Rimegepant for treating migraine

Part 1 Slides for public - contains NO confidential information [redacted]

Technology appraisal committee D - 10th August 2023

Chair: Megan John

Evidence review group: BMJ TAG

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Company: Pfizer

Process: STA 2018

RECAP

Background on migraines

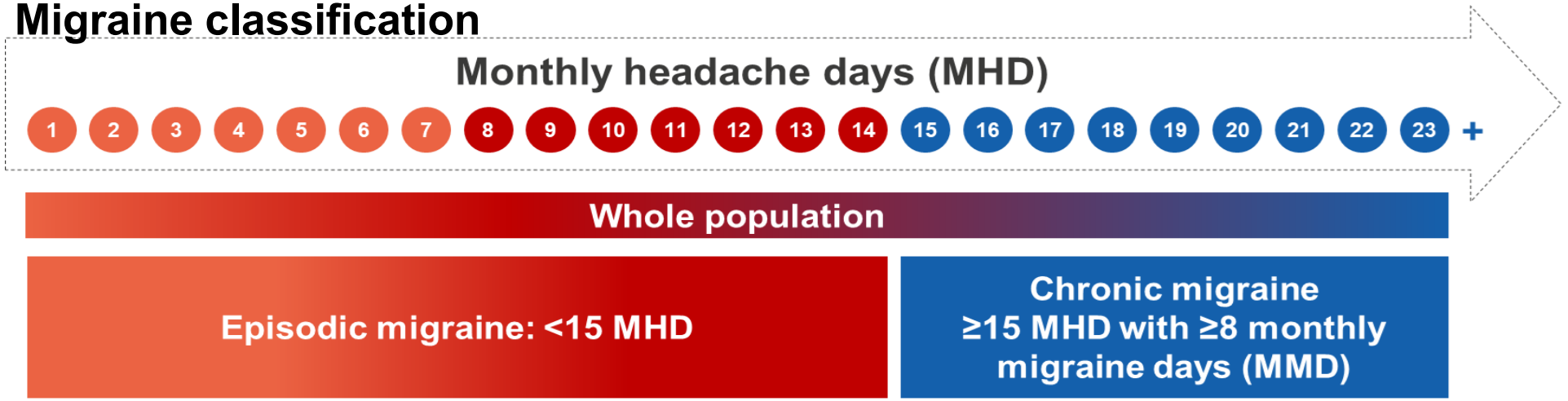
A migraine is a headache disorder with recurring attacks usually lasting 4–72 hours

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.



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Rimegepant (VYDURA, Pfizer)

Marketing authorisation (MHRA)	Rimegepant is indicated for: • Acute treatment of migraine with or without aura in adults. • Preventive treatment of episodic migraine in adults who have at least four migraine attacks per month – **TA906 recommended following ACM2.**
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 (**TA906**).
Price	List price per tablet: £12.90.

Abbreviations: MHRA, Medicines and Healthcare products Regulatory Agency; ACM, appraisal committee meeting

ACM2 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 cost-effectiveness estimates after accounting for the committee's preferred assumptions gave an ICER of £58,486 per QALY gained. This was above what NICE normally considers to be an acceptable use of NHS resources.

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Abbreviations: ACM, appraisal committee meeting; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio

ACD2 consultation comments

Comments received from:

- **Consultee comments, Pfizer:**
  - ACD response: time horizon, placebo response, stopping rule.
  - New evidence: triptan intolerant/contraindicated subgroup [redacted].
  - Base case and scenario analyses.
  - Other considerations: innovation and uncaptured benefits.
- **Patient group comments from:**
  - The Migraine Trust
- **Clinical expert & Professional group comments from:**
  - British Association for the Study of Headache (BASH)
  - Association of British Neurologists (ABN)
    - ↳Response endorsed by Royal College of Physicians
- **Web comment (n = 1)**

Abbreviations: ACD, appraisal consultation document; MMD, monthly migraine days

Consultation comments: The Migraine trust

Condition

- People with migraine are often stigmatised.
- Access to treatment early, without fear of MOH, could avoid fully developed, debilitating symptoms and prevent attacks impacting day-to-day lives.

