs	Included	Excluded from the base case and included in scenario analysis
Time horizon	20 years	2 years*
***only considered appropriate when reductions in MMDs by PRN rimegepant are removed**		

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Abbreviations: BSC, best supportive care; EAG, External Assessment Group; mITT, modified intention-to-treat; MMD, monthly migraine day; NMA, network meta-analysis; PRN, pro-re-nata

Company and EAG base case results

Rimegepant is cost-effective in the company's base case analysis, but not the EAG's.

Company probabilistic base case

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB (£20k /QALY)	NHB (£30k /QALY)
BSC	£2,413	7.87	-	-	-	-	-
Rimegepant	£9,810	8.30	£7,397	0.43	£17,359	0.050	0.173

EAG probabilistic base case

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB (£20k /QALY)	NHB (£30k /QALY)
BSC	£225	1.23	-	-	-	-	
Rimegepant	£2,015	1.27	£1,789	0.041	£43,437	-0.048	-0.018

Results do not include any confidential commercial discounts

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Abbreviations: QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; BSC, best supportive care; NHB, net health benefits; PSA, probabilistic sensitivity analysis

Impact of EAG preferred assumptions on company base case

Assumption		Company	EAG
1	Population	Subgroup with ≥2 triptan failures	mITT
2	Study BHV3000-310	Excluded	Included
3	Baseline distribution of MMDs	Observed data	Parametric distribution (Poisson)
4	Rimegepant responder discontinuation trajectories	BSC responders	BSC all-comers
5	Rimegepant PRN can reduce MMDs	Included	Excluded
6	Time horizon	20 years	2 years*

*only considered appropriate when reductions in MMDs by PRN rimegepant are removed

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£)
Company deterministic base case	£7,307	0.417	£17,521
1	£4,154	0.249	£16,671
1+2	£4,350	0.220	£19,743
1+2+3	£4,371	0.220	£19,857
1+2+3+4	£4,371	0.210	£20,803
1+2+3+4+5	£5,458	0.179	£30,495
1+2+3+4+5+6 (**EAG deterministic base case**)	£1,788	0.041	£43,883

Abbreviations: BSC, best supportive care; EAG, External Assessment Group; mITT, modified intention-to-treat; MMD, monthly migraine day; NMA, network meta-analysis; PRN, pro-re-nata

EAG deterministic scenario analysis

Scenario (applied to company base case)	Incremental costs (£)	Incremental QALYs	ICER (£)
Company deterministic base case	£7,307	0.417	£17,521
Parametric distribution (Poisson) to model the baseline distribution of MMDs	£7,447	0.412	£18,061
Removing the reductions in MMD associated with rimegepant PRN	£8,505	0.378	£22,529
Removing the reductions in MMD associated with rimegepant PRN (2-year time horizon)	£2,271	0.082	£27,851
mITT population	£4,154	0.249	£16,671
mITT population including study BHV3000-310	£4,350	0.220	£19,743
Patients who discontinue rimegepant follow BSC all-comer pain trajectories	£7,307	0.402	£18,155
Patients who discontinue rimegepant follow BSC non-responder pain trajectories	£7,307	0.394	£18,545

Abbreviations: EAG, external assessment group; MMD, monthly migraine days; PRN, pro-re-nata; mITT, modified intention-to-treat; BSC, best supportive care

