Rimegepant for treating or preventing migraine

Part 1 Slides for public only - Contains NO confidential information

Technology appraisal committee D - 13th April 2023

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Company: Pfizer

Process: STA 2018

NICE

Recap: background on migraines

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

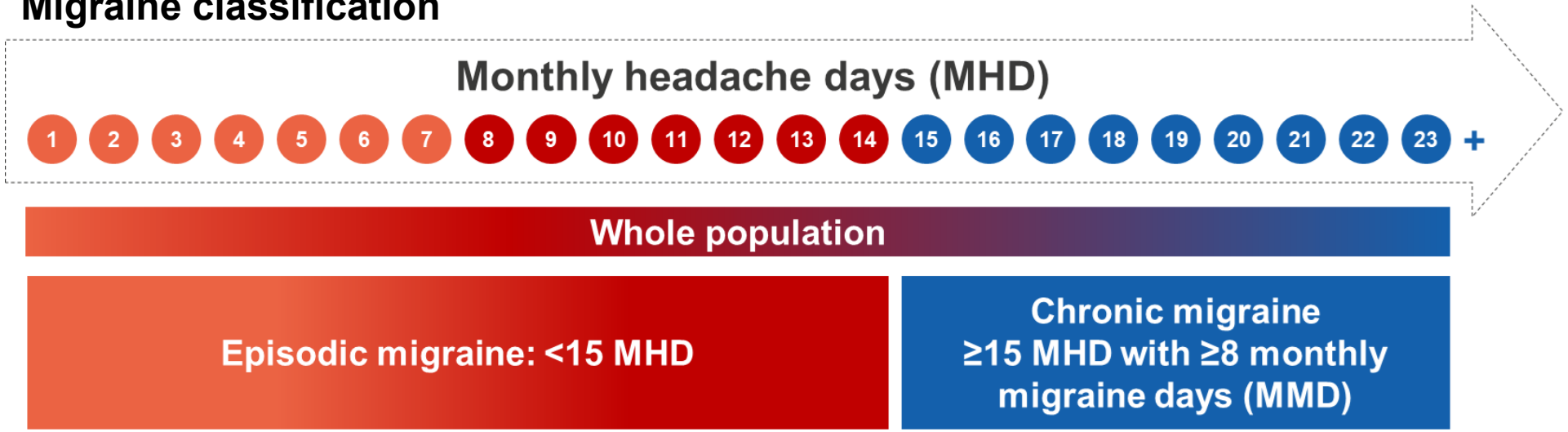
Symptoms: Migraines are usually more intense, painful and debilitating than headaches - often accompanied by nausea, vomiting, sensitivity to light/sound.

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.

Migraine classification



NICE

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. **Each indication will be considered separately**
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	• ACM1 list price per tablet: £20 • ACM2 updated list price per tablet: £13.55

Abbreviations: MHRA, Medicines and Healthcare products Regulatory Agency

ACD preliminary recommendations and conclusions

Acute population

Rimegepant is not recommended, within its marketing authorisation, for acute treatment of migraine with or without aura in adults.

- The committee considered both the 2- and 20-year time horizons but concluded that more explanation is needed to determine the appropriate time horizon.

Prevention population

Rimegepant is not recommended, within its marketing authorisation, for preventing episodic migraine in adults who have at least 4 migraine attacks per month.

- Incremental net health benefits were negative when rimegepant was compared with erenumab, galcanezumab and fremanezumab, at threshold values of £20,000 and £30,000 per QALY gained.

Issues resolved at ACM1

Acute issues	ACD section
Inclusion of BHV3000-310 study	3.6
Trial generalisability	3.7
Modelling rimegepant response	3.10
Baseline MMD distribution	3.11
MMD reductions with rimegepant PRN	3.12
Rimegepant responders discontinuation trajectories	3.13
Prevention issues	
NMA limitations	3.21
Exclusion of treatment history	3.22
Rimegepant response probability	3.24
NMA results application	3.25
Baseline EQ-5D	3.26

Abbreviations: ACM, appraisal committee meeting; NMA, network meta-analysis; MMD, monthly migraine days; PRN, pro-re-nata (as needed)