Workplace impact

- 43% financially impacted and 74% mentally impacted due to migraines affecting their work.
- Financial burden of absenteeism/presenteeism, ~£9bn in UK 2018 (*productivity not included in NICE reference case*).
- Unmet need for those yet to find a reliable treatment option that enables them to remain at work, when attacks occur

Disadvantaged groups

- Urgent need for effective and reliable treatments that are not associated with MOH risks.
    - ↳ Particularly for people in whom current treatments e.g., triptans or NSAID, are not an option.

Targeted treatments e.g., anti-CGRP

- An oral targeted treatment with good tolerability could reduce specialist referrals, costs and waiting times; give people control back; and give chance to receive in primary care setting.

Abbreviation: MOH, medication overuse headache; mAbs, monoclonal antibodies; CGRP, Calcitonin Gene-Related Peptide; NSAID, non-steroidal anti-inflammatory drugs

Consultation comments: ABN, BASH and web comment

ABN:

NSAID and Aspirin use

- High dose NSAID or aspirin combined with antiemetic not mentioned as a comparator.
  - ↳ Particularly relevant for people who are intolerant of / cannot take triptans.
  - ↳ Evidence suggests only slightly lower efficacy for NSAIDs in acute treatment than triptans.
- Web comment: *Triptans have never worked and rely on high doses of aspirin which are still not effective enough for me to work/live - unable to work in over a year. Desperate for rimegepant to be approved for acute use, it could allow me to be a functional member of society again.*

Chronic vs Episodic

- Well known that episodic and chronic migraines may differ in treatment responsiveness.
- Trials only include people with up to 8 MMD → extrapolating cost effectiveness from episodic to chronic population may be inappropriate.

BASH:

Primary care

- Rimegepant should be available in primary care and require clarity about who can prescribe it.
- Recommendations should be consistent with Scotland.

Abbreviation: ABN, Association of British Neurologists; BASH, British Association for the Study of Headache; NSAIDs, non-steroidal anti-inflammatory drugs; MMD, monthly migraine days

Key issues

ACM2 issues resolved	ACD section
Appropriate trial population (mITT vs prespecified/post-hoc subgroup)	3.5

ACM3 issues for discussion	ACD section and committee conclusion	ICER impact
1. Triptan intolerant /contraindicated subgroup	3.21 - Request further analyses using the clinical evidence for people who cannot have triptans	Small
2. Stopping rule for acute rimegepant treatment	3.10 - Request further information about stopping rules for rimegepant as an acute treatment	Unknown
3. Time horizon	3.13 & 3.14 - A 2-year time horizon is most appropriate.	Large
4. Placebo response	3.14 – There should be no loss of placebo response at 12 months	Large
5. MMD reductions with rimegepant PRN	3.12 - MMD reductions should be removed, but may be considered a small, potential, uncaptured benefit.	Large

Abbreviations: ACM, appraisal committee meeting; ACD, appraisal consultation document; MMD, monthly migraine days; PRN, pro-re-nata (as needed); ICER, incremental cost effectiveness ratio

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, Israel and Scotland.
- 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?