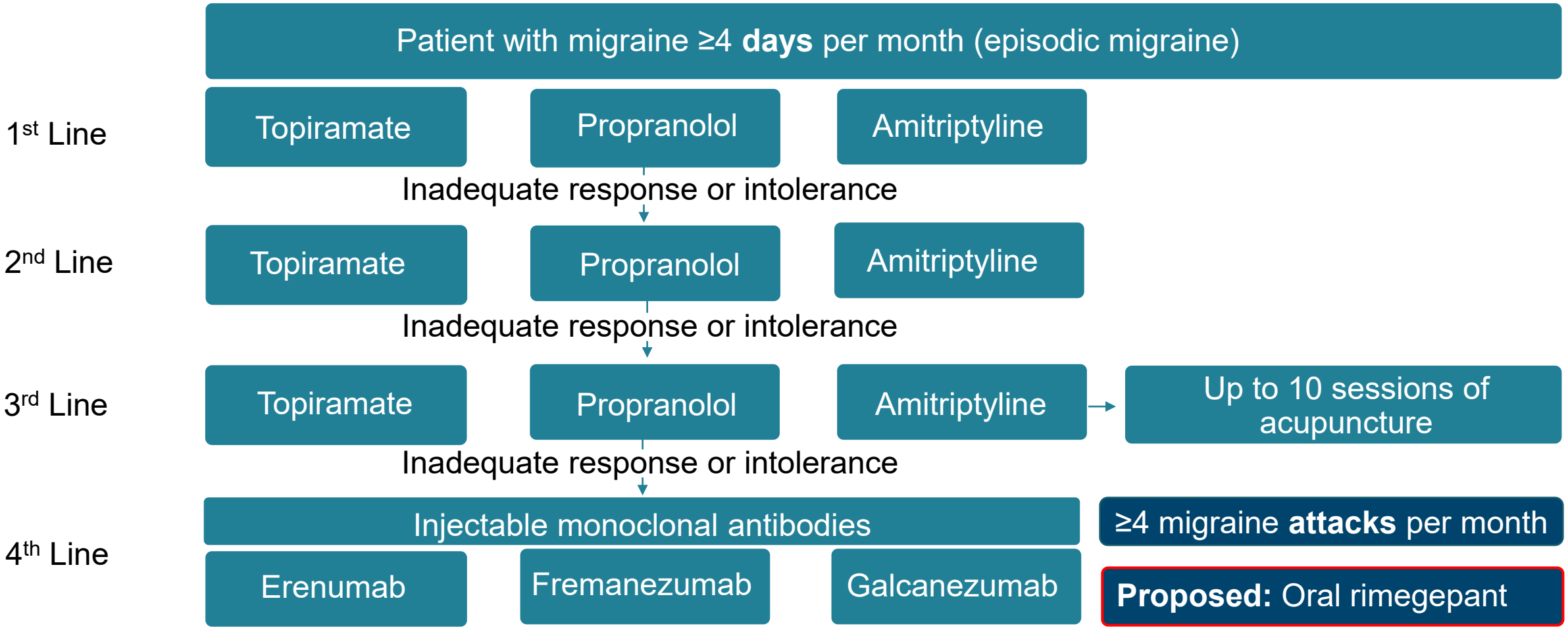
Preventing Migraine

Adults who have at least four migraine attacks per month

NICE National Institute for Health and Care Excellence

Treatment pathway: Migraine prevention

Rimegepant is proposed as a 4th line treatment for preventing episodic migraines



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Are injectable monoclonal antibodies the most appropriate comparators for rimegepant?

Decision problem: migraine prevention

	Final scope	Company	EAG
Population	Adults with Migraine	Adults with episodic migraine who have ≥4 but <15 migraine attacks per month and have not responded to ≥3 preventive drug therapies	Narrower population is reasonable.
Intervention	Rimegepant		-
Comparators	• Oral preventive treatments • Erenumab • Galcanezumab • Fremanezumab • Botulinum toxin type A • Best supportive care	• Erenumab • Galcanezumab • Fremanezumab	Agree with company.
Outcomes	• Frequency of headache and migraine days per month • Severity of headaches and migraines • Number of cumulative hours of headache or migraine on headache or migraine days • Reduction in acute pharmacological medication • Health-related quality of life • Adverse events		-

Key issues for preventative migraine treatment

Key Issue	Resolved?	Reason	ICER impact
Exclusion of treatment history	No	Unresolvable due to data limitations	Unknown
NMA limitations	No	Unresolvable due to data limitations	Unknown
Rimegepant response probability	No	Different opinions	Small
NMA results application	Partially	Different opinions	Small
Inconsistent population definition	Yes	-	-
Comparator acquisition costs	Yes	-	-
Reversion to baseline MMD	Yes	-	-
Additional issue			
Baseline EQ-5D	Partially	Different opinions	Unknown

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

Clinical effectiveness

Preventing Migraine

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Key clinical trials and outcomes: preventing migraine