ACM2 issues for discussion

Acute issues	ICER impact	ACD section
Trial population	Small	3.5
Time horizon	Large	3.12
Prevention issues		
Healthcare resource use	Small	3.31

Abbreviations: ACM, appraisal committee meeting; ICER, incremental cost-effectiveness ratio; ACD, appraisal consultation document

ACD consultation comments

Comments received from:

- **Web comments (including patients, carers and public) (n=85)**
- **Patient group comments from:**
  - The Migraine Trust
- **Clinical expert & Professional group comments from:**
  - British Association for the Study of Headache (BASH)
- **Commentator comments from:**
  - AbbVie
  - Teva
- **Consultee comments, Pfizer:**
  - ACD response
  - Proposed list price change
  - Revised base cases and sensitivity analyses; new evidence for acute prespecified subgroup

Web comments

Patients, carers & public comments: summary of responses

- The consultation received 85 individual comments from patients, carers and the public.
- We have reviewed all the comments and summarised the general themes.
- The majority of comments do not agree with the ACD decision.
- Comments are generally supportive of rimegepant being recommended, particularly for the acute migraine population.

Abbreviation: ACD, appraisal consultation document

Web comments

Patients, carers and public comments (1)

Impact of migraine	Current treatments
• Everyday life negatively affected • Can be severely disabling • Depression, anxiety, social isolation • Psychological and physical pain • Affects family and friends • Affects ability to work: unemployment, early retirement, frequent work absence, fear for job security • Lack of understanding of the condition; “invisible disability”; feeling isolated and dismissed • COVID-19 made migraines worse • Affects more women than men	• High unmet need for an effective and well-tolerated drug – more options needed, especially for acute use. • Existing treatments ineffective and have bad side effects e.g., MOH. • Current treatment options do not directly target migraines and many are injectable - not suitable for everyone. • No viable treatment options for people who cannot take triptans e.g., older people or people with other health issues. • Long waiting lists to access treatments and see specialists. • People try alternative ‘non-migraine’ medications to treat symptoms e.g., anti-depressants. • Treatments are not freely available and are limited in dose.

Abbreviation: MOH, medication overuse headache

Web comments

Patients, carers and public comments (2)

Rimegepant - effects	Rimegepant - Wider effects

• Important new treatment option shown to be effective.
• Specifically designed to treat migraine.
• Few side effects – help those with MOH.
• Tablet formulation – easier and preferable to use
• Not enough evidence collected in eligible populations.
• Outcome measures inappropriate, some treatments take >2 hours to provide pain relief.
• NMA not appropriate to make conclusion on because there are substantial limitations.
• Should consider rimegepant differently in preventative and acute setting.
	• Untreated migraine has enormous costs to the NHS and to the UK economy.
	• Analysis did not consider wider benefits
	  ○ Could reduce sickness absence loss of productivity / enable return to work.
	  ○ Could reduce NHS costs related to mental health / suicides / other services.
	• Too expensive for private treatment – will have greater impact on those on low incomes.

Abbreviations: MOH, medication overuse headache; NMA, network meta-analysis

Consultation comments: The Migraine trust

Condition

- Migraine is a debilitating disorder with no cure and limited treatments. People with migraine are stigmatised, partly due to the lack of understanding and effective treatments, and the association to work productivity.
- Rimegepant could reduce the negative impact and frequency / intensity of migraine to enable productivity gain.

Costs

- The personal, economic and healthcare costs for migraine should be considered. 2018 UK migraine healthcare costs estimated at £1b per year, with £9b in absenteeism / presenteeism costs.

Disadvantaged groups

- People who cannot have or restrict triptans to avoid MOH are disadvantaged and have no good treatments. Better treatments are needed to improve migraine care, as per the Getting It Right First Time aims.
- Where triptans are not an option or give partial relief / side effects, opioids may be the only alternative. Opioid complications e.g., MOH, can worsen symptoms and cause greater disability and healthcare resource use.

Advantages to patients and the NHS

- An oral treatment with good tolerability could reduce specialist referrals, costs and waiting times; give control back to get timely relief; and give chance to receive in primary care setting, even if initiated in secondary care.

Preventive Use

- NICE mAbs appraisals also lacked long-term comparative data and their recommendation has benefitted many.