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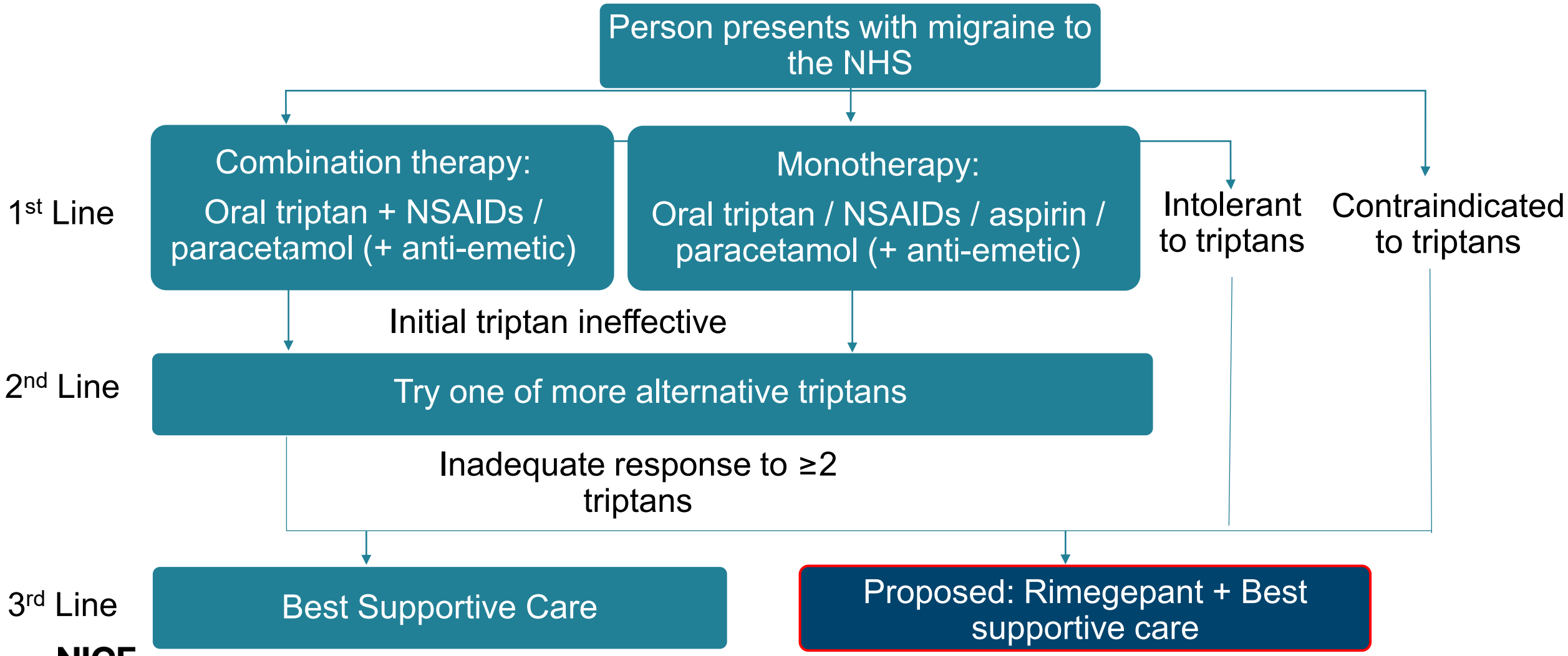
Treatment pathway

Rimegepant is proposed as 3rd line treatment for acute migraines



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Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs

Key clinical trials and outcomes

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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 with 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		
Secondary outcomes	• Reduction in headache pain • Pain relief at 2 hours		
Location	United States		
Modelled?	Yes	Yes	Yes

Abbreviations: MMD, monthly migraine days

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Additional clinical trials

	BHV3000-310 (Asian population) (n=1,340)	BHV3000-201 (long-term study) (n= 1197)
Design and duration	Multicentre, randomised, double-blind, Phase 3 trial. 11 weeks.	Multicentre, open-label, single arm, Phase 2/3 trial. 58 weeks.
Population	• Adults with 2-8 moderate-to-severe MMA • Less than 15 MMD	• Adults with 2-14 moderate-to-severe MMA
Intervention	Rimegepant 75mg	Rimegepant 75mg
Comparator	Placebo	None
Formulation	Oral dispersible tablet	Tablet
Primary outcome	• Freedom from pain at 2 hours • Freedom from MBS at 2 hours	Safety and tolerability
Secondary outcomes	• Reduction in headache pain • Pain relief at 2 hours	Post-hoc: change from baseline in mean MMD
Location	Asia	United States
Modelled?	Yes	Yes

Abbreviations: MMD, monthly migraine days; MMA, monthly migraine attacks; MBS, most bothersome symptom

Clinical trial results

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

	Base case analysis (4 RCTs*, mITT population)	Indication analysis (3 RCTs, post hoc subgroup with ≥2 triptan failures)
Outcome	Risk difference between rimegepant and placebo (95% CI; p-value)	
Pain relief at 2 hrs**	[redacted]	[redacted]
Pain freedom at 2 hrs	[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 considered mild to moderate, with low rates of severe/serious events.

