Single Technology Appraisal

Rimegepant for treating acute migraine [ID1539]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Rimegepant for treating acute migraine [ID1539]

Contents:

The following documents are made available to stakeholders:

1. **Response to consultee, commentator and public comments on the appraisal consultation document (2)**

2. **Comments on the appraisal consultation document (2) from** Pfizer**:**
   a. Main response
   b. Appendix
   c. Response to ERG clarification questions on ACD2 response
   d. Additional data in response to ERG clarification point in ACD2 response critique (document 5).

3. **Consultee and commentator comments on the appraisal consultation document (2)** from:
   a. Migraine Trust
   b. Association of British Neurologists – endorsed by the Royal College of Physicians
   c. British Association for the Study of Headache

4. **Comments on the appraisal consultation document (2) received through the NICE website**

5. **External Academic Group critique of company response to the appraisal consultation document (2)**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Appraisal title

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Company	Pfizer	**An indefinite placebo response is implausible and generates perverse results –** ICERs reduce significantly with a more appropriate (although still highly conservative) assumption of 1 year placebo response in the triptan refractory population. 1. The committee is indirectly concluding that acute migraine in the placebo population does not require any treatment given they can receive no treatment and have an indefinite response. It is clinically implausible for a placebo response to last indefinitely (2 years+) which was further supported by clinical survey and the literature; therefore, it should remain at the conservative duration of 1 year. 2. The Committee's preferred inputs effectively translate to an assumption that patients who discontinue rimegepant experience worse migraine attacks than indefinite placebo responders; furthermore, this	Thank you for your comment. The committee considered the additional evidence provided regarding the most appropriate placebo response duration. Please see FAD section 3.14. This a summary of the company's response. To see the full response, please go to page 5 of the company's ACM2 response.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			results in rimegepant not being cost-effective at zero-cost with longer time horizons. • A correction has been supplied so that migraine impact is comparable for rimegepant discontinuers and placebo, albeit an indefinite placebo response remains clinically implausible. • The correction reduces the ICER from £58,486 to £43,989 under the Committee's preferred assumptions. 3. Given concerns raised during ACM2, clarification on the implication of the placebo response stopping after 1 year in the model is provided.	
2	Company	Pfizer	**Company's current conservative placebo response approach -** ICERs decrease with the application of triptan refractory subgroup data and the inclusion of BSC costs. 1. Impact of a larger placebo response from application of the wider mITT population in the model vs. the refractory sub-population was not adequately considered. Additionally, this is supported by previous studies whereby a low placebo response in treatment experienced patients was observed. • It is worth noting, with the Committee's and	Thank you for your comment. The committee considered the additional evidence provided regarding the most appropriate placebo response duration. Please see FAD section 3.14. This a summary of the company's response. To see the full response, please go to page 8 of the company's ACM2 response.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Company's preferred assumptions all scenarios are cost-effective under a £25,000 WTP threshold, when using the refractory population, for whom rimegepant is proposed. 2. No BSC (placebo) healthcare costs have been considered. Maintaining full placebo response without additional specialist patient support, as provided in a trial is implausible. • The ICER lowers when BSC (placebo) healthcare costs are included in the analyses. 3. Greater conservatism in placebo response than previously accepted by NICE was not considered further supported by clinician survey.	
3	Company	Pfizer	**Time horizon -** rimegepant remains cost-effective with 5/10/20 year time horizon. 1. Unreasonable conclusion in light of clear evidence from trial demographics, KOLs and patient testimonial disease beyond 20 years and prescription data beyond 5 years. 2. Evidence suggest that a significant proportion of patient will receive Rimegepant long-term and the alternative for these patients is to receive no treatment where they would continue to experience	Thank you for your comment. The committee considered the additional evidence provided regarding the most appropriate time horizon. Please see FAD section 3.13. This a summary of the company's response. To see the full response, please go to page 11 of the company's ACM2 response.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			the full detrimental quality-of-life impact of their migraines, it is reasonable to conclude there are significant QALY gains to be accounted well beyond 2 years. 3. The model structure supports the need for a longer time horizon as patients who are not gaining benefit early whilst incurring costs in the model move to non-responders, therefore average QALY gain for patients on rimegepant improves over-time. 4. Rimegepant remains cost-effective under a £25,000 WTP threshold with an ICER of £18,914 per QALY with a 20 year time horizon under the Company's base case.	
4	Company	Pfizer	**Stopping rule** To address Committee concerns, clarity around a stopping rule has been provided.	Thank you for your comment. The committee considered the additional evidence provided regarding the stopping rule for rimegepant as an acute treatment. Please see FAD section 3.10. This a summary of the company's response. To see the full response, please go to page 13 of the company's ACM2 response.
5	Company	Pfizer		Thank you for your comment. The

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			[redacted] - reinstating MMD reduction in the model reduces the ICER significantly. [redacted] 2. Analyses reinstating MMD reduction in the model lowers the Company's base case to an ICER of £13,255 per QALY, further highlighting the conservative approach taken in the Company's current base case.	committee considered the additional evidence provided regarding the inclusion of reduced MMD from rimegepant PRN (pro-re-nata [as needed]). Please see FAD section 3.12. This a summary of the company's response. To see the full response, please go to page 13 of the company's ACM2 response.
6	Company	Pfizer	**Contraindicated and intolerant to triptans subgroup analyses** demonstrate cost-effectiveness similar to the company base case and supported the population for which rimegepant is proposed. 1. The subgroup analysis requested by committee was provided for completeness, with similar results to the Company's base case and supportive of recommendation in the full population for which rimegepant is proposed. 2. It is worth noting, with the Committee's and Company's preferred assumptions all scenarios are cost-effective under a £25,000 WTP threshold, when	Thank you for your comment. The committee considered the additional evidence provided regarding the cost-effectiveness of rimegepant in the contraindicated and intolerant to triptans subgroup. Please see FAD section 3.6. This a summary of the company's response. To see the full response, please go to page 15 of the company's ACM2 response.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			applying the MMD reduction.	
7	Company	Pfizer	**Uncaptured benefit** – likely to be conservative to the cost-effectiveness of Rimegepant. 1. The model does not include MOH or chronification.	Thank you for your comment. The committee considered the uncaptured benefits of rimegepant as an acute treatment in its decision making. Please see FAD section 3.20. This a summary of the company's response. To see the full response, please go to page 15 of the company's ACM2 response.
8	Company	Pfizer	**Risk to new innovative medicine** as cost-effectiveness is difficult to prove under stringent assumptions. The current Committee position threatens future innovation within the acute migraine space and creates inequalities for acute migraine patients who have already lost out on access to new innovations. • Rimegepant is cheaper than 42.2% of currently prescribed triptans. • Proving cost-effectiveness is impossible (increasing the time horizon of the committee's preferred analysis finds that rimegepant is not cost	Thank you for your comment. The committee considered the innovative nature of rimegepant as an acute migraine treatment in its decision making. Please see FAD section 3.20. This a summary of the company's response. To see the full response, please go to page 15 of the company's ACM2 response.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			effective at £0.00). • Lasmiditan did not enter the UK market as could not prove cost-effectiveness. • No new therapies have entered the market in the past 20 years.	
9	Company	Pfizer	**Revised acute model and scenario analyses –** rimegepant remains cost-effect with new list price in the company's base case. 1. The Company's revised and conservative base case demonstrates rimegepant is a cost-effective use of NHS resources with an ICER of £18,914.	Thank you for your comment. The additional evidence and updated cost effectiveness analyses were considered by the committee. Please see FAD section 3.17. This a summary of the company's response. To see the full response, please go to page 17 of the company's ACM2 response.
10		Association of British Neurologists headache and pain advisory group (ABN) – response endorsed by Royal College of Physicians (RCP).	There is no mention of the use of high dose NSAID or aspirin combined with an antiemetic as a comparator treatment. This is particularly relevant for people who are intolerant of / cannot take triptans. Evidence suggests an only slightly lower efficacy for NSAIDs in acute treatment than triptans. (VanderPluym. Acute Treatments for Episodic Migraine in Adults: A Systematic Review and Meta-analysis. *JAMA.* 2021;325(23):2357–2369)	Thank you for your comment. The committee considered the most appropriate comparators for rimegepant as an acute treatment. Please see FAD section 3.3.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
11		ABN – response endorsed by RCP.	Modelling response 3.10: we consider that it is not reasonable to consider failure to respond to one dose of rimegepant to assume there never would be a response: it would be standard practice to encourage a patient to try a treatment for 2 or 3 attacks to assess efficacy.	Thank you for your comment. The committee considered the stopping rule and the appropriateness of modelling rimegepant response. Please see FAD section 3.10.
12		ABN – response endorsed by RCP.	As discussed in the appraisal, it is widely recognised that episodic and chronic migraine may differ in their responsiveness to acute and preventive medication and that the RCTs only included those with up to 8 migraine days /month and therefore extrapolation of cost effectiveness to the high-frequency episodic and chronic population may not be appropriate.	Thank you for your comment. The committee considered the generalisability of the trial results. Please see FAD section 3.7.
13		ABN – response endorsed by RCP.	The time horizon modelling for cost effectiveness is difficult: although people with migraine may need acute treatment for approx. 20 years they may be tolerant of triptans (or NSAIDs) in their younger life but intolerant in later life as cardiovascular risks accrue and so may need to switch to other acute therapies for only a few years in later life	Thank you for your comment. The committee considered the most appropriate time horizon. Please see FAD section 3.13.
14		ABN – response endorsed by RCP.	Placebo response 3.14: we do not agree that people having response to placebo no longer have any benefit after 12 months; there may be some waning of placebo response over time but this is uncertain. We agree that a 2-year time line may be reasonable for cost effectiveness estimates may be reasonable but including at least a partial placebo response in the 2nd year. A 20-year time horizon for cost-effectiveness estimates with no placebo response after 12 months is less reasonable.	Thank you for your comment. The committee considered the most appropriate placebo response duration. Please see FAD section 3.14.
15		British	**Has all of the relevant evidence been taken into**	Thank you for your comment. The

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		Association for the Study of Headache (BASH)	**account?** BASH agrees that most of the relevant evidence has been taken into account, but we would like to draw the committee's specific attention to the data supporting the potential efficacy of rimegepant in triptan non-responders, including the subgroup analysis presented by the company in their response to the original draft ACD, as well as the following recently published paper: Lipton RB, Blumenfeld A, Jensen CM, Croop R, Thiry A, L'Italien G, et al. Efficacy of rimegepant for the acute treatment of migraine based on triptan treatment experience: Pooled results from three phase 3 randomized clinical trials. Cephalalgia. 2023;43(2):3331024221141686	committee considered the additional evidence provided regarding the cost-effectiveness of rimegepant in the contraindicated and intolerant to triptans subgroup. Please see FAD section 3.6.
16		BASH	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** BASH do not believe that the summaries of clinical and cost effectiveness currently represent a reasonable interpretation of the evidence. We have two major areas of concern. Firstly, we do not think that the time horizon that the committee has chosen to use to capture the potential benefits and costs of treatment is reasonable. The decision of the committee to use a two-year time horizon goes against virtually all the clinical opinions provided to it, comprising the considered views of GPs, neurologists involved in headache management, and, for the avoidance of doubt, BASH. We regard a 20-year timescale as appropriate to capture the costs and	Thank you for your comment. The committee considered the additional evidence provided regarding the most appropriate time horizon, the reduction in MMD from rimegepant PRN and the cost-effectiveness of rimegepant in the contraindicated and intolerant to triptans subgroup. Please see FAD section 3.6, 3.12 and 3.13.

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			benefits associated with the acute treatment of migraine, and we call on the committee to use this timescale in deriving their cost effectiveness data. We also believe that it would be appropriate to derive cost effectiveness data with due regard to the data contained in the subgroup analyses that present the response rates in triptan non-responders (our opinion is here supported by the data in the paper cited in the answer to the previous question). We do not feel that the potential preventive effects of the acute use of the measurement should be taken into account for the specific analysis of rimegepant as an acute medication, however.	
17		BASH	**Are the recommendations sound and a suitable basis for guidance to the NHS?** We do not think that this is the case, because of the issues raised above. We also request greater clarity in the final determination about who can prescribe rimegepant. The view of BASH remains that the drug should be available for prescription in primary care, and that the situation in England and Wales should insofar as it is possible be made consistent with that in Scotland.	Thank you for your comment. The committee considered the potential use of rimegepant in primary care. It is anticipated that it will be initiated under a specialist in secondary care and prescribed in primary care. Please see TA906 FAD, section 3.13.
18		BASH	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race,**	Thank you for your comment.

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			religion or belief, sex or sexual orientation? We have no concerns in this area.	
19		The Migraine Trust	**The Workplace Impact** We feel that the current recommendation does not fully incorporate the impact of performance at work on the individual with migraine as well as society overall, and the crucial role of an effective acute treatment in mitigating this. From our latest 2023 workplace survey of 1002 people, the lighting (83%), stress (79%), screen use (58%) and noise (54%) came out as significant triggers. Respondents were quoted as saying: "*I'm considering taking a demotion to reduce stress which triggers migraines*" and "*I try to manage my migraines around work and I go to bed when I finish. I'm very lonely, no social life or quality of life with any friends. Feel restricted in life as abiding triggers. Feel like I let me children down*". In our previous submission we highlighted the financial burden of reduced productivity (presenteeism and absenteeism). We believe this demonstrates an unmet need for this significant group of people with migraine, who are yet to find an reliable treatment option that enables them to	Thank you for your comment. The reference case stipulates that the perspective on outcomes should be all direct health effects whether for patients or, where relevant, other individuals (principally carers). The perspective adopted on cost should be that of the NHS and PSS. If the inclusion of a wider set of costs or outcomes is expected to influence the results significantly, such analysis should be presented in addition to the reference case analysis; see section 5.1.7–5.1.10 of the Guide to the methods of technology appraisal. Please see FAD section 3.19.

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			function and remain at work, when attacks occur.	
20		The Migraine Trust	**Stigma, Discrimination and Equality Issues** Stigma is associated with migraine. When we asked people with migraine to describe in one word, how migraine made them feel, we received responses such as: 'debilitated, despair, isolated, trapped, misunderstood, frustrated, disadvantaged, traumatised, sick, scared, helpless..' (2023) In our previous submission, our surveys highlighted the lack of understanding people with migraine found and the negative impact on work, mental health and relationships. This is again reflected in our 2023 workplace survey. Unfortunately, people with migraine continue to report this experience. • 30% felt harassed or victimised at work, • 34% felt discriminated at work, • 43% felt they haven't been believed when taking sick leave due to a migraine attack and • 34% don't feel their colleagues take migraine seriously. Migraine also plays a large part in people's mental health, the same 2023 survey showed that 74% of people said that migraine has had a negative affect on their mental health. The majority of people affected by migraine are women	Thank you for your comment. The committee considered this evidence in its decision making and takes matter of equalities into careful consideration during the appraisal process – see FAD section 3.1 and 3.19.