Abbreviation: MOH, medication overuse headache; mAbs, monoclonal antibodies

Consultation comments: BASH

Clinical evidence

- Disappointed there was no trial data for the target preventative UK population in line with previous appraisals to allow indirect comparison.
- Agree post hoc analysis may be flawed and welcome a future trial to evaluate the preventative nature of rimegepant in the UK when used daily / on alternative days.

Dosing

- Would like clarification of uncertainties about repeat dosing of rimegepant and the reliability of response for acute migraine.
- Welcome seeing repeat dosing studies as occurred with triptans for acute migraine.
- Keen to access rimegepant in the UK but recognise the need for reliable and robust data to support sustained efficacy both as an acute and preventive therapy in those prescribed this medication.

Primary care

- Rimegepant should be available for primary care prescription following specialist recommendation to ensure appropriate prescribing as part of the pathway for people with migraines in the UK.

Abbreviation: BASH, British Association for the Study of Headache

Consultation comments: Teva & AbbVie

Interplay between the acute and preventative indications

- Need to consider practical delivery of rimegepant and clinical pathway implications for the interplay between acute and prevention indication, given the potential for overlap.
- 2 indications have 2 distinct populations with small overlap. Potential misuse risk, particularly if people are eligible only 1 setting. Safety but not efficacy of combined use tested in long-term trial.
- Misuse could displace another preventive / acute medication, which is likely more cost-effective. This reduces rimegepant cost-effectiveness due to higher costs with little / no efficacy benefits.

Clinical evidence uncertainties

- The NMA has high degree of uncertainty as found in previous migraine appraisals, plus significant additional uncertainties (e.g., exclusion of relevant patient population, treatment history heterogeneity).
- Ongoing rimegepant trials could provide relevant data and would address some of the uncertainties.

Acute trials may incorrectly use triptans, causing eligibility for rimegepant (failed >2 triptans)

- If used correctly, a cheaper and equally effective triptan could provide relief, which may reduce the cost-effectiveness of rimegepant which is more expensive and has no additional benefit.
- Well-defined guidance statements related to triptan use could reduce impact and prevalence.

Abbreviation: NMA, network meta analysis

Consultation comments: Teva & AbbVie

Innovation in the preventive treatment setting

- Orally administered CGRP inhibitors may open doors to novel prescribing pathways.
  - ↳ Enable NHS to streamline current clinical care pathway, optimise delivery of care, relieve capacity issues with migraine management, and achieve efficiencies in terms of saved specialist time.
- The simple to use, oral, well-tolerated nature will be a welcome alternative for patients to access care quicker and help shorten the NHS waiting list.
- Limited UK specialist headache centres = extensive waiting lists to access specialist preventive treatment.
  - ↳ Migraine Trust (2021) - average waiting time to access mAbs is between 3-5 months in the UK, and can take up to 2 years to access specialist headache clinics.

NMA shows mAbs superior to rimegepant, but efficacy inputs assumed the same

- Excluding additional mAb benefit could underestimate differences in efficacy. Including the benefit would reduce the mAbs overall MMDs, increase QALYs and lower costs compared to rimegepant.
- Treatment discontinuation rates assumed the same across rimegepant and mAbs. Unlikely due to different dosing schedules, administration routes, efficacy and tolerability profiles.
- Imposing class effect between mAbs based on erenumab long-term discontinuation rate would be fair.

Abbreviation: CGRP, calcitonin gene-related peptide; mAbs, monoclonal antibodies; MMDs, monthly migraine days; QALYs, quality-adjusted life years

ACD consultation comments (Pfizer)

Summary of company's comments & updated evidence

- New proposed list price

Acute

- Revised base case including all committee's preferred assumptions
    - Time horizon remains at 20 years
- Provided clarification on differences between the prespecified and post hoc subgroup

Preventative

- Revised base case including all committee's preferred assumptions
- Updated healthcare resource use costs – from a primary care perspective

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.
- Rimegepant available in the US, Europe, United Arab Emirates and Israel.
- People with migraines who are older or have other health conditions who are unresponsive to, or unable to use, other interventions.
- People with migraines who are pregnant cannot have some current treatments due to gestational/maternal safety considerations of continuous dosing.
- People in more deprived areas of the country are at greater risk of becoming disabled by migraine, of losing their jobs, and falling into severe financial hardship.