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

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Abbreviations: CI, confidence interval; mITT, modified intention-to-treat; RCTs, randomised controlled trials.

Issue 1: Triptan intolerant/contraindicated subgroup (1/3)

ACM2 conclusions

- mITT population is the most appropriate trial population to use.
- Recognise unmet need when triptans are not tolerated/contraindicated and there are no further standard treatments.
- Request more analyses to see if rimegepant could be cost effective in this group.

Company ACD response

- Provided freedom from pain and pain relief at 2hr results from:
  - Contraindicated/intolerant to triptans population: people contraindicated due to cardiovascular indications and/or those that stopped at ≥1 prior triptan due to side effects.
  - Triptan refractory population: ≥2 previous triptans not worked (due to intolerability/efficacy).
  - Pooled mITT: All randomised patients who had a migraine attack of moderate to severe pain intensity, took a dose of study treatment and had ≥1 efficacy assessment.
- Believe contraindicated/intolerant subgroup results are similar to broader population subgroup.
- Given base case results are similar to full population, deemed representative and support population for which rimegepant is proposed (≥2 triptan failures).

Other considerations

BASH: Post-hoc analysis data supports potential efficacy of rimegepant in triptan non-responders.

Abbreviations: BASH, British Association for the Study of Headache

Issue 1: Triptan intolerant/contraindicated subgroup (2/3)

Comparison of results across different analysis populations

	mITT population (4 RCTs*)	Post hoc subgroup with ≥2 triptan failures (3 RCTs)	Pooled population contraindicated or intolerant to triptans (3 RCTs)
Outcome	Risk difference between rimegepant and placebo (95% CI; p-value)		
Pain relief at 2 hrs**	[redacted]	[redacted]	[redacted]
Pain freedom at 2 hrs	[redacted]	9.8 [redacted] p=0.0131	[redacted] p= 0.005

*Includes BHV3000-310 trial based on Asian population

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

Abbreviations: CI, confidence interval; mITT, modified intention-to-treat; RCTs, randomised controlled trials.

Issue 1: Triptan intolerant/contraindicated subgroup (3/3)

ERG ACD response

- Unsure how applicable subgroup analysis is to clinical practice and committee request.
  - ↳ Only required intolerance to 1 triptan - not specific to people intolerant to ≥2 triptans.
  - ↳ Clinical expert: try multiple triptans before consider ineffective. Intolerant to 1 does not rule out using others.
  - ↳ Need clarification on people in analysis: numbers are larger than ≥2 triptan failures post-hoc analysis - suggests new subgroup analysis is not limited to those with at ≥2 triptan failures.
- Notable difference in pain relief at 2 hrs (outcome in model) but freedom from pain is similar.
  - Unsure if company suggests that because subgroup results similar to mITT population = mITT analyses are applicable to contraindicated / intolerant of triptans group.
- Subgroup has baseline imbalances that may be a concern (migraine severity, aura, MBS).
- Prefer to use mITT population including 4 RCTs.

In light of the new evidence provided, is the committee satisfied that rimegepant is effective in people for whom triptans are not tolerated, or contraindicated?

Abbreviations: mITT, modified intention to treat; MBS, most bothersome symptom

Issue 2: Stopping rule for acute rimegepant treatment

ACM2 conclusions

- No continuation/stopping rule for acute migraine but included for preventing migraine (TA906).
- Given dual indication and misuse potential, committee requested acute stopping rule information.