	Study BHV3000-305 (n = 741)
Design	Multi-centre, randomised, double-blind, placebo-controlled, Phase 2/3 trial
Population	• Adults with ≥1-year history of migraine with or without aura or chronic migraine (23%) • 4 -18 migraine attacks of moderate-to-severe intensity per month, • Migraine attacks, on average, lasting 4 to 72 hours if untreated • ≥6 but ≤18 migraine days during the 4-week lead-in observation period
Intervention	Rimegepant 75mg
Comparator(s)	Placebo
Duration	12 weeks
Formulation	Tablet
Primary outcome	Mean MMD in the last 4 weeks of treatment phase
Key secondary outcomes	• 50% reduction from baseline in mean number of moderate to severe MMD in last 4 weeks of treatment phase • Adverse events, reduction in medication, safety and tolerability, and health-related quality of life
Locations	United States

Abbreviations: MMD, monthly migraine days

Clinical trial: results

Rimegepant is more effective at reducing monthly migraine days than placebo

	Rimegepant (n=348)	Placebo (n=347)
≥50% reduction in mean MMDs compared to baseline	**n (%)**	
BHV3000-305 trial definition: moderate or severe migraine days per month during weeks 9 to 12 (used in company's model for rimegepant response probability)	171 (49.1%)	144 (41.5%)
NMA definition: migraine days (any severity) per month overall during the double-blind treatment period (used in company's model for NMA for relative effects, and EAG's base case for rimegepant)	[redacted]	[redacted]

Adverse events are considered mild to moderate, with only low rates of severe/serious events.

- Not included in the model.

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Abbreviations: MMD, monthly migraine days; NMA, network meta-analysis; CI, confidence intervals; EAG, evidence assessment group

Network meta-analysis

Rimegepant is less effective at reducing monthly migraine days than erenumab, galcanezumab and fremanezumab

Outcomes from random effects model adjusted for baseline risk

Intervention	≥50% reduction in MMDs (any severity) from baseline over 12 weeks (used in model) Median OR (95% CrI)	Mean change from baseline in MMDs at 12 weeks (measured weeks 9-12) Median mean difference (95% CrI)
Compared to rimegepant		
Erenumab 140 mg	[redacted]	[redacted]
Galcanezumab 120 mg	[redacted]	[redacted]
Fremanezumab 225 mg	[redacted]	[redacted]
* Statistically significant at 5% level		

Abbreviations: CrI, credible interval; MMDs, monthly migraine days; NMA, network meta-analysis; OR, odds ratio.

Key issue: Exclusion of treatment history (1/2)

The RCT and NMA exclude people that had no response to ≥3 prior treatments.

Background

- Decision problem: people with episodic migraines that had no response to ≥3 prior preventative treatments.
- RCT: excludes people with non-response to ≥2 preventative treatments.
- NMA: 11/14 studies exclude people with history of non-response to prior treatment.

Company

- Unresolvable – no data collected to assess impact of no response to prior treatment on rimegepant efficacy.
- [redacted]
  - ↳ Results conservative for rimegepant in refractory population.

EAG

- Differences in refractory and non-refractory not substantial and [redacted].
  - ↳ Do not agree with company's conversative conclusion.
- Clinician: non-response to multiple prior treatments indicates refractory migraine → more difficult to treat and higher risk of failing on new treatment.
- Key trial is not well aligned with decision problem.
  - ↳ Applicability of results to target population and effect on ICER = uncertain.

Abbreviations: RCT, randomised controlled trial; NMA, network meta-analysis; ICER, incremental cost-effectiveness ratio

Key issue: Exclusion of treatment history (2/2)

Considerations from clinical experts, BASH, ABN and comparator companies

Other considerations

- Reasonable to assume history of non-response to prior treatments indicates refractory migraines.
  - Such people will likely have higher burden of headache- and migraine-related disability → uncertainty in generalisability.
  - ↳ However, clinician noted that refractory migraines ≠ more difficult to treat with new drug classes.
- Company have not presented clinical trial data to support the positioning they are pursuing.
  - ↳ Extrapolating from the comparator trials in refractory population is unlikely to provide accurate data.
  - ↳ Results from the trial cannot be applied to those with no response to ≥3 prior treatments.
- Comparator appraisals used subgroup data of patients with no response to ≥3 prior treatments.
  - ↳ This NMA uses full trial populations not subgroup = indirect comparison inconsistent with comparator appraisals.

Is the clinical evidence (RCT and NMA) generalisable to people that had no response to ≥3 prior preventative treatments?