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			who unfortunately live with the disadvantages associated with frequent migraine and their needs should be addressed with appropriate treatment. We believe that people who can treat early, at the first signs of a migraine attack, can avoid the fully developed, debilitating symptoms. Furthermore, access to an acute treatment that can be used in the early stages, without a fear of associated medication overuse issues and is well tolerated, could avoid attacks developing to a stage that impacts on activities and function and hence avoid much of the associated stigma and discrimination.	
21		The Migraine Trust	**Disadvantaged groups** People who are not able to use an existing acute treatment due to side effects, contraindications (for example cardiovascular conditions) and risks of medication overuse continue to be severely disadvantaged. • 43% (and 57% for chronic migraine), said they had been impacted financially because of how migraine affected their career or employment status (TMT workplace survey, 2023). Career choice was impacted, where 25% felt they had to leave their job, 29% chose to work part time instead of full time, 22% faced disciplinary action for absence due to migraine, and the negative mental health impact (74%) have been significant.	Thank you for your comment. The committee takes matter of equalities into careful consideration during the appraisal process – see FAD section 3.19.

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22		The Migraine Trust	**The role of appropriate targeted treatments such as anti-CGRP medicines** Our CGRP mAb survey conducted earlier this year (n= 500), found a greater than 80% benefit for respondents in terms of reduced migraine attack frequency and overall quality of life. We feel that a treatment that specifically targets cgrp in migraine, such as Rimegepant, should be made available as it has the potential to alleviate the devastating personal and economic costs of migraine. As an acute treatment, the oral route of administration of rimegepant gives control back to the patient, who can treat early and appropriately to get the best relief. As an oral treatment with good tolerability, it could provide an excellent opportunity for patients to receive the treatment in the primary care setting. Effective and reliable acute treatments which crucially, do not have associated risks of medication overuse headache are urgently needed for people with migraine and for the hugely disadvantaged group of people for whom the currently recommended triptans and NSAIDs are not an option. Treating acute attacks better could reduce the number of referrals to specialists and associated costs and waiting times.	Thank you for your comment. The committee considered the additional evidence provided regarding the cost-effectiveness of rimegepant in the contraindicated and intolerant to triptans subgroup. Please see FAD section 3.6.
23		Web	I am desperate for this to be approved for acute use. I	Thank you for your comment. The

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		comment	have never had any effectiveness from triptans, and I'm out of hope. I rely on high doses of aspirin which still doesn't work enough for me to work/live my life. I'm an NHS worker but haven't been able to go in for over a year. This could make me a functional member of society again. Please.	committee recognised that migraine is a debilitating condition that substantially affects physical, social, psychological and professional aspects of life. See FAD section 3.1.

Rimegepant for treating acute migraine [ID1539]

DG 2 Company Comments

Summary

Pfizer is disappointed that National Institute for Health and Care Excellence (NICE) have chosen not to recommend rimegepant for the treatment of acute migraine following the second Appraisal Committee Meeting (ACM) on April 13th, 2023.

It is important to remind the Committee that there is a considerable unmet need in England and Wales for people suffering with acute migraine, particularly for those who cannot take or do not respond to non-steroidal anti-inflammatory drug (NSAIDs) and triptans. Pfizer believe that rimegepant can support the optimal management of acute migraine within primary care and avoid the need for costly referrals to neurology or for expensive injectable/nasal options. Rimegepant can further aid the optimal management of migraine by minimising chronification and medication overuse headaches (MOHs) at first use.

The current Committee position threatens any future innovation within the acute migraine space and creates inequalities for acute migraine patients who have already lost out on access to new innovations. Pfizer remains committed to securing a positive outcome which will enable patient access to rimegepant. To support this, we wish to respond to the draft guidance (DG) document and highlight some major concerns with the Committee's preferred cost-effectiveness analysis:

- ***An indefinite placebo response is implausible and generates perverse results –*** Maintaining placebo response in the absence of treatment for the entire time horizon as assumed by the Committee is clinically implausible and unreasonable in light of the evidence provided. The committee is indirectly concluding that acute migraine in this population does not require any treatment given they can receive no treatment and have an indefinite response. In addition, the Committee's preferred base case generates perverse results in the model for which a correction has been provided.
- ***Company's current conservative placebo response approach –*** Pfizer believes the Committee did not fully take into consideration the overall conservative placebo assumptions including:
    - Stronger placebo response from the modified intention to treat (mITT) population.
    - No Best supportive care (BSC, i.e., placebo) arm costs included in the base case.
    - Placebo assumption is more conservative than previously accepted by Committee D.
- ***Time horizon*** – Pfizer believes that the Committee's preferred 2-year time horizon does not adequately reflect the nature of the condition and is unreasonable in light of the evidence presented.

In addition, Pfizer believe that it is worth noting several other considerations that support a positive recommendation for rimegepant:

- [redacted]

- The uncaptured benefit of MOH and chronification.
- Lower treatment cost per acute migraine than other acute migraine treatments that the NHS makes available without restriction.

The cost of rimegepant was previously reduced from £20 to £12.90 per tablet (daily cost) which is significantly below that of other last resort triptans (injectable & nasal). With this list price, Rimegepant remains cost-effective with the company's base case with an ICER of £18,914 per QALY or less in scenarios. Furthermore, with the correction to the committee base-case, incorporation of either the reduction in MMD or the utilisation of the correct refractory population alone also results in cost-effectiveness below £25,000 per QALY.

Pfizer's response is summarised in Table 1 below, followed by the response in full.

Table 1 A summary of the Company's response

#	Item and impact	Summary
1	**An indefinite placebo response is implausible and generates perverse results –** ICERs reduce significantly with a more appropriate (although still highly conservative) assumption of 1 year placebo response in the triptan refractory population.	1. The committee is indirectly concluding that acute migraine in the placebo population does not require any treatment given they can receive no treatment and have an indefinite response. It is clinically implausible for a placebo response to last indefinitely (2 years+) which was further supported by clinical survey and the literature; therefore, it should remain at the conservative duration of 1 year. 2. The Committee's preferred inputs effectively translate to an assumption that patients who discontinue rimegepant experience worse migraine attacks than indefinite placebo responders; furthermore, this results in rimegepant not being cost-effective at zero-cost with longer time horizons. • A correction has been supplied so that migraine impact is comparable for rimegepant discontinuers and placebo, albeit an indefinite placebo response remains clinically implausible. • The correction reduces the ICER from £58,486 to £43,989 under the Committee's preferred assumptions. 3. Given concerns raised during ACM2, clarification on the implication of the placebo response stopping after 1 year in the model is provided.
2	***Company's current conservative placebo response approach*** **-** ICERs decrease with the application of triptan refractory subgroup data and	1. Impact of a larger placebo response from application of the wider mITT population in the model vs. the refractory sub-population was not adequately considered. Additionally, this is supported by previous studies whereby a low placebo response in treatment experienced patients was observed. • It is worth noting, with the Committee's and Company's preferred assumptions all scenarios are cost-effective under a £25,000 WTP

	the inclusion of BSC costs.	threshold, when using the refractory population, for whom rimegepant is proposed. 2. No BSC (placebo) healthcare costs have been considered. Maintaining full placebo response without additional specialist patient support, as provided in a trial is implausible. • The ICER lowers when BSC (placebo) healthcare costs are included in the analyses. 3. Greater conservatism in placebo response than previously accepted by NICE was not considered further supported by clinician survey.
3	**Time horizon -** rimegepant remains cost-effective with 5/10/20 year time horizon.	1. Unreasonable conclusion in light of clear evidence from trial demographics, KOLs and patient testimonial disease beyond 20 years and prescription data beyond 5 years. 2. Evidence suggest that a significant proportion of patient will receive Rimegepant long-term and the alternative for these patients is to receive no treatment where they would continue to experience the full detrimental quality-of-life impact of their migraines, it is reasonable to conclude there are significant QALY gains to be accounted well beyond 2 years. 3. The model structure supports the need for a longer time horizon as patients who are not gaining benefit early whilst incurring costs in the model move to non-responders, therefore average QALY gain for patients on rimegepant improves over-time. 4. Rimegepant remains cost-effective under a £25,000 WTP threshold with an ICER of £18,914 per QALY with a 20 year time horizon under the Company's base case.
4	**Stopping rule**	To address Committee concerns, clarity around a stopping rule has been provided.
5	[redacted] - reinstating MMD reduction in the model reduces the ICER significantly.	1. [redacted] Analyses reinstating MMD reduction in the model lowers the Company's base case to an ICER of £13,255 per QALY, further highlighting the conservative approach taken in the Company's current base case.
6	**Contraindicated and intolerant to triptans subgroup analyses** demonstrate cost-	1. The subgroup analysis requested by committee was provided for completeness, with similar results to the Company's base case and supportive of recommendation in the full population for which rimegepant is proposed.

	effectiveness similar to the company base case and supported the population for which rimegepant is proposed.	2. It is worth noting, with the Committee's and Company's preferred assumptions all scenarios are cost-effective under a £25,000 WTP threshold, when applying the MMD reduction.
7	**Uncaptured benefit** – likely to be conservative to the cost-effectiveness of Rimegepant.	1. The model does not include MOH or chronification.
8	**Risk to new innovative medicine** as cost-effectiveness is difficult to prove under stringent assumptions.	The current Committee position threatens future innovation within the acute migraine space and creates inequalities for acute migraine patients who have already lost out on access to new innovations. • Rimegepant is cheaper than 42.2% of currently prescribed triptans. • Proving cost-effectiveness is impossible (increasing the time horizon of the committee's preferred analysis finds that rimegepant is not cost effective at £0.00). • Lasmiditan did not enter the UK market as could not prove cost-effectiveness. • No new therapies have entered the market in the past 20 years.
9	**Revised acute model and scenario analyses –** rimegepant remains cost-effect with new list price in the company's base case.	1. The Company's revised and conservative base case demonstrates rimegepant is a cost-effective use of NHS resources with an ICER of £18,914.

1. An indefinite placebo response is implausible and generates perverse results

Pfizer has several concerns regarding the Committee's conclusion regarding the placebo response which are described below, in terms of:

- Implausibility of an indefinite placebo response
- Unintended and implausible consequence of the Committee's proposed application of placebo response

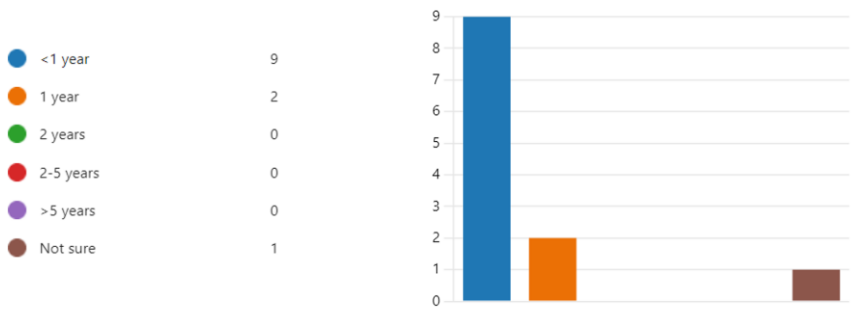
<u>Implausibility of an indefinite placebo response</u>

If the Committee maintains its view on a 2-year time horizon, it appears to also assume that placebo response is sustained indefinitely. A 2-year placebo response assumes patients will receive clinical improvement without active treatment and with no cost to the National Health Service (NHS) in that time. An indefinite placebo response is clinically implausible and not supported by clinical advice nor literature (further details below).

Clinical advice

Clinician insights highlight the clinically implausible nature of Committee's conclusion regarding placebo at ACM2. Clinicians were not present at the ACM2 and given the clinical nature of these discussions, we welcome input from clinicians at the next ACM.

- Clinical experts support a placebo duration of 1 year as per the Company's base case, both in a recent survey and at an advisory board. Given the absence of clinicians at ACM2, Pfizer sought input from Neurologists to better understand the potential benefits associated with a placebo response in acute treatment of migraine with or without aura in adults who have failed 2 or more triptans.
    - A survey of 12 Neurologists was conducted following ACM2 across the UK. The unanimous clinical view was that a placebo duration of 1 year or less is expected for the acute treatment of migraines.
        - Neurologists were asked 'Based on your experience and/or clinical judgement, for how many years on average do you think a placebo effect after a patient has failed two triptans, and remains on baseline standard care typically lasts in terms of the acute treatment for migraine?



- To remind the Committee, these results are consistent with an advisory board that was held in March 2022 with a broad range of consultants from primary, secondary, and tertiary care, including General

practitioners (GPs), GPs with special interest in headache, neurologists, pharmacists, nurse specialists, pain specialists, and health economists (Company Submission Document B, page 112). During the advisory board it was noted 12 months would be considered a long time for a patient to experience placebo response, whereas a 3 month duration would be more clinically plausible. Some experts accepted 6 months as a reasonable timeframe. This supported Pfizer's decision that placebo waning occurs over a period of 12 months.

Literature

Pfizer ask that the Committee reconsider the plausibility of an indefinite placebo response.

- The Committee raised concerns that "all effects associated with the placebo response would likely also be seen in the Rimegepant arm and so cannot reasonably be removed from 1 treatment arm but not the other". Pfizer acknowledge that both arms may be associated with a placebo response and disentangling the placebo response from the intervention arm may be challenging. However, in clinical practice, a placebo response could plausibly be experienced by patients receiving an active treatment such as rimegepant, but it is highly unlikely those receiving no treatment would benefit from any placebo response, thus we suggest it is reasonable to remove indefinite placebo response from the 'no-treatment/BSC' arm. This point is clearly demonstrated in a study of migraine where patients could receive no treatment, placebo or rizatriptan.[2] It found that:
    - There is a difference between no treatment and placebo - untreated patients performed 25% worse than patients who took anything labelled as placebo at 2 hours post "dose".
    - Untreated patients on average saw their pain increase at 2 hours post headache, whereas it declined in placebo patients, which supports the Company's model assumption of limited benefit for patients in the initial 2 hour window and therefore removing placebo response after 1 year is highly conservative if patients are truly on no treatment.
    - Only 0.7% of untreated patients achieved pain freedom at 2 hours, unlike placebo, which was approximately 7% and similar to the pooled mITT analysis ([redacted]
- Pfizer acknowledge that we cannot disentangle a placebo response for those receiving rimegepant, consequently a conservative approach was taken. But maintaining an indefinite placebo response for those patients who have no alternative treatment options is implausible and makes it almost impossible for any new acute treatment to demonstrate cost-effectiveness, confirmed by how if rimegepant is costed at £0.00 it remains not cost-effective over longer time horizons.