Company ACD response

- SmPC does not include a stopping rule, similar to other acute migraine treatment options.
- Stopping rule built into model: after 1st treatment, people assigned responders/non-responders.
  - Assume those with no response will not continue treatment beyond 1st treatment pack.
  - Anticipate people who do not achieve response of 2 consecutive treatments will discontinue.
- Assume rimegepant use in practice will align with trial design - discontinue after 1 dose.

↳ Non-responders costed for full pack - accounts for waste and multiple doses to assess response.

ERG ACD response

- Stopping rules are not formal but are based on what is anticipated will happen in practice.
- Decision to stop would be based on clinician/patient discussion - company expect many would discontinue after non-response to 1 dose but others may try multiple doses.
- Discontinuation after non-response to 2 consecutive treatments but does not seem a formal rule.

Other considerations

ABN: Unreasonable to assume no response after 1 dose. Usually try treatment for 2/3 attacks.

Does the model stopping rule reflect NHS practice? Is potential misuse sufficiently addressed?

Abbreviations: SmPC, summary of product characteristics; ABN, Association of British Neurologists

Issue 3: Time horizon (1/2)

ACM2 conclusions

Costs and benefits of acute rimegepant treatment would likely be accounted for in 2-year time horizon.

Company ACD response

2 years is an unreasonable conclusion given the evidence submitted:

- ACM2 evidence:
  - >10-year time horizon (clinical expert), 20+ year disease duration (trial and ACD comments), and some remain on migraine treatment ≥5 years (RWE prescription data).
  - Illogical and inconsistent to use different time horizon for the same disease in prevention model.
- New evidence:
  - BHV3000-201 extrapolation - most people expected to be on treatment beyond 5 years.
  - At year 5, [redacted]% discontinuation rate = 31% remain on treatment (≥2 triptan failures population).

Time horizon should be 20 years:

- Significant proportion remain on treatment long-term so will incur costs and benefits for full treatment duration and accrue more benefits than those who stop early.
- No other treatments for placebo arm so have full migraine QoL and QALY impact for beyond 2 years.
- As time horizon extends, initial high costs of determining response are offset by continued benefit.

Abbreviations: RWE, real-world evidence; QALY, quality-adjusted life years; QoL, quality of life

Issue 3: Time horizon (2/2)

ERG ACD response

- No new evidence been put forward that changes position - most arguments already discussed.
- 2-year time horizon still most appropriate - when MMD reductions removed, costs and HRQoL differences relate to a short period (each specific migraine episode).
- 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 time horizon.
- Time horizon has little ICER impact on new ERG base case.
- Impact of shorter time horizon and cost of additional full pack wasted is small.

Other considerations

- BASH: 2-year time horizon not reasonable, 20-year time horizon more appropriate.
- ABN: Although acute treatment might be needed for ~20 years, people can become intolerant in later life so may need to swap to other acute therapies for only a few years.

Have the company provided appropriate/sufficient justification for why the costs and benefits of rimegepant as an acute treatment should be reflected in a time horizon longer than 2 years?

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Abbreviations: ABN, Association of British Neurologists; BASH, British Association for the Study of Headache; MMD, monthly migraine days; ICER, incremental cost-effectiveness ratio

Issue 4: Placebo response (1/4)

Background

- ACM2 conclusion: when time horizon 2 years, should be no loss of placebo response at 12 months.
- ACM3: placebo response modelled differently, removed after 1-year (company) / not removed (ERG)

Company ACD response

Implausibility of committee's preferred placebo response

- Accept a placebo response in both arms but cannot separate it in rimegepant arm.
- 2-year time horizon = 2-year placebo response (sustained indefinitely) → assumes clinical benefit without active treatment at no NHS cost.

1. Clinical advice: expect placebo response ≤1 year. 3-6 months more plausible than 12 months.
2. Literature: placebo response is plausible on active treatment, but unlikely on no treatment.
   - People pain free at 2 hrs: 0.7% (untreated) vs 7% (placebo) – similar to [redacted]% (pooled mITT).
   - ↳ Removing response after 1-year is conservative if people not on treatment.