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?

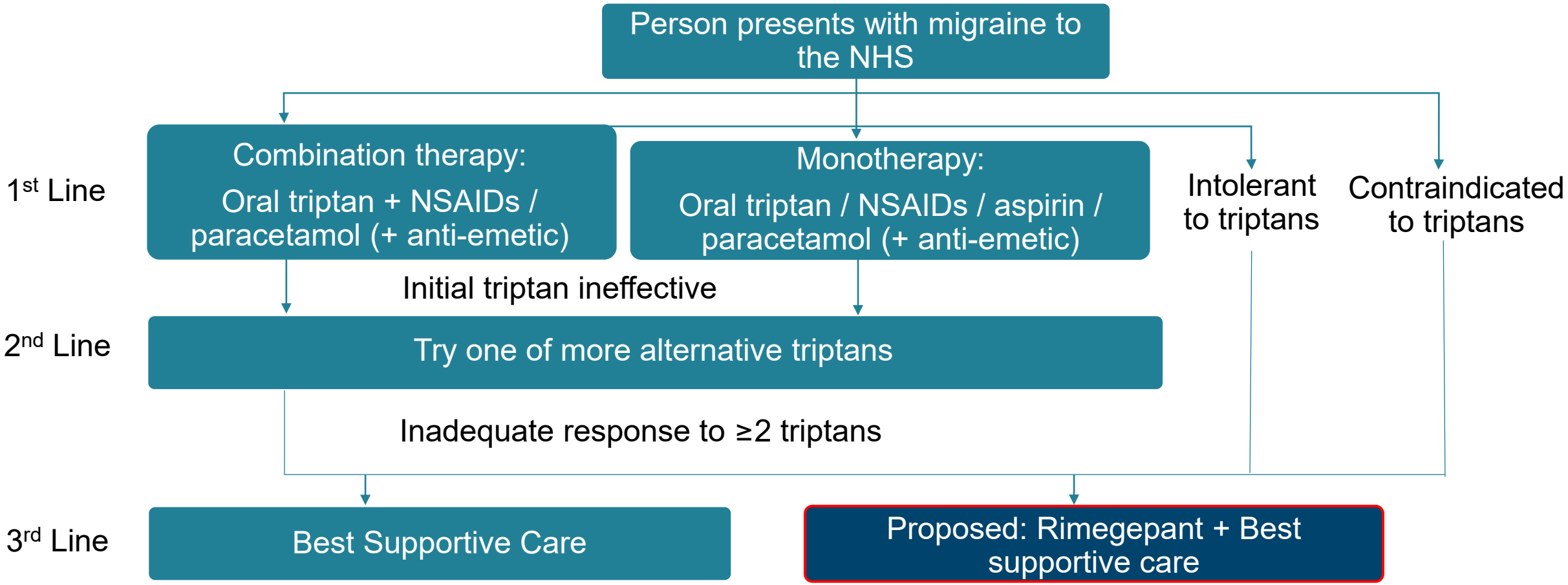
Acute Migraine

People with or without aura.

NICE National Institute for Health and Care Excellence

Recap: acute migraine treatment pathway

Rimegepant is proposed as 3rd line treatment for acute migraines



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Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs

Recap: acute migraine key clinical trials and outcomes

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

Recap: acute migraine additional clinical trials

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?	Yes	Yes (long-term parameters)

Abbreviations: MMD, monthly migraine days

Recap: acute migraine clinical trial results

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

	ERG's preferred analysis (4 RCTs*, mITT population)	Company's preferred analysis (3 RCTs, post hoc 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]	9.8 [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.

NICE

Abbreviations: CI, confidence interval; ERG, External Review Group; mITT, modified intention to treat; RCTs, randomised controlled trials.