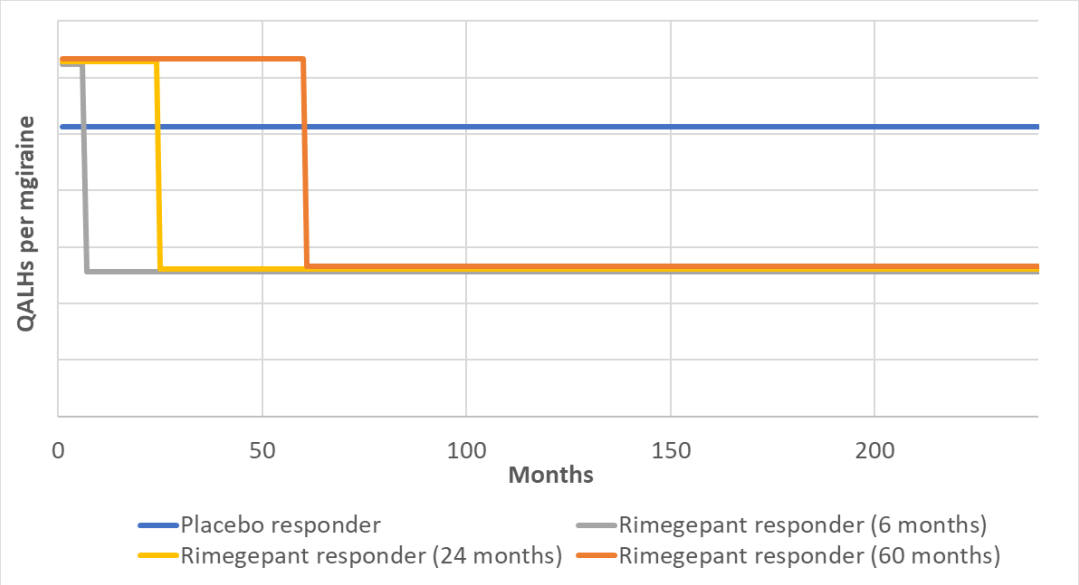
<u>Misconception in the application of placebo response</u>

A corrected model has been supplied to inform decision making appropriately.

There is an unintended consequence of the Committee's preferred model settings when removing the placebo waning assumptions in the model. When the placebo waning assumptions are removed, it results in those receiving rimegepant experiencing worse migraine attacks compared to placebo responders, which is illogical.

- Figure 1 demonstrates the extent to which those taking rimegepant are penalised compared to a placebo responder in the current committee preferred scenario. Patients who respond to rimegepant could for example receive treatment for 6, 24 or 60 months, respectively, and then discontinue treatment. These patients would then proceed to have worse migraine attacks compared to a patient that responded to placebo and maintained an indefinite response.
- As a correction of the committee's preferred analysis a logic was applied in the model to ensure that a patient who had received rimegepant for any duration does not result in having worse migraine attacks than a placebo patient.
- The assumptions applied in Figure 1 contradict clinical expert opinion, are not supported by clinical data and from a lay perspective cannot be considered logical.

Figure 1 Placebo responders versus rimegepant discontinuers overtime



- The Company have provided corrected analyses below, equalizing the effect in both arms, presented inTable 2, which decreases the incremental cost-effectiveness ratio (ICER) from £58,486 to £43,989. Additionally, the corrected ICERs now decrease over time. Please note, the correction is explained in detail in the Appendix and does not apply to the company base case.

Table 2 Committee's preferred placebo response assumption by time horizon – uncorrected and corrected

Scenarios	Incremental QALYS	Incremental costs	ICER (£/QALY)
Uncorrected*			
2 year time horizon (Committee's preferred base case)	0.0202	£1,182	£58,486
5 year time horizon	0.0234	£2,329	£99,561
10 year time horizon	-0.0094	£3,373	Rimegepant dominated

20 year time horizon	-0.0949	£4,180	Rimegepant dominated
Corrected			
2 year time horizon (Committee's preferred base case)	0.0265	£1,167	£43,989
5 year time horizon	0.0624	£2,253	£36,126
10 year time horizon	0.1133	£3,148	£27,788
20 year time horizon	0.1898	£3,655	£19,250

**Please note, these results were carried out using the previous model without the model correction to equalize rimegepant discontinuers and placebo responders.*

Clarification point

Given the potential confusion around the implication of the application of placebo response stopping after 1 year in the model during ACM2. Pfizer would like to clarify when the model assumes that placebo response stops after 1 year, the model still incorporates natural resolution of the migraine for all patients. This is demonstrated in the 48-hour pain trajectory heat maps presented in the Appendix, Figure 1. When placebo response is removed, placebo patients' migraines still improve and resolve over each 48-hour period.

2. Company's current conservative placebo response approach

We request that the Committee acknowledge the conservative approach taken by the Company in relation to modelling the placebo response and ask them to take it into consideration in their decision making.

Pfizer acknowledge there are challenges when accounting for placebo responses in models and therefore a considerably conservative approach in terms of placebo assumptions were made in our base case. Taking into account previous Technology Appraisal (TAs) precedent and clinical opinion, the Company believes that this further demonstrates its conservative approach. We do not think that these have fully been taken into consideration by the Committee as a whole, thus they are noted below.

Conservative assumption regarding mITT population placebo response

We request the Committee acknowledge the mITT population in the base case present with a stronger placebo response than that of the population for which rimegepant is proposed, as a result the placebo response is inflated, and the modelling approach is conservative.

The placebo response is stronger in the wider mITT population (the Committee's preferred population) than in that of the narrower refractory population (failed ≥2 triptans) for whom rimegepant is proposed, as demonstrated in Table 1 of the Appendix. This exacerbates the sensitivity of the economic model to assumptions of placebo response duration.

Rimegepant is cost-effective under the £25,000 WTP using the Committee's preferred assumption using the narrower refractory population (failed ≥2 triptans) for whom rimegepant is proposed (Table 3), with an ICER of £22,719 per QALY.

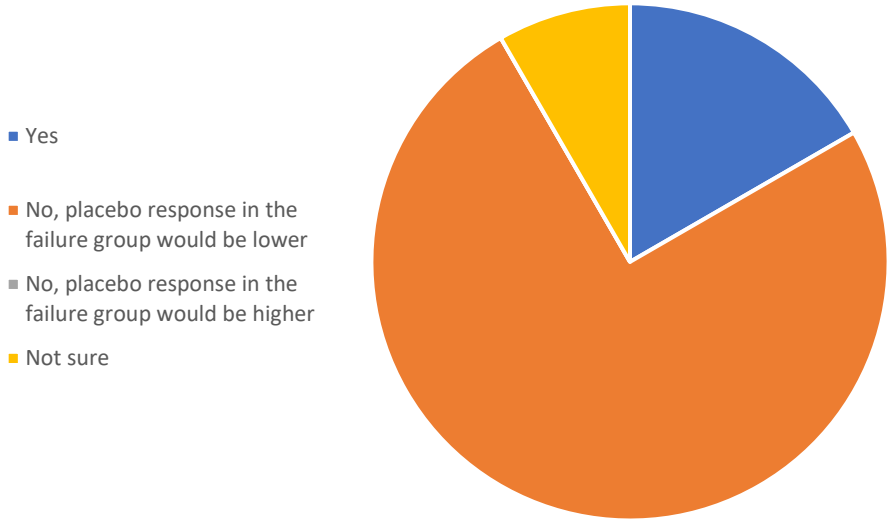
Table 3 Refractory population scenario analyses

Scenarios	Incremental QALYS	Incremental costs	ICER (£/QALY)
Committee's preferred base case *			
2 year time horizon	0.0265	£1,167	£43,989
5 year time horizon	0.0624	£2,253	£36,126
10 year time horizon	0.1133	£3,148	£27,788
20 year time horizon	0.1898	£3,655	£19,250
Committees 's preferred base case including ≥2 triptan failures (refractory) population			
2 year time horizon	0.0637	£1,447	£22,719
5 year time horizon	0.1399	£2,959	£21,147
10 year time horizon	0.2316	£4,424	£19,101
20 year time horizon	0.3417	£5,515	£16,142

**Please note, the analyses use the corrected Committee's base case as noted in item 1.*

The results are supported by evidence from clinicians who acknowledge a placebo response would be stronger in those receiving their first acute migraine treatment compared to those patients who are eligible for rimegepant (i.e., have failed ≥2 triptans).

- Neurologist were asked 'In your experience, if patients have failed 2 or more acute migraine treatments are they likely to experience a placebo effect for the same length of time as patients who are receiving their first acute treatment?'



Further support comes from a prevention study where it was noted how refractory populations tended to have a low placebo response.[3] Prior experience of treatment success or failure is considered to be an important determinant of the size of the placebo response. Supportive evidence for a reduced placebo response in patients who have failed prior treatments was also shown in a meta-regression of placebo data from mAb trials in the prevention of migraine.[3] The authors concluded that a higher proportion of patients having failed 2+ prior preventatives were predictors of lower MMD reduction over weeks 1-12 in the placebo arms.[3]

Additionally, in Rimegepant's migraine prevention appraisal [ID6275] it was noted refractory populations tended to have a low placebo response to the overall mITT population.

- Pain relief at 2 hours the mITT placebo responder percentage was [redacted] while for the refractory population (≥ 2 triptans) [redacted]% respectively (please see Table 52 of the original submission, page 152).

Conservative approach to BSC healthcare resource use (HCRU) costs in the model

We request the Committee acknowledge the conservative approach taken by the Company by excluding BSC (placebo) HCRU costs in the base case and ask that it is taken into consideration in their decision making. The Company acknowledge the uncertainty surrounding a placebo response, consequently a conservative approach to exclude the cost of BSC (i.e., placebo) was taken in the base case. In practice it is not possible to administer a placebo or for a placebo to have an indefinite response with no cost to the NHS. Given, patients with no treatment would undoubtedly incur HCRU costs, the Company have provided a scenario whereby patients in the placebo arm and rimegepant non-responders incur healthcare costs during the 2 year period. Please note, the details of the revised model to include BSC HCRU costs are described in the Appendix.

The inclusion of BSC HCRU costs and the loss of placebo response removed (Committee's preferred assumption) were applied in the model. Results demonstrate the conservative modelling approach taken by the Company with a lower ICER (Table 4).

Table 4 BSC scenario analyses

Scenarios	Incremental QALYS	Incremental costs	ICER (£/QALY)
Committee's preferred base case *			
2 year time horizon	0.0265	£1,167	£43,989
5 year time horizon	0.0624	£2,253	£36,126
10 year time horizon	0.1133	£3,148	£27,788
20 year time horizon	0.1898	£3,655	£19,250
Committee's preferred base case* + hospital based services cost			
2 year time horizon	0.0265	£767	£28,916
5 year time horizon	0.0624	£1,657	£26,581
10 year time horizon	0.1133	£2,392	£21,114

20 year time horizon	0.1898	£2,807	£14,787

Please note, the analyses use the corrected Committee's base case as noted in item 1.

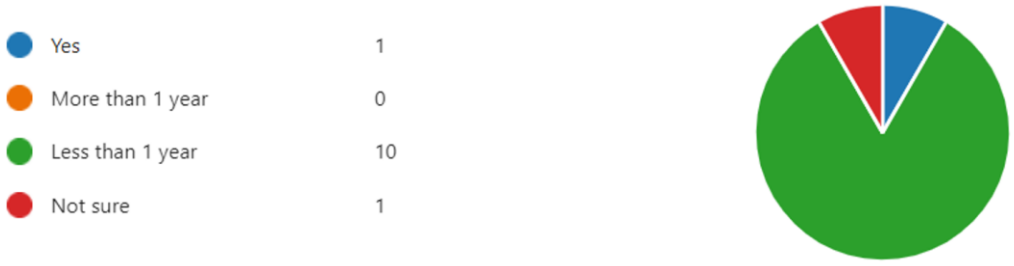
Conservative in comparison with previous technology appraisals

We request the Committee acknowledge the conservative modelling approach taken by the Company in relation to the placebo response duration guided by previous TAs and take it into consideration in their decision making.

Previous migraine prevention TAs suggest a placebo response should last no longer than 1 year (TA682 and TA764 for Erenumab and Fremanezumab).[4,5] Given there are no UK TAs in acute migraine to date, the Company sought guidance from the most recent migraine prevention TAs in terms of placebo duration, in both cases the Committee D preferred the placebo response to diminish after 1 year. The DG2 states 'Assumptions made in previous preventative migraine treatment appraisals do not necessarily apply.' However, we argue that they may be indicative.

Additionally, a survey of 10/12 neurologists noted a placebo response duration for an acute treatment would be shorter than that of a preventative migraine treatment.

- Neurologists were asked 'Given the 1-year duration of placebo effect described above is for preventative treatments, do you believe the placebo effect for an acute treatment would last the same amount of time?"



3. Time horizon

Given the evidence presented, we ask the Committee to consider a longer time horizon in the model.

Pfizer disagree with the Committee's conclusion on their preferred time horizon and believe that it does not adequately reflect the nature of the condition and is unreasonable considering the evidence presented. The time horizon should remain 20 years in the model, as patients who remain on treatment for longer periods of time incur both the clinical outcomes and economic costs of migraine for the time they remain on treatment. Furthermore, patients in the placebo arm have no alternative treatment, therefore there will be a long-term QALY impact.

Although placebo response modelling was a factor in the model's sensitivity to time horizon it was not the only factor. Due to the acknowledged long-term burden of migraine, patients who respond to treatment will remain on treatment and therefore accrue greater ~~and~~ benefits than those who discontinue early in the model

due to lack of efficacy. As the time horizon extends it is natural that the higher costs of determining response in the early stage of the model are counterbalanced by ongoing benefit.

The Company do not believe the Committee have reached a reasonable conclusion in terms of the most appropriate time horizon to capture all relevant cost and QALY impacts, given the evidence submitted:

- Patient comments in response to the DG1 and trial demographic show disease duration beyond 20 years.
- As noted in the company's response to the DG1 clinical experts support a time horizon of longer than 10 years to properly capture benefits and cost relating to acute treatment of migraine.
- Discontinuation data from extension study and extrapolation support long-term use of Rimegepant (Company Submission Document B, page 155) and with no alternative treatment options, there are important long-term outcome and cost difference to capture long-term outcome and costs.
- RWE in terms of migraine prescription data supports the inclusion of a time horizon longer than 5 years (Company's response to DG1, noting data beyond 5 years was not available).
- Consistency with rimegepant preventative treatment time horizon of the same condition (Company Submission Document B, page 209).
- The stopping rule at 12 weeks due to lack of response applied in the model supports a longer time horizon, offsetting short term costs, while capturing long-term outcomes and costs.