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Abbreviations: BASH, British Association for the Study of Headaches; ABN, Association of British Neurologists; RCT, randomised controlled trial; ICER, incremental cost-effectiveness ratio.

Key issue: NMA limitations

The NMA has unresolvable uncertainties remaining

Background

- Uncertainties around the comparability of NMA trials: treatment history heterogeneity, differences in analysis populations and missing data handling, 2/14 studies included people with chronic migraines.

Company

- Acknowledge there is a lack of direct evidence from an RCT comparing rimegepant and mAbs.

EAG

- There are measures taken to reduce uncertainty, but outstanding limitations are unresolvable.
- Rimegepant trial is limited in terms of how well the population reflects the decision problem.
- Data availability for comparator trials is likely to be too limited to better address any remaining concerns.

Other considerations

- Direct comparisons between trials cannot be made due to variability in study design and placebo response.
- Comparator appraisals had NMAs based on data from subgroup with non-response to ≥3 prior treatments.
  - ↳ This NMA based on the full trial populations of included studies = inconsistent with comparator appraisals in terms of the indirect evidence due to the lack of subgroup rimegepant data.
- The fact that the rimegepant RCT excluded the most relevant patient population limits the NMA and its applicability to this appraisal.

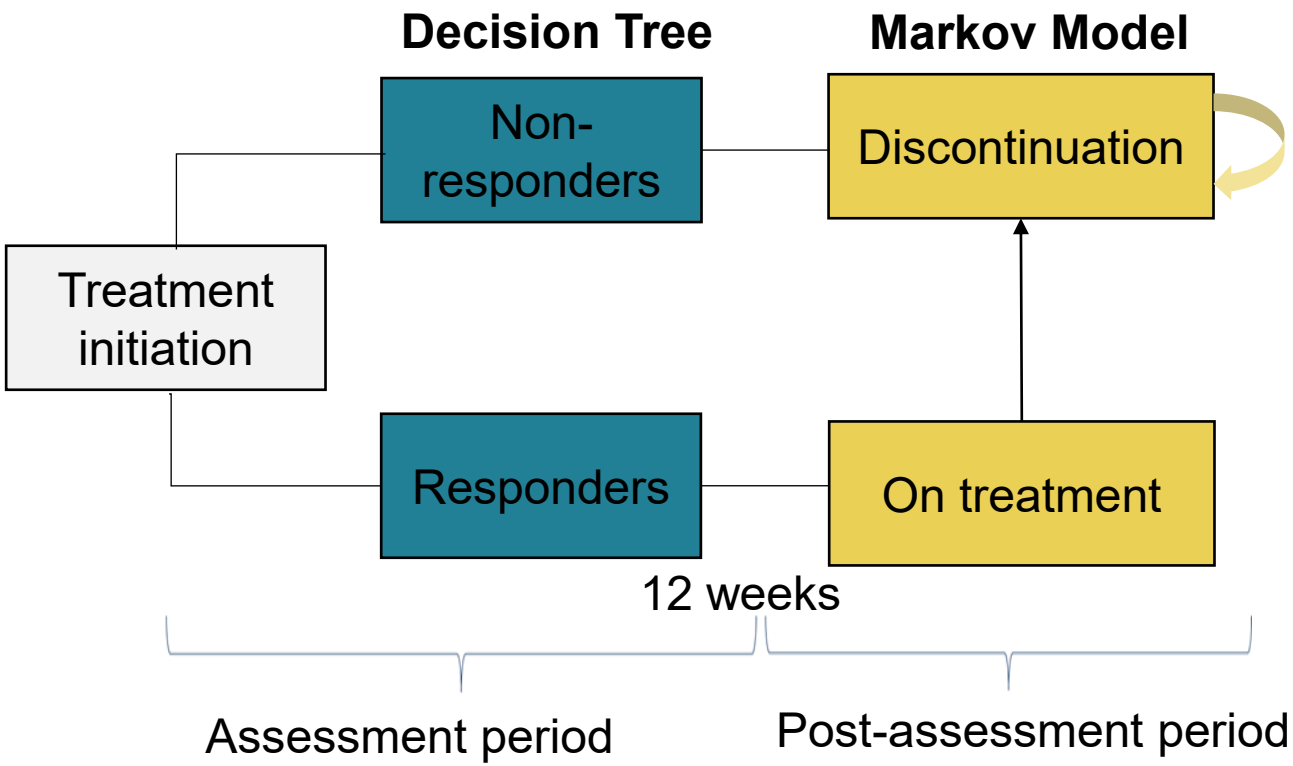
Is the NMA suitable to inform the efficacy of rimegepant versus the comparators?