Company revised base case

ACM1 assumptions	Committee preference	Revised base case
Population	mITT	Included
Study BHV3000-310	Included	Included
Baseline distribution of MMDs	Parametric distribution (Poisson)	Included
Trajectories of rimegepant responders after discontinuation	BSC all-comers	Included
MMD reductions with rimegepant PRN	Removed	Included
Time horizon	Undetermined, <5 years	20 years

Additional changes since ACM1:

- Company: change in list price, provided prespecified subgroup clarification

ACM2 issues	Company	ERG
Time horizon	20 years	2 years
Trial population	mITT, but provided prespecified subgroup clarification	mITT

NICE

Abbreviations: ACM, appraisal committee meeting; ERG, external review group; PRN, pro-re-nata (as needed); mITT, modified intention to treat; BSC, best supportive care

Issue: trial population clarification

ACM1 conclusions

- mITT population is most appropriate because it allows use of all trial data, including BHV3000-310 study.
- Committee requested clarification of difference between the prespecified and post hoc subgroups.

Company ACD response

- Prespecified definition: any subject where ≥2 molecular entities have not worked for efficacy reasons. All routes of administration that the subject tried for the molecular entity must not have worked.
- Strict prespecified definition of triptan non-responder = small sample size.
- Post hoc analysis modified definition to include all patients who reported ≥2 triptans had not worked.

Definition	Prespecified subgroup	Post hoc subgroup
Reason treatment not worked	Efficacy only	Efficacy or intolerability
Number of administration routes required to fail	All routes (per molecular entity)	≥1 route (per product)

ERG ACD response

- Both subgroups have similar results for key endpoints - difference has limited impact on the ICER.
  - ↳ Risk differences [redacted] in the post hoc analysis, suggesting [redacted] for rimegepant vs placebo.
  - ↳ Agree uncertainty slightly reduced in the post hoc analysis due to higher sample size.
- ACM1 clinical experts: not unusual to try different administration routes for triptan before trying new one.
- Still prefer mITT population, including BHV3000-310 study (as per company revised base case).

Abbreviations: ACM, appraisal committee meeting; PRN, pro-re-nata (as needed); mITT, modified intention to treat; ICER, incremental cost-effectiveness ratio

Issue: trial population results

Small difference between prespecified and post hoc subgroup results

	Company's post hoc subgroup with ≥2 triptan failures (original base case)	Committee preference - mITT population* (revised base case)	Company's prespecified subgroup with ≥2 triptan failures (new analyses)
Outcome	Risk difference between rimegepant and placebo (95% CI; p-value)	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]	[redacted]
Pain freedom at 2 hours	9.8 [redacted]	[redacted]	[redacted]

*Includes BHV3000-310 trial based on Asian population

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

In light of the clarification provided, has the committee's conclusion changed about the most appropriate trial population?

Abbreviations: CI, confidence interval; mITT, modified intention to treat

Issue: time horizon (1/2)

ACM1 conclusions

- Costs and benefits of rimegepant as an acute treatment should be reflected in a time horizon shorter than 5 years and more explanation is needed to determine the most appropriate length.
- NICE methods: Time horizon should be long enough to reflect all important differences in costs or outcomes between the technologies being compared.

Company ACD response

- Time horizon of >10 years is appropriate to reflect the disease history of people with migraine.
- Survey on duration of migraine attacks over lifetime:
  - ↳ 164 GPs = 68% said >5 years and 24.4% said between >10 and ≤ 20 years.
  - ↳ 12 neurologists = 83% said >10 years. No data that the benefits will stop or wane over time.
- BHV3000-201 mean treatment duration: 2-8 migraines ([redacted] weeks), 9-14 migraines ([redacted] weeks).
- Illogical to use different time horizon for the same disease in prevention model.
- RCT participants had average disease history of 20 years (disease onset age, 21 and enrolment age, 39) - indicates disease duration substantially longer than 2 years.
- RWE, migraine prescription data (2010-2022) ~16 to 24% had >1 triptan prescription for ≥5-year period between the first and last prescription.
  - ↳ Data conservative - unavailable beyond 5 years and does not measure non-prescribed medication.