<u>Difference in costs and clinical outcomes suggest a longer time horizon is appropriate</u>

We request the Committee reconsider the time horizon in the economic model to fully capture the long term benefits and costs incurred by patients and the NHS.

The DG states '..that a time horizon shorter than a person's lifetime could be justified if there is no differential mortality effect between treatments, and the differences in costs and clinical outcomes relate to a relatively short period.' Rimegepant evidence suggests patients will continue beyond 2 years, so there is an important QALY impact beyond 2 years which needs to be captured for patients that continue treatment.

The extrapolation of BHV3000- 201 study indicate that most patients would be expected to be on treatment beyond 5 years (Figure 2 in the Appendix). Originally, a discontinuation rate of [redacted]% over a one-year was applied in the model based on the KM curves (Figure 3 in the Appendix), however, the Committee preferred to use a discontinuation rate of [redacted]%, again reducing the uncertainty within the model by taking a more conservative approach. At 5 years, with the Committee's preferred discontinuation rate, 31% of patients remain on treatment, again highlighting the need for a longer time horizon.

Given there is clear evidence that a significant proportion of patient will receive Rimegepant long-term and the alternative for these patients is to receive no treatment where they would continue to experience the full detrimental quality-of-life impact of their migraines, it is reasonable to conclude there are significant QALY gains to be accounted well beyond 2 years.

Stopping rule built into the model

The summary of product characteristics does not include a stopping rule (see item 4 below for more details as requested by the Committee).

However, the DG2 states '*The Committee said that it understood that migraine is a chronic and lifelong disease, and rimegepant is an acute treatment that could be used repeatedly over many years. It highlighted that these facts were not in any doubt and explained that the issue is the mechanism by which the model produces different cost-effectiveness estimates over different time horizons*.'

Please note, the model is structured so that after the first treatment patients are allocated as responders or non-responders, therefore the model essentially has a stopping rule built in. It assumes patients who do not respond will not to continue their treatment beyond their first treatment supply. This supports the need for a longer time horizon, as patients who are not gaining benefit early in the model move to non-responders but accruing the cost of a full pack, are offset with patient responding long-term, and consequently the average QALY gain improves over-time.

4. Stopping rule

The Committee requested further information about a stopping rule for rimegepant as an acute treatment (DG, section 3.21). To recap, the summary of product characteristics does not include a stopping rule, which is also the case for other migraine specific acute treatment options.

It is expected that if patients do not respond they do not to continue their treatment beyond their first treatment supply. Furthermore, patients are not anticipated to continue treatment if they do not achieve effective treatment of two consecutive treatments.

However, recognising that patients are unlikely to persist with treatment that is ineffective, the model essentially has a stopping rule built in that patients discontinue after 1 failed response to rimegepant, and it is assumed that rimegepant will be used in practice consistent with the trial design. Recognizing that patients may take multiple doses to determine response and that wastage may occur, patients that do not respond are allocated the entire cost of a rimegepant pack.

5. [redacted]

The Company's updated base case reflects the conservative approach taken excluding a reduction in MMDs and requests that this should be considered by the Committee.

The Committee concluded that MMD reduction with rimegepant PRN is plausible, given Rimegepant's preventative characteristics, but decided it should not be included in the model as there is not enough clinical evidence to support this (DG, section 3.12). However,

[redacted]

[redacted]

Table 5 Reduction in MMD baseline during 12 weeks

Trial	≥30% reduction in MMD	≥50% reduction in MMD
BHV3000-201	[redacted]%	[redacted]%
BHV3000-318	[redacted]%	[redacted]%

The Committee acknowledges *'there is biological plausibility in the suggestion that taking rimegepant as needed may reduce MMDs'*, and that 'removing the assumption from the model 'may be considered as a small, potential uncaptured benefit' (DG, section 3.12). However, the scenario analyses show that removing the MMD reduction experienced by patients taking rimegepant PRN has a considerable impact on QoL benefit (Table 8).

Given the stage of the appraisal (3rd ACM), we have not reintroduced it to the base case but provided the impact of reduced MMDs in scenario analysis. It is important to note that by excluding the reduction in MMDs, the Company's updated base case reflects the overall conservative approach taken and requests that this should be considered by the Committee. Including the MMD reduction decreases the company's base case ICER from £18,914 to £13,255. Furthermore, Rimegepant is cost-effective under the £25,000 WTP using the Committee's preferred assumption and including a reduction in MMD with Rimegepant PRN (Table 6), with an ICER of £22,641 per QALY.

Table 6 Reduction in MMD scenario analyses

Scenarios	Incremental QALYS	Incremental costs	ICER (£/QALY)
Committee's preferred base case* including reduction in MMD			
2 year time horizon	0.0589	£1,334	£22,641
5 year time horizon	0.0818	£1,858	£22,720
10 year time horizon	0.1397	£2,593	£18,564
20 year time horizon	0.2195	£3,009	£13,711
Company's base case including reduction in MMD			
2 year time horizon	0.0505	£925	£18,326
5 year time horizon	0.1197	£1,721	£14,374
10 year time horizon	0.1762	£2,377	£13,495
20 year time horizon	0.2073	£2,748	£13,255

**Please note, the analyses use the corrected Committee's base case as noted in item 1.*

6. Contraindicated or intolerant to triptans subgroup analyses

Subgroup analyses requested by committee aligned with proposed Rimegepant population.

The Committee requested further analysis for those contraindicated or intolerant to triptans (DG, section 3.21). These subgroup clinical analyses demonstrate similar results to those of the broader population (Table 2 in the Appendix). The subgroup economic analyses demonstrates that rimegepant remains cost-effective under a £25,000 WTP threshold with an ICER of £16,318 (Table 3 in the Appendix). Given the base case results are similar to the full populations they are deemed representative and support the population for which rimegepant is proposed.

7. Uncaptured benefit

We request the Committee consider the uncaptured benefit further adding to the conservative modelling approach taken by the Company in their decision making.

The model approach does not incorporate MOH or chronification which is likely to be conservative with regard to the cost-effectiveness of rimegepant.

- Uncaptured benefit of MOH induced by acute migraine treatments are not included in the model. Certain analgesics and front-line abortive medicines, like triptans, are associated with greater risk of MOH.[8]
    - Rimegepant has no evidence of MOH occurring in patients in pre-clinical and clinical trials.
    - Post marketing safety data showed 21 cumulative non-serious cases of MoH were reported as of 27th February 2023, out of a total estimated cumulative post-marketing experience exposure to rimegepant in the EU and the Rest of the World of approximately 85 patient-years, and in the US estimated to be 762,251 patients.[9]
- Chronification due to suboptimal acute migraine management is also not captured in the model.[10]

8. Risk to new innovative medicine

We request the Committee consider the implications for acute migraine innovation in their decision making.

The current highly conservative assumptions present a risk of discouraging innovation in acute migraine, with which there is a considerable unmet need for different treatment options, particularly for those who are those who do not respond to or are unable to use triptans. Pfizer would like to highlight the vast efforts made to come to an agreement with the Committee, including lowering the list price considerably, increasing certainty in the model by accepting 7/9 of their preferred assumptions and taking an overall conservative modelling approach.

Currently, the lowered list price of rimegepant, (from £20.00 to £12.90 per pill; from £160.00 to £103.20 per 8 pack), is significantly below that of other triptans currently available on the market (see highlighted in green in Table 7). In fact, rimegepant is cheaper than 42.2% of triptans prescribed, including redosing, which is a common requirement with triptan use.

There has been little innovation in the acute migraine space, triptans, which were originally developed in the 1990s, and NSAIDs have dominated the acute treatment paradigm with no new therapies approved in the UK in over 20 years. Under the Committee's preferred assumptions, rimegepant would not be cost-effective at zero price over time horizons of 10 years and above. We believe this approach threatens any future innovation within the acute migraine space and creates inequalities for acute migraine patients who have already lost out on access to new innovations (e.g., lasmitidan is not launching in the UK despite being reimbursed elsewhere in Europe).[11]

Table 7 Acquisition costs for triptans for acute treatment of migraine in adult patients (please note, Formulations with a cost per dose or maximum daily cost above £10.00 shown only.)

Formulation	Pack size	Drug Tariff VIIIA June 2023 Price [1]	Cost per dose	Maximum Daily Dose Cost	Open Prescribing data 12 months to March 23 Spend (% of total triptan spend)[12]
Rimegepant oral dispersible (OD) tablets					
Rimegepant 75mg as needed (PRN)	8 OD tablets	£103.20 (list price)	£12.90	£12.90	
Sumatriptan subcutaneous injection*					
Sumatriptan 6mg/0.5ml solution for injection pre-filled disposable devices	2 pre-filled disposable injections	£45.00	£22.50	£45.00	£3.94m (10%)
Sumatriptan 6mg/0.5ml solution for injection syringe refill	2 pre-filled disposable injections	£48.49	£24.24	£48.48	£2.14m (5.4%)
Sumatriptan 6mg/0.5ml solution for injection pre-filled syringes with device	2 pre-filled disposable injections	£50.96	£25.48	£50.96	£4.9m (12.4%)
Sumatriptan 3mg/0.5ml solution for injection pre-filled disposable devices	2 pre-filled disposable injections	£39.50	£19.75	£39.50 (Repeat dose 6mg = £59.25)	£0.9m (2.3%)
Sumatriptan nasal spray**					
Sumatriptan 20mg/0.1ml nasal spray unit dose	6 unit doses	£42.47	£7.08	£14.16	£3.1m (7.9%)
Sumatriptan 10mg/0.1ml nasal spray unit dose	2 unit doses	£14.16	£7.08	£14.16 (Repeat dose 20mg = £21.24)	£1.7m (4.2%)
Zolmitriptan nasal spray***					
Zolmitriptan 5mg/0.1ml nasal spray unit dose	6 unit doses	£36.50	£6.08	£12.17	£3.3m (8.3%)
Zolmitriptan tablets******					
Zolmitriptan 5mg tablets	6 tablets	£36.00	£6.00	£12.00	£1.2m (3.1%)

** Initially 3–6 mg for 1 dose, followed by 3–6 mg after at least 1 hour if required, to be taken only if migraine recurs (patient not responding to initial dose should not take second dose for same attack), maximum 12 mg per day.*

*** Initially 10–20 mg, to be administered into one nostril, followed by 10–20 mg after at least 2 hours if required, to be taken only if migraine recurs (patient not responding to initial dose should not take second dose for same attack); maximum 40 mg per day].*
**** 5 mg, dose to be administered as soon as possible after onset into one nostril only, followed by 5 mg after at least 2 hours if required, dose to be administered only if migraine recurs: maximum 10 mg per day.*
***** 2.5 mg, followed by 2.5 mg after at least 2 hours if required, dose to be taken only if migraine recurs, then increased if necessary to 5 mg, dose to be taken only for subsequent attacks in patients not achieving satisfactory relief with 2.5 mg dose; maximum 10 mg per day.*

9. Revised acute model and scenario analyses

We request the Committee consider the entirety of the scientific evidence provided, the conservative approach taken and the lowering of the list price of rimegepant in their decision making.

We have included the cost-effectiveness results with the new lowered list price of rimegepant (from £20.00 to £12.90 per pill; from £160 to £103.20 per 8 pack). Rimegepant is cost-effective under a £25,000 WTP threshold, detailed in Table 8.

We believe the overall conservative approach provides an overestimation of the ICER and that Rimegepant value in the NHS is greater than the Company's base case. The model has incorporated 7/9 assumptions suggested by the External Assessment Group (EAG) and preferred by the Committee, summarised in Table 4 in the Appendix. Incorporating these assumptions has considerably decreased uncertainty in the model and in turn increased the ICERs, which has been offset by a substantial decrease in the list price of rimegepant.

Table 8 Cost-effectiveness results and scenario analyses

Scenarios	Incremental QALYS	Incremental costs	ICER (£/QALY)
Committee's preferred base case*			
Indefinite placebo response & 2 year time horizon	0.0265	£1,167	£43,989
5 year time horizon	0.0624	£2,253	£36,126
10 year time horizon	0.1133	£3,148	£27,788
20 year time horizon	0.1898	£3,655	£19,250
Company's base case by time horizon			
2 year time horizon	0.0408	£1,126	£27,621
5 year time horizon	0.1013	£2,325	£20,889
10 year time horizon	0.1512	£2,932	£19,391
20 year time horizon (Company's preferred base case)	0.1794	£3,394	£18,914
20 year time horizon (Company's preferred base case PSA)	0.1214	£2,235	£18,444
Company's base case including ≥2 triptan failures (refractory) population			

2 year time horizon	0.0786	£1,412	£17,958
5 year time horizon	0.1845	£2,837	£15,375
10 year time horizon	0.2870	£4,216	£14,690
20 year time horizon	0.3629	£5,238	£14,432
Company's base case including reduction in MMD included			
2 year time horizon	0.0505	£925	£18,326
5 year time horizon	0.1197	£1,721	£14,374
10 year time horizon	0.1762	£2,377	£13,495
20 year time horizon	0.2073	£2,748	£13,255
Company's base case including ≥2 triptan failures (refractory) population and reduction in MMD included			
2 year time horizon	0.0887	£1,237	£13,955
5 year time horizon	0.2047	£2,475	£12,095
10 year time horizon	0.3161	£3,674	£11,623
20 year time horizon	0.3974	£4,562	£11,478

* *Please note, the analyses use the corrected Committee's base case as noted in item 1.*

10. Stopping rule further clarification

1. "If patients do not respond to rimegepant, they do not continue their treatment beyond their first treatment supply".
    a. Does treatment supply here mean the first pack of rimegepant or a single dose of rimegepant?

    Treatment supply in this context refers to the first pack of rimegepant not a single dose. In the model, non-responders who discontinue in the first model cycle incur the cost of a whole pack of rimegepant (eight doses).

2. "It is assumed that rimegepant will be used in clinical practice consistent with the trial design". The trial assumes that after 1 dose of rimegepant, people are allocated as a responder or non-responder. However, we heard in ACM1 that treatments for acute migraine are usually tried for at least three attacks before conclusions about non-response are made.
    a. Could you clarify if the expected stopping rule in clinical practice will be to stop treatment with rimegepant after one dose if there is no response?

    The SmPC does not include a stopping rule, which is also the case for other migraine specific acute treatments, therefore the choice to discontinue treatment would be a patient and clinician decision. It is anticipated patients will discontinue if they do not respond to treatment i.e., they will discontinue after one dose aligned to the model. However, we acknowledge this may not be the case for each patient some patients may take multiple doses to determine response, therefore as noted above, patients that do

not respond are allocated the entire cost of a rimegepant pack (eight tablets) in the model.

b. Will this be a definitive stop to treatment (treatment cannot restarted), or for a certain period of time?