Cost effectiveness

Preventing Migraines

NICE National Institute for Health and Care Excellence

Company's model overview: preventing migraine



Technology affects **costs** by:

- Reducing the number of MMDs which reduces healthcare costs.
- Lower unit price compared to comparators.
- Given as a tablet, rather than intravenously.

Technology affects **QALYs** by:

- Reducing the number of MMDs.

Assumptions with greatest ICER effect:

- Response at 12-weeks;
- Long-term discontinuation rates;
- The utility values according to MMD and treatment.

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

Key issue: Rimegepant response probability

Inconsistent methods informing response probabilities in the model.

Background

Treatment response probabilities for ≥50% MMD reduction from baseline are from different sources and definitions:

- Rimegepant: response at 12-weeks in moderate-to-severe-migraines (from trial definition).
- NMA relative effect: average response over 12-weeks in mild-to-severe migraines (from NMA definition).

≥50% MMD reduction from baseline	Company preference	EAG preference
Rimegepant response probability	49.1% (trial)	[redacted] (NMA)
Assessment time point	At week 12	Average over 12 weeks
Migraine severity	Moderate-to-severe	Mild-to-severe

Company

- Disagree the same outcome definition needs to be used in the model to inform response probabilities.
- NMA used average over 12-weeks only to broaden evidence base → using at 12-weeks would have excluded galcanezumab.
- Studies using both outcome definitions found similar relative effects (not specific to rimegepant).
- Over 12-weeks would cause some 12-week responders to be treated as non-responders = underestimation.
- Company advisors – 85% agreed with assessment at 12 weeks.
  - GP and pain specialist (not in headaches) preferred average over 12 weeks.
  - Neurologists with migraine interest preferred at 12 weeks.

Key issue: Rimegepant response probability

Average response over 12 weeks in mild-to-severe population should be used throughout the economic model.

EAG

- Rimegepant response probability and relative effects of rimegepant compared to comparators should be informed by same definition of response.
  - Not appropriate to use different definitions to inform model.
- Understand in practice, response assessment may be taken at 12 weeks.
- Uncertain if similar ORs, regardless of how the time-point is defined, would remain true for comparisons between rimegepant and mAbs, as found for mAbs vs placebo.
- Company not commented on population differences: mild-to-severe or moderate-to-severe.

Other considerations

- Average response over 12 weeks in people with mild-to-severe migraine attacks should be used for all response rates in model – need for consistency.

Should the response probability be measured at 12 weeks in moderate-to-severe MMDs or over 12 weeks in mild-to-severe MMDS?

Abbreviation: ICER, incremental cost-effectiveness ratio; mAbs, monoclonal antibodies; MMD, monthly migraine days, OR, odds ratio

Key issue: NMA results application (1/2)

Treatment benefits can be experienced and should be applied before week 12.

Background

- NMA response probability assessed over 12-weeks, but applied in cycle 3 (weeks 9-12) in model.
- Key trial and comparator trials show significant reduction in MMDs in first few weeks of treatment.
  - ↳ Should results be applied earlier in the model to account for this?

Company

- Agree benefits may be accrued before week 12.
- Presented 2 alternative options:
  - Option 1 – full 12-week benefit from original base case applied at week 4.
  - Option 2 – benefit observed prior to week 12 in NMA responders applied at week 4 (estimated using alternative regression).

Methods for applying the NMA predicted mean MMDs

Assessment	Original base case		Revised base case – option 1		EAG preferred – option 2	
	Responder	Non-responder	Responder	Non-responder	Responder	Non-responder
Baseline (cycle 0)						
Week 4 (cycle 1)						
Week 8 (cycle 2)						
Week 12 (cycle 3)						

Key issue: NMA results application (2/2)

Incremental improvements in response can be seen between cycle 1 to 3

EAG

- Application of NMA response probability affects both costs and QALYs.
- Option 2 is preferred method as allows for incremental improvements between cycles 1-3.
  - Enables non-responders MMD distribution to be predicted by non-responders (not all patients).
- Option 1 limitations:
  - Non-responder predicted mean is the same as original company base case – would expect this to be higher, or the original to be in the middle of the revised responder and non-responder estimates.