Model assumes a natural migraine resolution

- When response removed, placebo patients' migraines still improve over each 48-hour period.

Model corrections for when there is no loss of placebo response

- Response removed = rimegepant arm had worse migraines than placebo responders (illogical).
  - ↳ Corrected to equalise migraine impact in both arms.

Abbreviations: mITT, modified intention-to-treat

Issue 4: Placebo response (2/4)

Company ACD response continued

Conservative assumption regarding mITT population placebo response

- Placebo response stronger in mITT population than ≥2 triptans failure (refractory) population (eligible for rimegepant) – model sensitive to placebo response duration assumptions.
  - Clinical experts: placebo response stronger after 1st acute treatment vs after ≥2 triptans.
  - Prevention study: refractory population tends to have lower placebo response to CGRP mAb.
  - TA906 (rimegepant): refractory population had lower placebo response vs mITT population ([redacted] vs [redacted]).

Conservative approach to BSC healthcare resource use

- Base case excluded BSC costs but in practice not possible to have BSC with no NHS cost.
- Scenario: all BSC arm and rimegepant non-responders incur healthcare costs during the 2-years.

Conservative comparison to previous technology appraisals

- No acute appraisals, took guidance from recent migraine appraisals - may be indicative.
- 10/12 neurologists: placebo response would be shorter in acute treatment than preventative.

Abbreviations: mITT, modified intention-to-treat; BSC, best supportive care; CGRP, calcitonin gene related peptide; mAb, monoclonal antibody

Issue 4: Placebo response (3/4)

ERG ACD response

Implausibility of committee's preferred placebo response

- Evidence suggests placebo effect may not last >1 year and 12 months may be conservative.
  - ↳ However, 12-months not based on literature and may be uncertainty about correct duration.
- Company acknowledge placebo response in rimegepant arm but has not removed it from model.
- Agree unlikely to get benefit from no treatment, but in clinical practice, people on BSC will have some treatment and may have a response.
- No long-term comparative evidence showing efficacy waning in placebo arm but not rimegepant.

Model assumes natural migraine resolution

- Model shows migraine severity improved at 2 hrs, but data is from whole placebo arm, not placebo non-responders.
- Unclear if company assumes that migraines could improve at 2hr when not having active treatment.

Model corrections for when there is no loss of placebo response

- Agree with correction to equalise migraine impact in both arms.
- Found another correction that gives significantly worse outcomes for people on BSC vs rimegepant non-responders (overcorrection) → ERG corrected this, and company accept change.

Abbreviations: BSC, best supportive care

Issue 4: Placebo response (4/4)

ERG ACD response continued

Conservative assumption regarding mITT population placebo response

- Accept placebo response may differ depending on number of prior treatment failures and those with more may have lower placebo effect.

↳ However, any differences equally apply to rimegepant arm = using mITT result not conservative.

- Limitations identified with ≥2 triptan failure analysis remain, particularly the baseline imbalances.

Conservative approach to BSC healthcare resource use

- Excluding BSC costs is conservative, but scenario not applied to rimegepant arm = inappropriate

Conservative comparison to previous technology appraisals

- Other migraine appraisals used 1-year response, but committee noted these were for prevention.

Other considerations

- Committee placebo response assumption is dependent on 2-year time horizon (wanted placebo effect beyond 1 year). It is not independent to mean an indefinite placebo response.
- ABN: disagree that no placebo benefits after 12 months, may be waning over time but uncertain.
  - 2-year time horizon with partial placebo response in 2nd year is reasonable .
  - 20-year time horizon with no placebo response after 12 months is less reasonable.

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Have the company provided sufficient justification for the 1-year placebo response? Which placebo response modelling is preferred (removed after 1-year/not removed)?