This would be a patient and clinician decision. We anticipate patients will discontinue indefinitely if they do not respond to treatment and would not restart treatment at a later date.

3. "If they do not achieve effective treatment of two consecutive treatments":
    a. Does this mean:
        i. A patient would be expected to achieve response on at least two consecutive treatments in order to continue? or
        ii. If those not achieving response on two consecutive treatments would likely discontinue?"

It means ii) those not achieving response on two consecutive treatments would likely discontinue and hence the cost of an entire pack has been included for non-responders.

Rimegepant for treating acute migraine [ID1539]

DG 2 Company Comments Appendix

Supplementary tables and figures

Table 1 Results by population

	Rimegepant, n/N (%)	Placebo, n/N (%)	Risk difference, percentage points (95% CI) p-value
Refractory population (failed ≥2 triptans, rimegepant proposed population)			
Pain freedom at 2 hours post-dose	30/148 (20.0)	18/177 **(10.2)**	9.8 ([redacted]) p=0.0131
Pain relief at 2 hours post-dose	[redacted]	[redacted]	[redacted]
Pooled mITT population			
Pain freedom at 2 hours post-dose	[redacted]	[redacted]	[redacted]
Pain relief at 2 hours post-dose	[redacted]	[redacted]	[redacted]

Figure 1 mITT 48 hour pain trajectory

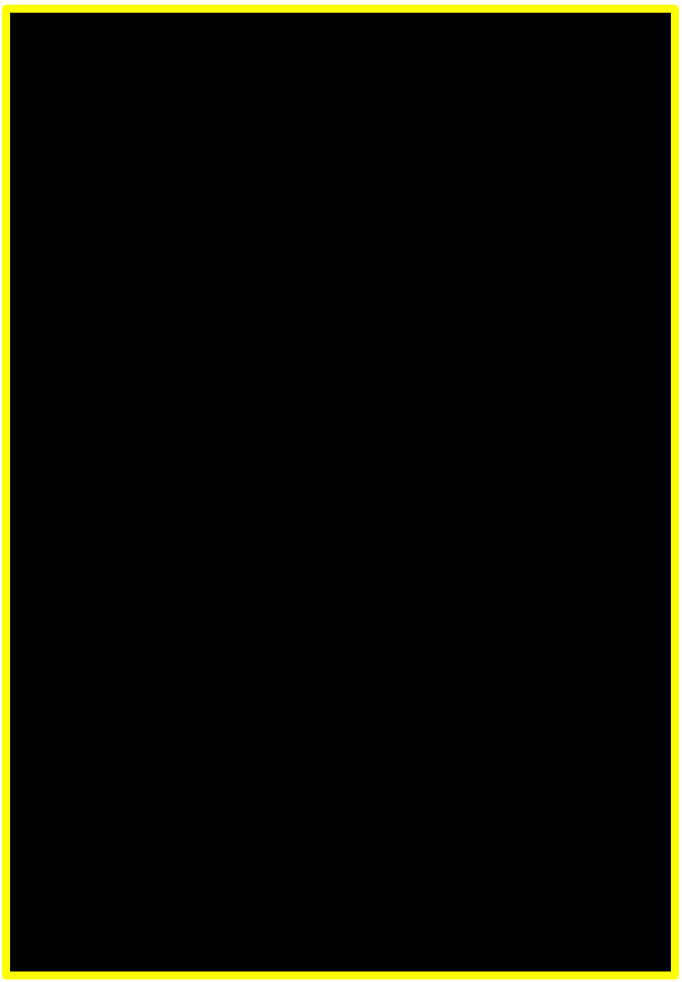


Figure 2 BHV3000-201 discontinuation extrapolation curve

Figure 3 Kaplan Meier curve for patients discontinuing rimegepant treatment due to adverse event, lack of efficacy, or withdrawal by subject (responders with ≥2 triptan failures)

Table 2 Contraindicated and intolerant to triptans subgroup efficacy endpoints results

	Rimegepant, n/N (%)	Placebo, n/N (%)	Risk difference, percentage points (95% CI); p-value
Pooled refractory population (failed ≥2 triptans, rimegepant proposed population)			
BHV3000-301, -302 and -303			
Pain freedom at 2 hours post-dose	30/148 (20.0)	18/177 (10.2)	9.8 ([redacted]); p=0.0131
Freedom from MBS at 2 hours post-dose	64/148 (43.0)	38/177 (21.5)	21.5 ([redacted]) p<0.0001
Pain relief at 2 hours post-dose	[redacted]	[redacted]	[redacted]
Pooled mITT population			
BHV3000-301, -302 and -303			
Pain freedom at 2 hours post-dose	[redacted]	[redacted]	[redacted]
Freedom from MBS at 2 hours post-dose	[redacted]	[redacted]	[redacted]
Pain relief at 2 hours post-dose	[redacted]	[redacted]	[redacted]
Pooled CV contraindicated or intolerant to triptans			
BHV3000-301, -302, and -303			
Pain freedom at 2 hours post-dose	[redacted]	[redacted]	[redacted]
Freedom from MBS at 2 hours post-dose	[redacted]	[redacted]	[redacted]
Pain relief at 2 hours post-dose	[redacted]	[redacted]	[redacted]

Table 3 Subgroup cost-effectiveness analyses

Scenarios	Incremental QALYS	Incremental costs	ICER (£/QALY)
Company's base case	0.1794	£3,394	£18,914
Contraindicated and intolerant subgroup analysis	0.3029	£4,942	£16,318

Table 4 EAG and Committee's preferred assumptions and Company base case

Model assumption	Original Company base case	EAG/Committee's preferred assumption	EAG/Committee's preferred assumption included in company's revised base case
Trial efficacy data	BHV3000-301 - 303 pooled ≥2 triptan failures (rimegepant proposed population i.e., the refractory population)	BHV3000-301 – 303 pooled mITT (wider population comprising of patients with no historic use of triptan failure & and those who failed ≥1 triptans)	Included
Trial efficacy data include Asian study	Exclude BHV3000-310	Include BHV3000-310	Included
Trial population characteristics	BHV3000-201 triptan failures	BHV3000-301 – 303 pooled mITT including BHV3000-310	Included
Rimegepant discontinuation	9.7%	13.5%	Included
MMD baseline distribution	Empirical	Poisson	Included
Discontinue rimegepant pain trajectory	Revert to placebo responder	Revert to placebo all comers	Included
MMD reductions	Include	Exclude	Included
Time Horizon	20-years	2 years (EAG's preferred time horizon), Committee undecided and concluded more explanation is needed to determine the most appropriate length for the time horizon.	20-years Scenarios included
Placebo effect (time to lost placebo effect)	Lasts 1 year (time to lost placebo effect is 1 year)	Last 2 years (time to lost placebo effect is 0, as it is not lost)	Lasts 1 year (time to lost placebo effect is 1 year) Corrected

Revised model guide

Table 5 Model updates - rationale and description

Update and rationale	Model update details
Parity for rimegepant QALH assumptions when placebo waning is turned "off" In the prior model, rimegepant responders who discontinue were assumed to maintain their response only for the period of time specified in Settings cell J59, to correspond with the period of time for which placebo response is maintained. However, if placebo patients losing response is set to "No" then this time point is no longer relevant, and it is disproportionately penalizing rimegepant to use this time point for rimegepant discontinuers to transition to non-responder status. As an alternative, patients who initially respond to Rimegepant and then discontinue will then experience the QALH trajectory of a placebo all-comer, i.e., assuming that they would become a "typical" placebo patient from this point forwards. This has been updated as per the description to the right.	This is implemented in the model via updates to columns R and Z in the rimegepant trace sheet. Column R represents the QALY adjustment made to rimegepant discontinuers to allow for maintenance of some response benefit during the placebo waning period (e.g. 12 months). If the placebo waning toggle is set to 'No', this adjustment is now defined to be zero. In Column Z, an additional 'if' statement is included such that if the placebo waning strategy is set to 'No', untreated rimegepant responders also do not experience waning, and the placebo all-comer QALH per migraine continues to apply.
Discontinuation of BSC responders over time Given that the current NICE base case maintains placebo response based on interpreting BSC as an active therapy, the model has incorporated discontinuation for BSC to reflect patients discontinuing this active therapy and shifting over to untreated / over-the-counter treatments only. Real world evidence suggests is a common treatment pathway for migraine patients, particularly the triptan intolerant/contraindicated patients.	The hazard ratio for BSC discontinuation relative to rimegepant is set in cell J64 of the Settings sheet. The resulting discontinuation rate per cycle is calculated in cell N13 of the UC trace sheet. In the UC trace sheet, initially patients are divided into treated responders (column L) and untreated non-responders (column O) based on the response rate from the trial. In the updated model version, treated BSC patients discontinuing therapy also transition each cycle from

Discontinuation rates are characterized relative to rimegepant discontinuation rates from long-term safety study 201, via a hazard ratio.	column L to column O. If the hazard ratio on the Settings sheet is set to 0, this discontinuation does not occur.
Incorporation of additional health care practitioner (HCP) visits for BSC Based on clinical feedback, BSC patients are expected to require regular neurologist visits to manage their condition. The model now allows for a combination of specialist visits to be incorporated, both for patients in the BSC arm as well as discontinued and non-responding rimegepant patients.	Inputs are on the Settings sheet, rows 76 and below. The initial toggle determines whether these costs are considered at all. If the toggle is set to 'yes': - Cell J78 defines the proportion of BSC patients who have a single visit in the first model cycle - Cell L78 defines the weighted average of GP vs. specialist-costed visits - Cell J80 defines the subsequent number of visits per month (set in the default to be one per 6 months) - In the model traces, see column AJ of both the RIM and UC trace sheets for incorporation into the health services costs. - For Rimegepant patients, the cost is only applied to those off therapy. - Note that the initial baseline visit is only applied to the BSC arm; following that rimegepant discontinuers are eligible for visits

BSC (placebo) HCRU costs

Given the unreasonable assumption in the Committee's preferred model assumes patients who receive no treatment (placebo/BSC) for 2 year, at no cost to the NHS. The Company have provided a scenario whereby patients in the placebo arm and rimegepant non-responders incur healthcare costs in that time.

20% of BSC patients would require a referral to secondary care (please see above for full responses).[1]

Of those who were referred the mean number of times patient sees HCP in the last 12 months for migraine was assumed to be 0.2.[1]

An overall hospital based service cost was inputted from Osummuli et al. 2017. Please note, inpatient stays and Emergency department visits have been excluded due to the potential for double counting, as they are already captured by the model.[2]

The cost reflects current prices inflated to the most recent 2021 costs using National Health Service cost inflation index (NHSCII).[3]

Table 6 Acute migraine hospital based services

Service	Mean cost per 4 months	Mean cost per 4 months inflated to March 2023	Annual inflated costs
Clinical decision unit	£15.00	£17.30	£51.91
Head or brain CT/MRI	£29.00	£33.45	£100.36
Neurology outpatient	£195.00	£224.95	£674.84
Other outpatient service	£46.00	£53.06	£159.19
Total cost	£285.00	£328.77	£986.30

Sources:

1. Pfizer. Data on File. Adelphi migraine VII (2022_2023) DSP. 2023.
2. Osumili, B., McCrone, P., Cousins, S., & Ridsdale, L. (2018). The economic cost of patients with migraine headache referred to specialist clinics. *Headache: The Journal of Head and Face Pain*, *58*(2), 287-294.
3. Jones K, Burns A. Unit Costs of Health and Social Care Canterbury (Kent), UK: Personal Social Services Research Unit, University of Kent; 2021 [Available from: https://kar.kent.ac.uk/92342/ (last accessed May 2023)

Forthcoming abstract

[redacted]

[redacted]

Stakeholder comments references

1. Diener HC, Schorn C, Bingel U, et al. The importance of placebo in headache research. Cephalalgia 2008;28:1003-1011.
2. Kam-Hansen, S., Jakubowski, M., Kelley, J. M., Kirsch, I., Hoaglin, D. C., Kaptchuk, T. J., & Burstein, R. (2014). Altered placebo and drug labeling changes the outcome of episodic migraine attacks. Science translational medicine, 6(218), 218ra5-218ra5.
3. Regnier, S. A., & Lee, X. Y. (2023). Meta-regression to explain the placebo effects in clinical trials of anti-CGRP monoclonal antibodies for migraine prevention.
4. National Institute for Health and Clinical Excellence. Fremanezumab for preventing migraine Technology appraisal guidance (TA764) Manchester: NICE; 2022 [updated 3 June 2020. Available from: https://www.nice.org.uk/guidance/ta764 (last accessed May 2023)
5. National Institute for Health and Clinical Excellence. Erenumab for preventing migraine: Technology appraisal guidance (TA682) Manchester: NICE; 2021 [updated 10 March 2021. Available from: https://www.nice.org.uk/guidance/ta682/resources/erenumab-for-preventing-migraine-pdf-82609376694469 (last accessed May 2023)

6. Yu, S., Ma,L., Zhong, Q., Zhu,H. (*Forthcoming*). Interim Results of a Long-Term Safety Study of 75 mg Rimegepant Administered as Needed in Acute Treatment of Migraine Among Chinese Adults. International Headache Congress 2023 Sept 14–17, 2023; Seoul
7. Biohaven Pharmaceuticals Inc. Data on File: Clinical study report BHV3000-201: A multicenter, open-label long-term safety study of BHV-3000 in the acute treatment of migraine. 2020.
8. Thorlund K, Sun-Edelstein C, Druyts E, Kanters S, Ebrahim S, Bhambri R, et al. Risk of medication overuse headache across classes of treatments for acute migraine. J Headache Pain. 2016;17(1):107.
9. Data on File PP-NNT-GBR-0653: EMA Periodic Safety Update Report (PSUR) 27 August 2022 through 26 February 2023.
10. Lipton RB, Fanning KM, Serrano D, Reed ML, Cady R, Buse DC. Ineffective acute treatment of episodic migraine is associated with new-onset chronic migraine. Neurology. 2015 Feb 17;84(7):688-95. doi: 10.1212/WNL.0000000000001256. Epub 2015 Jan 21. PMID: 25609757; PMCID: PMC4336107
11. National Institute for Health and Clinical Excellence. Lasmiditan for treating acute migraine: Technology appraisal guidance (ID3759) Manchester: NICE; 2021 [updated 10 March 2021. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10807 (last accessed May 2023)
12. OpenPrescribing.net, Bennett Institute for Applied Data Science, University of Oxford, 2023. [Accessed June 2023]

Please can you provide the following?

- **The following reference, which we've not been able to locate online: Regnier, S., & Lee, X. Y. (2022, December). Placebo effects in clinical trials of anti-CGRP monoclonal antibodies for migraine prevention. In *JOURNAL OF HEADACHE AND PAIN* (Vol. 23, No. SUPPL 1). CAMPUS, 4 CRINAN ST, LONDON N1 9XW, ENGLAND: BMC.**

  Apologies, there was an error with the reference submitted. Please find the correct reference below, the PDF uploaded and the appendix updated.