Abbreviations: MMD, monthly migraine days

Issue: time horizon (2/2)

ERG ACD response

- 2-years time horizon most appropriate: after MMD reductions removed, differences in costs and HRQoL are modelled as short-term and acute; each specific migraine episode.
- Acknowledge company evidence supports that people experience migraines for longer than 2 years so would need acute treatment for much longer than 2 years. However, this should not dictate the time horizon.
- NICE methods: Time horizon shorter than a lifetime can be justified if there is no differential mortality effect between technologies and the differences in costs and clinical outcomes relate to a relatively short period.
- Short-term time horizon removes long-term uncertainty and captures all relevant costs and consequences.
- Rimegepant more cost-effective over a longer period almost exclusively due to loss of response at 12 months in placebo arm = worse health outcomes for patients in the placebo arm for all subsequent years.

Other considerations

- Clinical experts:
  - ↳ ACM1: if having migraines often enough to have preventative benefit from acute treatment, should be having a preventative treatment such as erenumab, fremanezumab or galcanezumab.
  - ↳ ACD: 20-year time horizon suitable, but anticipate prevention action will minimise need for acute.
- ACD commentor: agree 2 years should capture all costs and benefits of acute migraine treatment, particularly when modelling is based on the response to a single administration of rimegepant.

NICE Have the company provided appropriate/sufficient justification for why the costs and benefits of rimegepant as an acute treatment should be reflected in a longer time horizon than 5 years?

Abbreviations: MMD, monthly migraine days; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio

Deterministic scenario analyses

Company base case is below £20,000 per QALY gained and ERG base case is above £20,000 per QALY gained

Key difference	Company base case	ERG base case
Time horizon	20 years	2 years

Scenario	Inc QALYs	Inc costs (£)	ICER (£)
Applied to company's deterministic base case			
15-year time horizon	↑	↓	↑
10-year time horizon	↑	↓	↑
5-year time horizon	↓	↓	↑
2-year time horizon (ERG base case)	↓	↓	↑
MMD reduction included (20-year time horizon)	↑	↓	↓
Post-hoc triptan failure subgroup analysis	↑	↑	↓
Prespecified triptan failure subgroup analysis	↑	↑	↓
Applied to ERG's deterministic base case			
20-year time horizon with no loss of placebo response in BSC arm	↓	↑	↑
1-year time horizon with immediate loss of placebo response	↓	↓	↓