Abbreviations: ABN, Association of British Neurologists; mITT, modified intention-to-treat; BSC, best supportive care

Key issue 5: MMD reductions with rimegepant PRN (1/2)

ACM1 conclusions

- Acknowledge biological plausibility that taking rimegepant PRN (as needed) may reduce MMDs due to preventative properties, but not enough clinical evidence to support this.
- Should remove assumption, but it may be considered as a small, potential, uncaptured benefit.

Company

- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

Trial results at 12 weeks	≥30% reduction in MMD	≥50% reduction in MMD
BHV3000-201	[redacted]%	[redacted]%
BHV3000-318	[redacted]%	[redacted]%

- Not included in base case, but as a scenario: considerable impact on QoL benefit (0.179 vs 0.207)

Abbreviations: MMD, monthly migraine days; PRN, pro-ne-rata (as needed); QoL, quality of life

Key issue 5: MMD reductions with rimegepant PRN (2/2)

ERG ACD response

- [redacted]
- [redacted] unsure why baseline MMD reduction not compared.
- 12-month data [redacted]
- [redacted] that led to removing MMD assumption in ACM1.
- Acknowledge assumption increases incremental QALYs, but evidence insufficient to change conclusion.

Other considerations

- BASH: potential preventive effects of acute rimegepant treatment, should be taken into account.

In light of the new evidence provided, has the committee's conclusion changed about the exclusion of MMD reductions from rimegepant PRN (as needed)?

Abbreviations: BASH, British Association for the Study of Headache; MMD, monthly migraine days; PRN, pro-re-nata (as needed); QALY, quality-adjusted life years

Other considerations

Innovation

Company

- Unmet need for treatment options, particularly for those who do not respond to or unable to use triptans - people already lost out on access to new innovations e.g., lasmitidan not launching in UK.
- Rimegepant cheaper than 42.2% of triptans prescribed (accounting for redosing).
- Triptans and NSAIDs dominant treatments, no new UK approved therapies in 20+ years.

ERG: Similar risks to NHS exist e.g., resources of recommended medicines that are not cost-effective.

Uncaptured benefits

Company

- Model is conservative because it does not capture MOH or chronification (development of chronic migraines in people with episodic migraine).
    - Rimegepant has no evidence of MOH occurring in patients in pre-clinical and clinical trials
    - Only 21 cumulative non-serious MOH cases reported in post marketing safety data.

ERG

- Reduced MOH risk may be an uncaptured benefit, but limited evidence as not assessed in RCTs and unclear how robustly MOH was assessed in long-term studies.
- Poor acute treatments efficacy may increase risk of chronification, but current evidence is not conclusive, and extent of any potential benefit is unclear.

Abbreviation: NSAID, non-steroidal anti-inflammatory drugs; MOH, medication overuse headache; RCT, randomised controlled trials

Company and ERG base case assumptions

The company and ERG differ on 2 key assumptions

ACM2 assumptions	ERG base case	Company base case
Population	mITT	mITT
Study BHV3000-310	Included	Included
Baseline distribution of MMDs	Parametric distribution (Poisson)	Parametric distribution (Poisson)
Trajectories of rimegepant responders after discontinuation	BSC all-comers	BSC all-comers
MMD reductions with rimegepant PRN	Removed	Removed
Time horizon	2 years	20 years
Placebo response	Not removed	Removed after 1 year

Model corrections only impact cost-effectiveness estimates that include no loss of placebo response assumption (ERG base case)

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Abbreviations: PRN, pro-re-nata (as needed); mITT, modified intention-to-treat; BSC, best supportive care; MMD, monthly migraine days

Company and ERG base case results

Rimegepant is under £30,000 per QALY gained in both base cases

Company probabilistic base case

Technology	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	£1,320	9.46	-	-	-
Rimegepant	£3,556	9.58	£2,235	0.12	£18,444

ERG probabilistic base case

Technology	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	£111	1.34	-	-	-
Rimegepant	£860	1.36	£749	0.03	£29,281

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Results do not include any confidential commercial discounts