  Regnier, S. A., & Lee, X. Y. (2023). Meta-regression to explain the placebo effects in clinical trials of anti-CGRP monoclonal antibodies for migraine prevention.

- **CSR for study -318 if available, including all tables/figures of results (i.e. section 14)**

  Please the file uploaded, named *BHV3000-318 CSR-V1.0*.

- **Tables and figures of results from the CSR for study -201 (i.e. section 14)**

  BHV3000- 201 analysis came from post-hoc analysis therefore no specific CSR is available for this analysis.

- **Table 8 cited in the company's response to ACD2 (mentioned on page 14, referring to impact on QoL benefit)**

  Please note, Table 8 is referring to Table 8 within company's response to ACD 2 (Table 8 Cost effectiveness results and scenario analyses, page 17).

  On page 14, the response acknowledges the large impact on QALYs compared to the Committee's preferred base case when excluding a reduction in MMDs. The use of the word significant has now been replaced with considerable in the above text in the response.

- **EMA periodic safety updated report, said to be data on file and listed as reference 9 in the company's response**

  Please see the file uploaded, named *Rim Data on File PSUR 2023 for GCMA v2.*

- **Adelphi migraine reference 2022/2023, said to be data on file (reference 1 in the appendix provided)**

  Please see the file uploaded, named *Adelphi migraine VII (2022_2023) DSP*.

Additionally, please can you confirm whether there are errors in Table 2 of the appendix provided - the EAG notes that the results for pain relief at 2 h for refractory and mITT populations do not match the same groups in Table 1 of the appendix and does not consider this to be correct. Should these values instead match those in Table 1?

Apologies, the wrong labels were included in the tables, these have now been updated in the appendix.

Also, with regards to the additional subgroup analysis the committee requested (contraindicated or intolerant to triptans, item 6 in the company's response) – the EAG has some questions about this and some further data that would be useful to provide a critique, particularly as it was something requested by the committee:

- **Can the company confirm which patients were included in this subgroup and whether this was just from the -301, -302 and -303 trials?**

  Only patients from BHV3000-301, -302 and 303 were included in the analysis as BHV3000-310 study did not collect data one contraindicated or those who were intolerant to triptans.

- **Was it only patients that were intolerant of or contraindicated to triptans or were some that failed based on efficacy included?**

  The table below summarises the definition of both the contraindicated and the intolerant group. Please note, for the triptan intolerant group patients who also state lack of efficacy in addition to “treatment caused side effects” for the same triptan are included.

Group	Definition	Comments
Triptan contraindicated	Patients identified with pre-specified cardiovascular indications as per pre-specified analysis in from pooled mITT of rimegepant acute trials BHV3000-301, BHV3000-302 and BHV3000-303.	As per existing definition in pre-specified analysis. Expect 17 rimegepant and 12 placebo.

Triptan intolerant	Patients who have discontinued 1 or more previous triptans and included a reason of "treatment caused side effects" for at least one triptan with a frequency of either "Most or all of the time" or "Some of the time" from pooled mITT of rimegepant acute trials BHV3000-301, BHV3000-302 and BHV3000-303. Regardless of dose or route of administration.	patients who also state lack of efficacy in addition to "treatment caused side effects" for the same triptan are included. Includes patients who fail one triptan for "treatment caused side effects" but have failed other triptans for other reasons. For example, a patient who fails first triptan for side effects, but then fails triptan 2 and 3 for lack of efficacy would be classed as triptan intolerant. Provides largest possible population.

- **The EAG is surprised that the number analysed in this subgroup is higher than the refractory subgroup, given only small numbers (as in Table 36 of the CS appendices) were reported to be contraindicated to triptans in these studies.**

Table 36 in the CS appendices refers the contraindicated subgroup; therefore the numbers are smaller. The table below presents the sample sizes for each group by arm.

Please note, some patients were captured as triptan contraindicated and intolerant therefore the final number takes this into account so not to double count patients. The final sample sizes for each group are bolded in the table below.

Population	rimegepant	placebo
mITT	**1749**	**1758**
Refractory	**148/1749 (8.46%)**	**177/1758 (10.06%)**
Triptan contraindicated	17/1749 (0.97%)	12/1758 (0.68%)
Triptan intolerant	272/1749 (15.56%)	249/1758 (14.16%)
Triptan contraindicated + intolerant	1/1749 (0.05%)	3/1758 (0.17%)
Triptan contraindicated or intolerant	**288/1749 (16.47%)**	**258/1758 (14.68%)**

Can the company describe how this subgroup analysis was implemented in the model as a scenario? Was it just the response rate for pain relief at 2 h that was changed?

- **What about other model inputs such as probability of experiencing migraine, modelling of pain hours (including pain trajectories) and baseline characteristics?**
- **Please ensure the scenario in the model makes full use of the subgroup population, as was originally done when the refractory group was favoured as the company's base case**
- **please provide the data for any other model inputs mentioned in the previous bullet point**

We can confirm that the scenario was implemented for all relevant inputs utilizing the same sources for data (as per the other subgroups in the model).
Specific cell references are as follows (the values in these cells are utilized when the subgroup is selected on the Settings sheet):

- Baseline characteristics – Settings cells R33-R50. Note that as per the other trial populations, the % with prior prophylaxis use is not available in the acute trials and was thus taken from BHV3000-201
- % pain relief – Efficacy cells AD32-AG38
- Time in pain categories (raw data for rim & placebo) - Efficacy cells BN43-BW59
- QALH regression - Efficacy cells BE76-BM95
- Proportion with moderate/severe event at 24 hours – Costs cells R37-V52 (note here that then labelling in cells R37 and R48 was not updated and should say “Triptan intolerant or contraindicated” but the data inputs have been updated

Please provide baseline characteristics for this subgroup in rimegepant and placebo arms, including those in Table 19 of the CS and the proportion with severe migraine at baseline.

Please find a table below with baseline characteristics for this subgroup in rimegepant and placebo arms, including those in Table 19 of the CS and the proportion with severe migraine at baseline.

Baseline characteristics for contraindicated or intolerant in acute treatment from studies BHV3000-301, BHV3000-302 and BHV3000-303

	CV contraindicated or intolerant to triptans	
	rimegepant	**Placebo**
N	288	258
Age in years, mean (SD)	42.3 (11.85)	42.5 (11.50)
Males, n (%)	22 (7.6%)	21 (8.1%)
Females, n (%)	266 (92.4%)	237 (91.9%)
White	243 (84.4%)	218 (84.5%)
Black or African American	35 (12.2%)	37 (14.3%)
Asian	2 (0.7%)	-
Multiple	6 (2.1%)	2 (0.8%)
American Indian or Alaska Native	-	1 (0.4%)
Native Hawaiian or other Pacific Islander	1 (0.3%)	-
Not reported	1 (0.3%)	-
Body mass index in kg/m^2, N	288	258
BMI Mean (SD)	29.71 (7.465)	31.51 (8.973)
Migraine history, N	288	258
Attacks per month, mean (SD)[a]	4.7 (1.91)	4.6 (1.78)
Duration in hrs of untreated attacks, mean (SD)	35.3 (23.73)	34.2 (22.72)
Migraine with aura, n (%)	182 (63.2%)	152 (58.9%)
Migraine without aura, n (%)	106 (36.8%)	106 (41.1%)
MBS for treated attack, n (%)		
Photophobia	167 (58.0%)	140 (54.3%)

Phonophobia	37 (12.8%)	44 (17.1%)
Nausea	84 (29.2%)	74 (28.7%)
Not reported	-	-
Severe migraine at baseline	22.9%	27.1%

Errors corrected by Pfizer in their ACD response.

Please note in Table 3 (page 7 of the response) typos were identified for the results including the refectory population including ≥2 triptan failures (refractory) population, this has now been amended to the correct results. Our apologies for any inconvenience this may have caused.

Please note in Table 6 (page 14 of the response) typos were identified for the results for the Committee's preferred base case including reduction in MMD for the 2 year time horizon only, this has now been amended to the correct results. Our apologies for any inconvenience this may have caused.

For the contraindicated/intolerant subgroup, if you have results for pain relief at 2 h (as this is the outcome used in the model), as Table 2 of the ACD2 response appendices only presents pain freedom at 2 h and freedom from MBS at 2 h.

Please note thee requested result have been added to Table 2 in the appendix.

NICE National Institute for Health and Care Excellence

Rimegepant for treating acute migraine [ID1539]

Appraisal consultation document comments form

Consultation on the appraisal consultation document – deadline for comments 5pm on 21 June 2023. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	The Migraine Trust

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Rimegepant for treating acute migraine [ID1539]

Appraisal consultation document comments form

Consultation on the appraisal consultation document – deadline for comments 5pm on 21 June 2023. Please submit via NICE Docs.

Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state the name of the company, amount, and purpose of funding.	• £29,194 from Abbvie to support our work in devolved nations • £20,000 from Lundbeck for our support services. • £34,500 from Lilly to support a GP migraine awareness campaign • £157,500 from Pfizer to support two research fellowships
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	Robert Music

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	**The Workplace Impact** We feel that the current recommendation does not fully incorporate the impact of performance at work on the individual with migraine as well as society overall, and the crucial role of an effective acute treatment in mitigating this. From our latest 2023 workplace survey of 1002 people, the lighting (83%), stress (79%), screen use (58%) and noise (54%) came out as significant triggers. Respondents were quoted as saying:

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NICE National Institute for Health and Care Excellence

Rimegepant for treating acute migraine [ID1539]

Appraisal consultation document comments form

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	"I'm considering taking a demotion to reduce stress which triggers migraines" and "I try to manage my migraines around work and I go to bed when I finish. I'm very lonely, no social life or quality of life with any friends. Feel restricted in life as abiding triggers. Feel like I let me children down". In our previous submission we highlighted the financial burden of reduced productivity (presenteeism and absenteeism). We believe this demonstrates an unmet need for this significant group of people with migraine, who are yet to find an reliable treatment option that enables them to function and remain at work, when attacks occur.
2	**Stigma, Discrimination and Equality Issues** Stigma is associated with migraine. When we asked people with migraine to describe in one word, how migraine made them feel, we received responses such as: '*debilitated, despair, isolated, trapped, misunderstood, frustrated, disadvantaged, traumatised, sick, scared, helpless..' (2023)* In our previous submission, our surveys highlighted the lack of understanding people with migraine found and the negative impact on work, mental health and relationships. This is again reflected in our 2023 workplace survey. Unfortunately, people with migraine continue to report this experience. • 30% felt harassed or victimised at work, • 34% felt discriminated at work, • 43% felt they haven't been believed when taking sick leave due to a migraine attack and • 34% don't feel their colleagues take migraine seriously Migraine also plays a large part in people's mental health, the same 2023 survey showed that 74% of people said that migraine has had a negative affect on their mental health. The majority of people affected by migraine are women who unfortunately live with the disadvantages associated with frequent migraine and their needs should be addressed with appropriate treatment.

NICE National Institute for Health and Care Excellence

Rimegepant for treating acute migraine [ID1539]

Appraisal consultation document comments form

Consultation on the appraisal consultation document – deadline for comments 5pm on 21 June 2023. Please submit via NICE Docs.

	We believe that people who can treat early, at the first signs of a migraine attack, can avoid the fully developed, debilitating symptoms. Furthermore, access to an acute treatment that can be used in the early stages, without a fear of associated medication overuse issues and is well tolerated, could avoid attacks developing to a stage that impacts on activities and function and hence avoid much of the associated stigma and discrimination.
3	**Disadvantaged groups** People who are not able to use an existing acute treatment due to side effects, contraindications (for example cardiovascular conditions) and risks of medication overuse continue to be severely disadvantaged. • 43% (and 57% for chronic migraine), said they had been impacted financially because of how migraine affected their career or employment status (TMT workplace survey, 2023). Career choice was impacted, where 25% felt they had to leave their job, 29% chose to work part time instead of full time, 22% faced disciplinary action for absence due to migraine, and the negative mental health impact (74%) have been significant.
4	**The role of appropriate targeted treatments such as anti-CGRP medicines** Our CGRP mAb survey conducted earlier this year (*n*= 500), found a greater than 80% benefit for respondents in terms of reduced migraine attack frequency and overall quality of life. We feel that a treatment that specifically targets cgrp in migraine, such as Rimegepant, should be made available as it has the potential to alleviate the devastating personal and economic costs of migraine. As an acute treatment, the oral route of administration of rimegepant gives control back to the patient, who can treat early and appropriately to get the best relief. As an oral treatment with good tolerability, it could provide an excellent opportunity for patients to receive the treatment in the primary care setting. Effective and reliable acute treatments which crucially, do not have associated risks of medication overuse headache are urgently needed for people with migraine and for the hugely disadvantaged group of people for whom the currently recommended triptans and NSAIDs are not an option.