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

Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include a confidential

list price

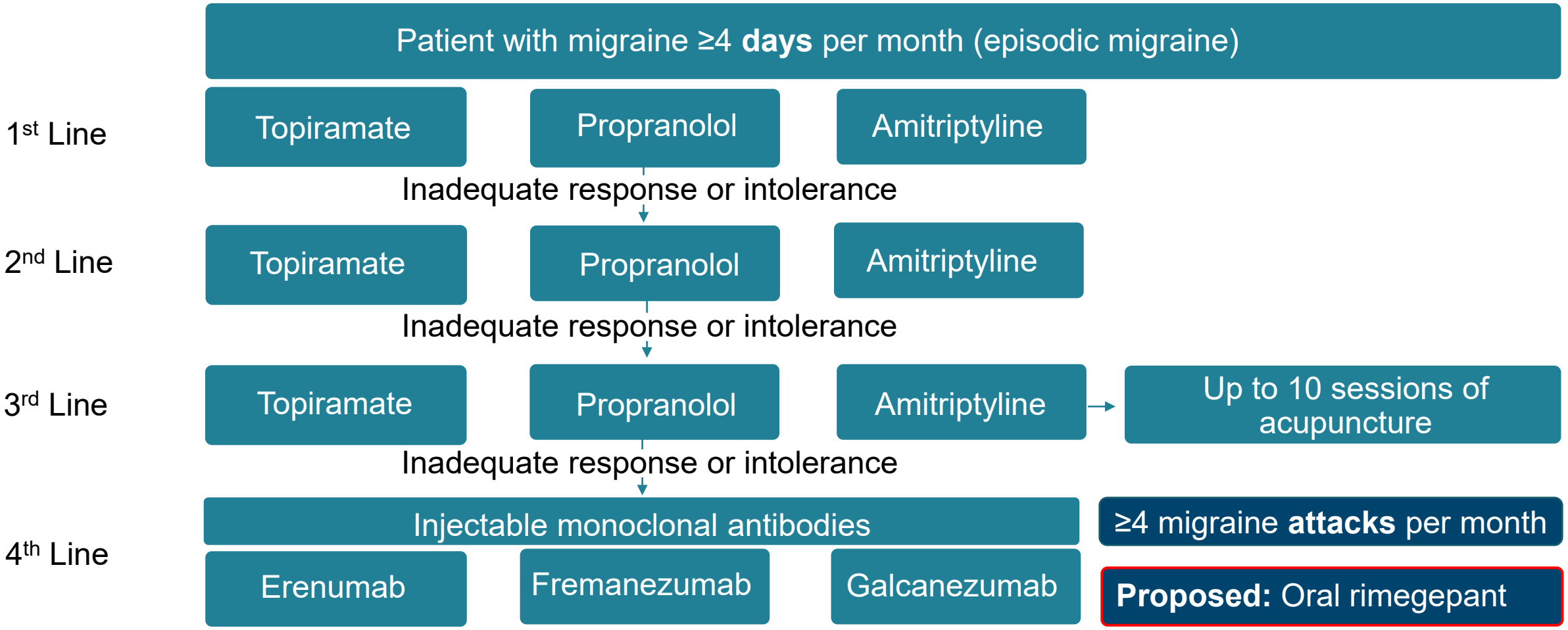
Preventing Migraine

Adults who have at least four migraine attacks per month

NICE National Institute for Health and Care Excellence

Recap: migraine prevention treatment pathway

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



Company revised base case

ACM1 assumptions	Committee Preference	Revised Base Case
Rimegepant response probability	Average over 12 weeks and mild-to-severe MMDs	Included
Regression used to predict MMD distributions during the assessment period	Option 2 (benefit observed prior to week 12 in NMA responders applied at week 4 (estimated using alternative regression)	Included

Additional changes since ACM1:

- Company
  - Change in list price
  - Updated healthcare resource use

ACM2 issues	Company	ERG
Primary care resource costs	Included	Excluded

Clinical trial and NMA results not presented as related issues were resolved in ACM1

NICE

Abbreviations: ACM, appraisal committee meeting; MMDs, monthly migraine days; ERG, external review group; NMA, network meta-analysis;

Issue: primary care resource costs

Background

- Company submission: rimegepant has potential for prescribing within primary care.
- NICE methods: for medicines that are mainly prescribed in primary care, prices are based on drugs tariff.
- Company unable to submit with approved commercial arrangement that makes rimegepant available in all applicable settings.

Company

- Revised base case updated to a more primary care centric approach. Includes:
  - ↳ One-off initiation cost and 3-month follow-up cost; with GP for rimegepant and neurologist for mAbs.
  - ↳ One-off neurologist referral cost has been added to the mAbs costed as one GP visit.
- Conservative approach - monitoring likely continue in primary care for rimegepant and secondary for mAbs.
- Clinical experts = rimegepant can provide resource use cost savings for patients in the community.
- First CGRP-targeted preventative treatment in primary care for patients with migraine.

ERG

- Not convinced by updated costings as the committee said rimegepant would require a specialist referral, diagnosis and treatment management, although it could eventually be used in primary care.

Other considerations

- Clinical expert: no reason why neurologist should only see patient once. At 6 months and then yearly. No reason why GP should not initiate.

Are the company's primary care healthcare resource use assumptions acceptable to the committee?

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

Key assumptions

Net health benefit is a summary statistic that represents the impact on population health of introducing a new intervention. It shows the value of an intervention in health terms at a given willingness-to-pay threshold.

Company and ERG model assumptions

Assumption	Company base case	ERG base case
Primary care resource costs	Included	Excluded

Impact of including the primary care resource costs on net health benefit

Assumption	NHB £20,000/QALY			NHB £30,000/QALY		
Rimegepant vs	Erenumab	Galcanezumab	Fremanezumab	Erenumab	Galcanezumab	Fremanezumab
Primary care resource costs	NHB improved	NHB unchanged	NHB unchanged	NHB unchanged	NHB improved	NHB unchanged

The net health benefit is negative in most scenarios

Abbreviations: ACM, appraisal committee meeting; ERG, external review group; QALY, quality-adjusted life years; NHB, net health benefits

Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential

comparator PAS discounts

NICE National Institute for Health and Care Excellence

Thank you.