Other considerations

- Rimegepant may work immediately although there may be an incremental response with time and hence applying results from cycle 1 to cycle 3 may not be accurate.
- In practice, efficacy assessments occur at 12-week and are based on response during this period.
- TA734 (fremanezumab) modelled responders and non-responders separately by treatment arm.
  - MMD distributions were then adjusted based on mean responders MMD from the trial.

Clinically, which of the response probabilities aligns closest with how rimegepant works to prevent migraines, option 1 or option 2?

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

Additional issue: Baseline EQ-5D

Non-significant utility differences at baseline between rimegepant and placebo.

Background

- Company derived utility values by mapping week 12 MSQv2 values from the trial to the EQ-5D.
  - Regression model was used to calculate utility values, adjusting for MMD and treatment arm.
  - Baseline values favour rimegepant, although the difference was not statistically significant.
- The trial was randomised, therefore, mapped EQ-5D should be similar at baseline.
  - If difference at baseline, including covariate 'treatment arm' could mean difference persists to week 12.

Company

- Non-significant difference in mapped EQ-5D score at baseline between rimegepant and placebo (0.016, 95% CI +/- 0.0214).
  - ↳ Rimegepant baseline utility higher (0.6136, n=348) than placebo (0.5976, n=346).

EAG

- Concerned the baseline difference is non-trivial and prefer regression to include the baseline mapped EQ-5D scores as covariates to ensure that the baseline utility for the treatment arms is as similar as possible.
  - ↳ mAbs have incremental QALY benefit over rimegepant in EAG base case.
  - ↳ If utility advantage persists, average patient in rimegepant arm is effectively 'gifted' with improved incremental utility compared to the mAbs.
- Impact on ICER unknown, but covariates in regression had large impact on ICER in OWSA.

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Should baseline EQ-5D data be included or excluded from the regression?

Abbreviations: EQ-5D, Euro QoL Five Dimensions; MSQv2, Migraine-Specific Quality of Life Questionnaire version 2; mAbs, monoclonal antibodies; OWSA, one way sensitivity analysis

Impact of EAG preferred assumptions on company base case ICER

↑ NHB increases

= NHB remains the same

Company and EAG model assumptions

Assumption	Company	EAG
Rimegepant response probability	At 12-weeks and moderate-to-severe MMDs	Average over 12 weeks and mild-to-severe MMDs
Regression used to predict MMD distributions during the assessment period	Option 1 (full 12-week benefit from original base case applied at week 4)	Option 2 (benefit observed prior to week 12 in NMA responders applied at week 4 (estimated using alternative regression).

Impact of individual EAG preferred assumptions compared with company base case

Preferred assumption	NHB £20,000/QALY			NHB £30,000/QALY		
	Ere	Gal	Fre	Ere	Gal	Fre
Rimegepant response probability as per the NMA	↑	↑	↑	↑	↑	↑
NMA applied from Cycle 1 using option 2	=	=	=	=	=	=

The net health benefit remains negative in all scenarios

Abbreviations: EAG, external assessment group; NMA, network meta-analysis; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years

Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential

comparator PAS discounts

Summary of unresolved issues

Acute issues	Reason	ICER impact
MMD reductions with rimegepant PRN	Different opinions	Large
Rimegepant responders discontinuation trajectories	Different opinions	Small
Trial population	Different opinions	Small
Baseline MMD distribution	Different opinions	Small
Inclusion of BHV3000-310 study	Different opinions	Small
Modelling rimegepant response	Unresolvable	Unknown
Trial generalisability	Unresolvable	Unknown
Prevention issues		
Rimegepant response probability	Different opinions	Small
NMA results application	Different opinions	Small
Baseline EQ-5D	Different opinions	Unknown
Exclusion of treatment history	Unresolvable	Unknown
NMA limitations	Unresolvable	Unknown

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Abbreviations: NMA, network meta-analysis; MMD, monthly migraine days; PRN, pro-re-nata

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Thank you.