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	Treating acute attacks better could reduce the number of referrals to specialists and associated costs and waiting times.
5	
6	

Insert extra rows as needed

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- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Association of British Neurologists headache and pain advisory group

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state the name of the company, amount, and purpose of funding.	Nil
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	There is no mention of the use of high dose NSAID or aspirin combined with an antiemetic as a comparator treatment. This is particularly relevant for people who are intolerant of / cannot take triptans. Evidence suggests an only slightly lower efficacy for NSAIDs in acute treatment than triptans. (VanderPluym. Acute Treatments for Episodic Migraine in Adults: A Systematic Review and Meta-analysis. *JAMA.* 2021;325(23):2357–2369)
2	Modelling response 3.10: we consider that it is not reasonable to consider failure to respond to one dose of rimegepant to assume there never would be a response: it would be standard practice to encourage a patient to try a treatment for 2 or 3 attacks to assess efficacy.
3	As discussed in the appraisal, it is widely recognised that episodic and chronic migraine may differ in their responsiveness to acute and preventive medication and that the RCTs only included those with up to 8 migraine days /month and therefore extrapolation of cost

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	effectiveness to the high-frequency episodic and chronic population may not be appropriate.
4	The time horizon modelling for cost effectiveness is difficult : although people with migraine may need acute treatment for approx. 20 years they may be tolerant of triptans (or NSAIDs) in their younger life but intolerant in later life as cardiovascular risks accrue and so may need to switch to other acute therapies for only a few years in later life
5	Placebo response 3.14: we do not agree that people having response to placebo no longer have any benefit after 12 months; there may be some waning of placebo response over time but this is uncertain. We agree that a 2 year time line may be reasonable for cost effectiveness estimates may be reasonable but including at least a partial placebo response in the 2nd year . A 20 year time horizon for cost-effectiveness estimates with no placebo response after 12 months is less reasonable.
6	

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Association for the Study of Headache (BASH)

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
Name of commentator person completing form:	[redacted], [redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Has all of the relevant evidence been taken into account?** BASH agrees that most of the relevant evidence has been taken into account, but we would like to draw the committee's specific attention to the data supporting the potential efficacy of rimegepant in triptan non-responders, including the subgroup analysis presented by the company in their response to the original draft ACD, as well as the following recently published paper: Lipton RB, Blumenfeld A, Jensen CM, Croop R, Thiry A, L'Italien G, et al. Efficacy of rimegepant for the acute treatment of migraine based on triptan treatment experience: Pooled results from three phase 3 randomized clinical trials. Cephalalgia. 2023;43(2):3331024221141686
2	

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	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? BASH do not believe that the summaries of clinical and cost effectiveness currently represent a reasonable interpretation of the evidence. We have two major areas of concern. Firstly, we do not think that the time horizon that the committee has chosen to use to capture the potential benefits and costs of treatment is reasonable. The decision of the committee to use a two-year time horizon goes against virtually all the clinical opinions provided to it, comprising the considered views of GPs, neurologists involved in headache management, and, for the avoidance of doubt, BASH. We regard a 20-year timescale as appropriate to capture the costs and benefits associated with the acute treatment of migraine, and we call on the committee to use this timescale in deriving their cost effectiveness data. We also believe that it would be appropriate to derive cost effectiveness data with due regard to the data contained in the subgroup analyses that present the response rates in triptan non-responders (our opinion is here supported by the data in the paper cited in the answer to the previous question). We do not feel that the potential preventive effects of the acute use of the measurement should be taken into account for the specific analysis of rimegepant as an acute medication, however.
3	**Are the recommendations sound and a suitable basis for guidance to the NHS?** We do not think that this is the case, because of the issues raised above. We also request greater clarity in the final determination about who can prescribe rimegepant. The view of BASH remains that the drug should be available for prescription in primary care, and that the situation in England and Wales should insofar as it is possible be made consistent with that in Scotland.
4	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?** We have no concerns in this area.

Insert extra rows as needed

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Single Technology Appraisal

Rimegepant for treating acute migraine [ID1539]

Comments on the appraisal consultation document (2) received through the NICE website

Name	[redacted]
Conflict	N/A
Comments on the ACD:	
I am desperate for this to be approved for acute use. I have never had any effectiveness from triptans, and I'm out of hope. I rely on high doses of aspirin which still doesn't work enough for me to work/live my life. I'm an NHS worker but haven't been able to go in for over a year. This could make me a functional member of society again. Please.	

Rimegepant for treating acute migraine (ID1539)

EAG response to company ACD2 comments

July 2023

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135416

1 Introduction

This document provides the Evidence Assessment Group (EAG)'s critique of the company's response to the appraisal consultation document 2 (ACD2; May 2023) produced by the National Institute for Health and Care Excellence (NICE) for the appraisal of rimegepant for treating acute migraine (ID1539).

As detailed in Section 3.21 of ACD2, the committee requested the following additional analyses be performed and provided by the company to inform discussions at the next committee meeting, in terms of whether rimegepant may be cost-effective for a specific subset of patients, that is considered to have a particularly high unmet need in terms of treatment options:

- results from the clinical trials BHV3000-301, BHV3000-302, BHV3000-303 and BHV3000-310, for people who cannot have triptans;
- and economic analyses using the clinical evidence for people who cannot have triptans.

The committee also asked for further information about stopping rules for rimegepant when used as an acute treatment.

The EAG notes that the company has provided the information requested but has also put forward some further arguments and reiterated previous statements in terms of some decisions made at the last committee meeting. The EAG is unsure whether the subgroup analysis provided matches that requested by the committee completely and there are also some imbalances in baseline characteristics between rimegepant and placebo arms for this subgroup.

Section 2 presents the EAG's critique of the comments made by the company in response to the ACD, the company's updated results are presented in Section 3 and Section 4 presents the EAG's updated base case and scenarios. Comments by the company are discussed according to comment number as per the company's response document to ACD. Table 1 below summarises these comments, including which area of the ACD they relate to and the EAG's response, as well as reference to which section they are discussed in more detail.

Table 1. Summary of issues covered in company's response to ACD2

Comment in company ACD response		Relevant sections of ACD	Company response	EAG comment
1	An indefinite placebo response is implausible and generates perverse results	3.14, 3.17	Arguments against the committee's preference for not removing placebo response at 1 year described	The EAG agrees with the committee's preference for response in the placebo arm to be maintained after 1 year. It only partially accepts the correction put forward by the company and has made its own additional correction. (Section 2.1)
2	Company's current conservative placebo response	NA	The company outlines features of the modelling for placebo response that it considers to be conservative and may not have been fully considered by the committee	The EAG does not consider the use of the mITT population to be conservative. It acknowledges that excluding BSC treatment costs is conservative but considers the scenario provided by the company to be inappropriate. (Section 2.2)
3	Time horizon	3.13, 3.17	The company reiterates previous arguments against using the 2-year time horizon preferred by the committee	The EAG considers most arguments put forward have already been discussed by committee. No evidence has been put forward that changes the EAG's position on the 2-year time horizon being most appropriate. (Section 2.3)
4	Stopping rule	3.21	Information around a stopping rule in the acute	The EAG notes that various options are

			setting has been provided, as requested by the committee	mentioned but that these are not formal stopping rules. Decisions on stopping would be based on a discussion between the patient and clinician. (Section 2.4)
5	[redacted]	3.12, 3.17	[redacted] in support of reinstating MMD reduction (the removal of which was favoured by committee) in the model	The [redacted], and does not change the EAG's opinion that an MMD reduction should not be included in the modelling. (Section 2.5)
6	Contraindicated and intolerant to triptans subgroup analyses	3.18, 3.21	Clinical and cost-effectiveness analyses for this subgroup have been provided, as requested by the committee	The EAG has concerns about how well the subgroup analysis provided matches that requested by committee and how relevant to clinical practice it is, as well as noting baseline imbalances between rimegepant and placebo arms in this subgroup. (Section 2.6)
7	Uncaptured benefit	NA	The company highlights that MOH and chronification are not considered in the modelling and may represent uncaptured benefits of rimegepant	The EAG does not dismiss the possibility that these could be potentially uncaptured benefits of rimegepant but notes the evidence available for them is limited and the extent of

				any impact is difficult to quantify. (Section 2.7)
8	Risk to new innovative medicine	NA	The company raises concerns about the difficulty of introducing new medicines in the acute migraine space	The EAG highlights the importance of cost-effectiveness in terms of NHS resources and cannot comment further on the risk described by the company. (Section 2.8)
9	Revised acute model and scenario analyses	NA	A revised company base case and scenario analyses are provided; the company's preferred base case includes 7/9 assumptions preferred by the committee (excluding the committee's preferences for time horizon and maintenance of placebo effect beyond 1 year)	Company base case and scenario results are presented in this section. (Section 2.9)

Abbreviations: ACD, appraisal consultation document; BSC, best supportive care; EAG, External Assessment Group; mITT, modified intention to treat; MMD, monthly migraine days; MOH, medication overuse headache; NA, not applicable; PRN, as-needed/*pro re nata*.

2 EAG's critique of company response to ACD

2.1 Comment 1. An indefinite placebo response is implausible and generates perverse results.

The company highlights that the maintenance of placebo response beyond 1 year (as preferred by the committee) is not plausible. The outline of the company arguments and the EAG response is contained in Table 2 and a discussion of the correction applied by the company is discussed in Section 2.1.1.

In the EAG's original report, clinical expert advice to the EAG was highlighted, which was that a small proportion of patients will maintain a response to best supportive care (BSC), and for one patient that loses response another may gain response. However, they were unable to suggest what proportion will maintain a response to BSC. In the report, the EAG concluded that consistency with previous NICE appraisals in migraine (TA764/TA631, TA659 and TA682) should be applied unless there is long-term clinical evidence or a numerical estimate based on clinical expert consensus for BSC that allows such a scenario to be reliably modelled.[1-3] Previous appraisals included a reversion to baseline over 1 year for BSC responders. However, the EAG acknowledges the committee's point that these appraisals were for migraine prevention rather than acute migraine treatment and may not necessarily apply. The company considers that while this is correct, they *"may be indicative".*

In the EAG's critique of the company's response to ACD1, the EAG explained that differences in cost-effectiveness across different time horizons were largely being driven by the removal of this placebo response after 1 year; while the EAG favoured the use of the 2-year time horizon, it did not change the assumption that placebo response disappears after 1 year for the BSC arm. The EAG acknowledges the arguments put forward by the company in terms of the plausibility of a placebo response being maintained after 1 year and considers that this requires further discussion with the involvement of clinical experts at the committee, for example, with regards to duration of placebo response for those receiving no treatment or BSC and whether this might be expected to differ between acute treatment and migraine prevention covered by previous appraisals.

However, the EAG notes that regardless of the agreed duration of placebo response, this is something that will also apply to those taking rimegepant and it would not be appropriate to only remove it from the BSC arm. This is because the same source of short-term efficacy data is used for placebo (which includes a placebo response) and rimegepant (acute trials) in the economic model,

which means that the data for rimegepant should also include a placebo response. Given the concerns raised by the committee at Appraisal Committee Meeting 2 (ACM2), including that this placebo response equally applies to rimegepant, and that there is no long-term comparative evidence to demonstrate that there is a waning of placebo response *only* in the placebo group, the EAG considers the most reasonable approach is to assume that this placebo response exists in both treatment group post 1-year and has revised its base case in line with the committee's preferred assumptions.

Table 2. Company case against indefinite placebo response and EAG comment

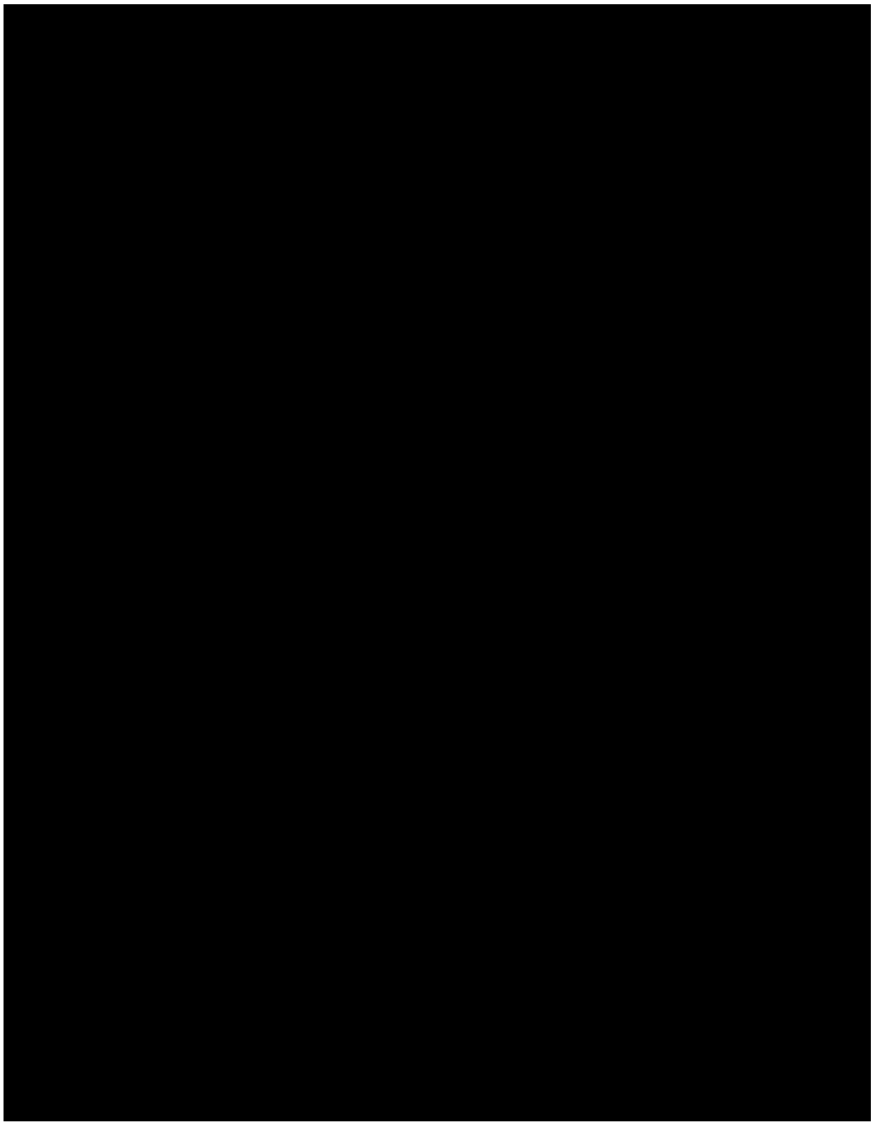
Company comment	EAG response
Clinical input at the next ACM is welcomed, and feedback from experts that the company consulted suggests that the committee's conclusion regarding placebo response is implausible: a placebo duration of 1 year, as in the company's base case, was supported by clinical experts in a recent survey and at an advisory board – in a recent survey of 12 neurologists, 11/12 responding to the question *"based on your experience and/or clinical judgement, for how many years on average do you think a placebo effect after a patient has failed two triptans, and remains on baseline standard care typically lasts in terms of the acute treatment for migraine?"* selected *"1 year"* or *"<1 year"*, with the other responding *"not sure"*;	The EAG acknowledges the results of the survey of neurologists carried out by the company that suggest placebo effect in acute migraine would not be expected to last longer than 1 year; however, the EAG is unsure as to the robustness of this survey given no further details are provided and it is unclear whether best practice methods were followed (such as the Sheffield Elicitation Framework; SHELF). Similar themes were identified as part of the company's advisory boards, including the statement that 1 year may be too long, but the EAG notes that the following is also stated in the advisory board summary: *"There are sparse data for the waning of placebo effect in acute; no studies were identified that covered a study period of 12 months. Waning of placebo was more accepted as relevant for prevention of migraine based on the limited data"*. The EAG notes that, as part of comment 2 in Section 2.1.1, the company also highlights evidence from their survey that 10/12 neurologists indicated the placebo response duration for an acute treatment would be shorter than that of a preventative migraine treatment. The EAG agrees that based on this feedback, specifying a time-point of 12 months for removal of placebo effect may be conservative given earlier time-points were mentioned, but also notes that this time-point is not based on any literature and there may be more uncertainty about placebo response duration in acute treatment of migraine. In addition, the EAG highlights that any placebo effect here would also apply to the rimegepant arm, which has not been removed from the model at the same time-point.
The company acknowledges that, as raised by the committee, both treatment arms may be associated with a placebo response and	The EAG acknowledges statements made by the company that a placebo effect in a trial may be different to a group of patients receiving no treatment or BSC in clinical practice, including a