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

Scenario analysis: applied to company base case

Scenario	Description
Company base case	20-year time horizon, placebo response removed at 1 year
1	Discontinuation of BSC responders
2	Including BSC costs (all BSC patients)
3	Including BSC costs (BSC non-responder patients)
4	Including MMD reduction
5	Including ≥2 triptan failures population
6	Including ≥2 triptan failures population and MMD reduction
7	Contraindicated and intolerant subgroup analysis

Time horizon	Company base case	1	2	3	4	5	6	7
2-years	£27,621	£26,566	£17,809	£21,338	£18,326	£17,958	£13,955	£22,049
5-years	£20,889	£20,552	£15,013	£17,562	£14,374	£15,375	£12,095	£17,773
10-years	£19,391	£19,179	£14,391	£16,391	£13,495	£14,690	£11,623	£16,712
20-years	£18,914	£18,738	£14,193	£15,395	£13,255	£14,432	£11,478	£16,318

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Results do not include any confidential commercial discounts

Abbreviations: MMD, monthly migraine days; BSC, best supportive care

Scenario analysis: applied to ERG base case

Scenario	Description
ERG base case	2-year time horizon, no loss of placebo response
1	Discontinuation of BSC responders
2	Including BSC costs (all BSC patients)
3	Including BSC costs (BSC non-responder patients)
4	Including MMD reduction
5	Including ≥2 triptan failures population
6	Including ≥2 triptan failures population and MMD reduction
7	Contraindicated and intolerant subgroup analysis

Time horizon	ERG base case	1	2	3	4	5	6	7
2-years	£29,833	£25,703	£19,218	£23,037	£19,311	£19,676	£15,094	£24,499
5-years	£29,327	£20,530	£21,265	£24,762	£18,985	£19,434	£14,917	£24,324
10-years	£29,115	£15,055	£21,819	£24,737	£18,938	£19,293	£14,854	£24,451
20-years	£28,925	£9,486	£21,895	£23,686	£18,919	£19,116	£14,780	£24,843

NICE

Results do not include any confidential commercial discounts

Abbreviations: MMD, monthly migraine days; BSC, best supportive care

Decision making framework

Questions	Possible answers
What is the committee's preferred ICER threshold?	• £20,000 / £30,000 per QALY gained • Other
What is the committee's preferred population?	• Contraindicated and intolerant subgroup analysis • Full indication population (≥2 triptan failures)
What is the committee's preferred ICER?	?
Is the ICER below the preferred ICER threshold? If yes, recommended for routine commissioning?	• Yes / No • Yes / No
What are committee's preferred assumptions? • Time horizon • Placebo response • BSC costs • MMD reduction • ≥2 triptan failures population	Assumptions: • Time horizon: 2 or 20 years • Placebo response: removed after 1-year / not removed • BSC costs: included / excluded • MMD reduction: included / excluded • Population: ≥2 triptan failures / mITT
What, if any, are the remaining uncertainties?	?

Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life years; MMD, monthly migraine days; BSC, best supportive care; mITT, modified intention-to-treat

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Thank you.

Model correction impact on committee preferred base case

Technology	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ACM2 committee base case (2-year time horizon, no loss of placebo response)			
Rimegepant vs BSC	£1,182	0.02	£58,486
1. Company model correction			
Rimegepant vs BSC	£1,182	0.02	£56,125
2. ERG revised base case (subsequent model correction, accepted by company)			
Rimegepant vs BSC	£1,124	0.04	£29,833

1. Previous model assumed rimegepant responders who discontinue maintain a response for same period as placebo response time. If placebo response not removed, these people default to placebo non-responder trajectories.
   - Company correction means that if placebo response not removed, people who initially respond to rimegepant and discontinue, now follow trajectory of placebo all-comer group (same as BSC arm).
2. People who do not respond to rimegepant in 1st cycle and discontinue adopt placebo non-responder trajectories. This is reasonable if placebo response is a limited time. But if not removed, results in rimegepant being unjustifiably disadvantaged vs BSC.
   - ERG changed this so all people who discontinue rimegepant (either initially or after a response) would have equivalent outcomes to BSC arm.

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