disentangling the placebo response from the rimegepant arm may be challenging; however, it notes that it is highly unlikely that those receiving no treatment in clinical practice would benefit from any placebo response, meaning it is reasonable to remove indefinite placebo response from the no treatment/ BSC arm. They note that the difficulty in disentangling placebo response from rimegepant is accounted for by taking the conservative approach of using 1 year for loss of placebo response in the BSC arm. Evidence from a migraine study where patients could receive no treatment, placebo or rizatriptan for various migraine attacks is highlighted, which demonstrated that outcomes for attacks that were untreated and those treated with placebo differed, with outcomes worse in those that were untreated.	statement that patients on no treatment in clinical practice would be unlikely to benefit from a placebo effect, meaning that it is reasonable to remove placebo effect by 1 year in those responding to BSC. However, in its response the company is only attempting to account for a placebo-response in the placebo group when, as the company acknowledges, this is also likely to impact the reported results for rimegepant. The EAG notes that The study presented by the company was a within-subject repeated measures study of EM.[4] A total of n=66 participants were included, each with seven separate documented migraine attacks (one untreated followed by six attacks randomly assigned to be treated with rizatriptan [10 mg Maxalt®] or placebo treatments). Each treatment was labelled once as 'Maxalt®', once as 'placebo' and once as 'Maxalt® or Placebo'. Rescue medications were permitted for use at 2.5 h after headache onset (2 h after treatment for the treated attacks). The EAG confirms that this study reports a difference between untreated attacks and attacks treated with placebo (increased reduction in pain in the placebo group at 2 h after treatment [2.5 h after headache onset]), even when participants were aware they were receiving placebo. The EAG considers that there being a difference between attacks that were untreated and those treated with placebo in the cited study makes sense; however, patients will be receiving some treatment as part of their BSC in clinical practice, to which they may experience some response. Furthermore, the company has not addressed the committee's key concern that, *"all effects associated with the placebo response would likely also be seen in the rimegepant arm and so cannot reasonably be removed from 1 treatment arm but not the other"*. This means that if the company base case time horizon was accepted rimegepant would be receiving the placebo benefit for 20 years. As a result, the EAG does not consider this argument to resolve the concerns raised by the committee.

Maintaining indefinite placebo response for those with no alternative treatment options makes it almost impossible for any new acute treatment to demonstrate cost-effectiveness, confirmed by the fact that when costed at £0.00, rimegepant remains not cost-effective over longer time horizons.	The EAG acknowledges this is an illogical outcome of the model and appears to be driven by the worse outcomes of patients who discontinue rimegepant compared to BSC patients. The EAG considers it to be reasonable to assume patients who discontinue rimegepant have equivalent trajectories to patients on BSC. It should be noted that this issue does not occur if the two corrections implemented by the company are included. These corrections are discussed in further detail in Section 2.1.1 below.
The company also clarifies any potential confusion around the implication of stopping placebo response after 1 year in the model; when the model assumes that placebo response stops after 1 year, it still incorporates natural resolution of the migraine for all patients, as demonstrated in the 48 h pain trajectory heat maps (Figure 1). When placebo response is removed, the migraines of placebo patients still improve and resolve over each 48 h period.	In terms of the company's clarification on how removing placebo response at 1 year impacts the model, the EAG still considers this to be unclear. The committee concluded that removing placebo response in the comparator arm assumes that, after the first year of the model, there is no potential for the migraine attack to improve at 2 h when not having active treatment. The heatmap provided by the company (Figure 1), shows some improvement in migraine severity by 2 h but this figure appears to represent the whole placebo groups pain trajectory, not the placebo non-responders referenced. The EAG requests that the company provide further clarification as to if the heatmap provided represents the modelled pain trajectory of non-responsive placebo patients. In addition, the company should clarify if they are making the case that the committee's statement on migraine improvement at 2 h, when not having active treatment, is inaccurate.

Abbreviations: ACM, Appraisal Committee Meeting; BSC, best supportive care; EAG, External Assessment Group; EM, episodic migraine.

Figure 1. mITT 48 h pain trajectory – reproduced from Figure 1 of the appendix of the company's response to ACD2



2.1.1 *Company model correction*

The company also explains an unintended consequence of removing the placebo waning assumptions in the model; it leads to those receiving rimegepant and discontinuing experiencing worse migraine attacks compared to placebo responders, which the company states is illogical:

- As indicated in Figure 2 below, patients who respond to rimegepant for 6, 24 or 60 months, and then discontinue treatment, proceed to have worse migraine attacks compared to a patient that has responded to placebo and maintained an indefinite response – these assumptions contradict clinical expert opinion, are not supported by clinical data;
- As a correction to the committee's preferred analysis, the company ensured that a patient who had received rimegepant for any duration does not subsequently have worse migraine attacks than a placebo patient when discontinuing;
- When the effect is equalised in both arms by applying this correction, the incremental cost-effectiveness ratio (ICER) for the committee's preferred analysis reduces from £58,486 to £43,989 (Table 3 below).

Figure 2. Placebo responders vs rimegepant discontinuers over time – reproduced from Figure 1 of the company's ACD2 response

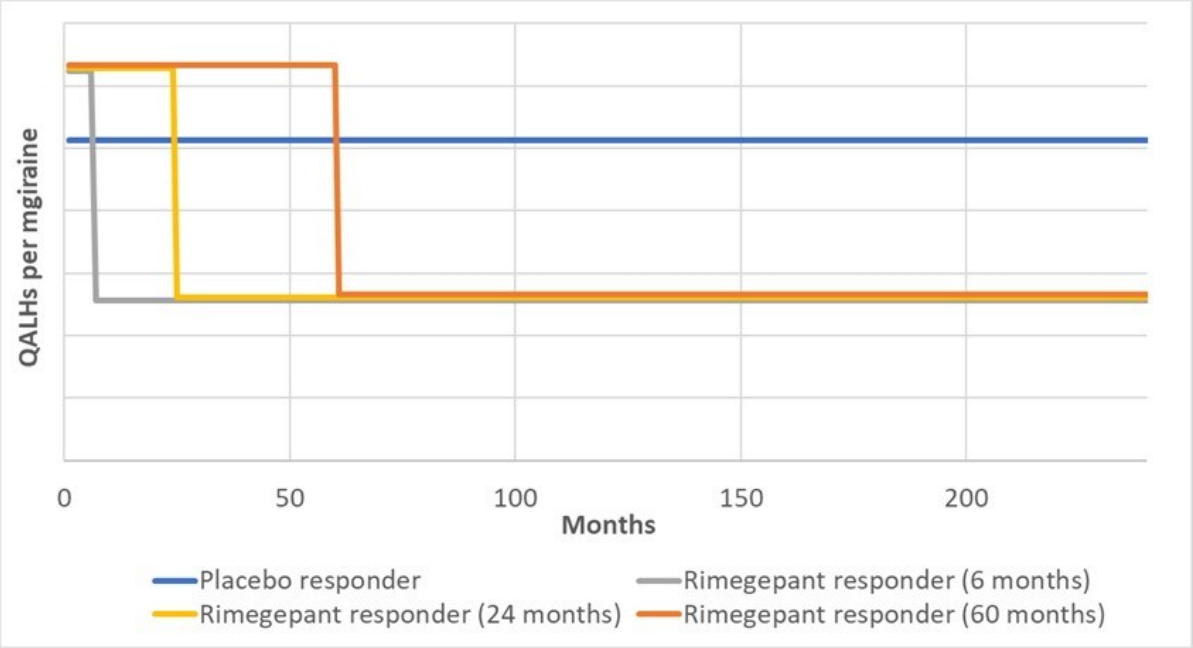


Table 3. Committee's preferred placebo response assumption by time horizon – uncorrected and corrected – reproduced from Table 2 of the company's ACD2 response

Scenarios	Incremental QALYS	Incremental costs	ICER (£/QALY)
Uncorrected*			
2-year time horizon (Committee's preferred base case)	0.0202	£1,182	£58,486
5-year time horizon	0.0234	£2,329	£99,561
10-year time horizon	-0.0094	£3,373	Rimegepant dominated
20-year time horizon	-0.0949	£4,180	Rimegepant dominated
Company-corrected			
2-year time horizon (Committee's preferred base case)	0.0265	£1,167	£43,989
5-year time horizon	0.0624	£2,253	£36,126
10-year time horizon	0.1133	£3,148	£27,788
20-year time horizon	0.1898	£3,655	£19,250

**Please note, these results were carried out using the previous model without the company's model correction to equalise rimegepant discontinuers and placebo responders.*

Abbreviations: ACD2, appraisal consultation document 2; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

The company made two adjustments to the model in order to produce these *corrected* results:

- The previous model assumed rimegepant responders who discontinue maintain a response for the same period as the placebo response time. If this is turned off, patients discontinuing default to non-responders. This has been corrected so patients who initially respond to rimegepant and then discontinue now follow the trajectory of a placebo all-comer.
- BSC is treated as an active therapy with a discontinuation rate determined by a hazard ratio relative to rimegepant discontinuation. This is to reflect patients shifting over to untreated/over the counter treatments.

The EAG agrees that it is not justified for patients who discontinue rimegepant to have worse outcomes than patients who are untreated. As a result, the first change to rimegepant patients who discontinue seems appropriate.

However, the second change appears to be an overcorrection, especially in combination with the first change. The company's first change attempts to align patients who discontinue rimegepant with BSC patients but the second change, only made to the BSC arm, results in significantly worse outcomes for patients on BSC vs rimegepant patients who discontinue. This is demonstrated in Table

4 which shows, even with ~100% annual discontinuation rate, patients in the rimegepant arm continue gaining a greater quality adjusted life year (QALY) advantage with a longer time horizon, despite not being on active treatment.

Table 4. Committee's preferred placebo response assumption by time horizon – company-corrected results rimegepant ~100% annual discontinuation rate

Scenarios	Incremental QALYs	Incremental costs	ICER (£/QALY)
Corrected			
2-year time horizon (Committee's preferred base case)	0.0252	£64	£2,533
5-year time horizon	0.0598	£64	£1,068
10-year time horizon	0.1097	£64	£582
20-year time horizon	0.1856	£64	£344

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Nevertheless, without further correction the model will still revert to negative QALYs over a longer time horizon. This is because the approximately 40% of patients who do not respond to rimegepant at initiation are assumed to discontinue and adopt placebo non-responder quality-adjusted life hours (QALH) outcomes for the remainder of the model time horizon, while patients who discontinue after this point are assumed to adopt placebo all-comer QALH outcomes. This means over a longer time horizon rimegepant patients' trend towards a QALH outcome between placebo-all comer and placebo non-responder while BSC patients maintain BSC-all comer QALH outcomes.

The EAG has therefore opted to alter its base case to address this issue, so treatment non-responders have placebo-all comer QALH outcomes in any model run where the loss of placebo response is turned off. This should mean patients discontinuing rimegepant, regardless of timing, have equivalent outcomes to patients in the BSC arm of the model. It should be noted that the company corrections only apply to runs where the placebo response is indefinite and have no impact on the company base case.

2.2 Comment 2. Company's current conservative placebo response

The company raises a number of factors with regards to the modelling of placebo response in the company's base case that it considers to be conservative and should be taken into account by the committee in decision-making:

- The wider modified intention to treat (mITT) population, favoured by the committee and EAG and subsequently applied to the company's base case, presents with a stronger placebo response for pain relief at 2 h than in the narrower, refractory population (≥2 triptan failures) for which rimegepant is proposed (Table 5 below):
    - The company states that this exacerbates the sensitivity of the model to assumptions of placebo response duration and highlights that when the committee's preferred assumptions are applied to this refractory subgroup, rimegepant has an ICER of £22,755 per quality-adjusted life year (QALY; with the correction discussed in Section 2.1 applied; Table 6).
    - The company also cites evidence from their own survey of neurologists, when asked *"in your experience, if patients have failed 2 or more acute migraine treatments are they likely to experience a placebo effect for the same length of time as patients who are receiving their first acute treatment?"*, that most would expect a placebo response to be stronger in those receiving their first acute migraine treatment compared to a group that have failed ≥2 triptans;
    - A prevention study noting the tendency for refractory populations to have a lower placebo response to anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies was also noted by the company – the EAG does not disagree conceptually that placebo response may be affected by number of prior treatments, as addressed in the EAG comment section below, but notes that the finding in the cited paper was not statistically significant;[5]
    - The company also highlights that as part of the prevention appraisal for rimegepant (ID6275), refractory populations in the acute migraine trials (BHV3000-301, -302 and -303) tended to have a lower placebo response compared to the overall population ([redacted] for mITT vs [redacted] for those with failure on ≥2 triptans) – the EAG considers these to be incorrect values, as the number analysed in the mITT population in Table 52 of the original company submission (CS) does not match Table 5 below or Table 14 of the CS for these trials (excluding BHV3000-310 subsequently included for base

case analyses). The EAG considers the correct values to be [redacted] for mITT and [redacted] for those with ≥2 triptan failures in these three specific trials;

- The company considers BSC healthcare resource use (HCRU) costs in the model to be conservative given the cost of BSC (i.e. placebo) was excluded from its base case. It notes that in practice it is not possible for placebo to have an indefinite response with no cost to the NHS. Given they would be expected to incur HCRU costs, the company have provided a scenario where patients in the placebo arm and rimegepant non-responders incur healthcare costs during the 2-year period. When applied to the committee's preferred assumptions, including not removing placebo response at 1-year, the company note that ICERs are reduced (£28,916 for the 2-year time horizon, when the correction described in Section 2.1 is also applied; Table 7).
- The company considers the modelling approach to be conservative and in line with previous technology appraisals in terms of placebo response duration. It highlights that its survey of neurologists indicated that a placebo response duration for an acute treatment would be shorter than that of a preventive migraine treatment, with 10/12 indicating it would last <1 year.

Table 5. Freedom from pain and pain relief at 2 h in the triptan refractory and pooled mITT populations from acute rimegepant trials – adapted from Table 1 of the appendix of the company's response to ACD2 and Table 20 of the original EAG report

Outcome	Rimegepant, n/N (%)	Placebo, n/N (%)	Risk difference, percentage points (95% CI) p-value
Refractory population (failed ≥2 triptans, proposed rimegepant population)[a,b] – three studies			
Freedom from pain at 2 h	30/148 (20.3)[c]	18/177 (10.2)	9.8 ([redacted]) p=0.0131
Pain relief at 2 h	[redacted]	[redacted]	[redacted]
Pooled mITT population[b] – three studies			
Freedom from pain at 2 h	[redacted]	[redacted]	[redacted]
Pain relief at 2 h	[redacted]	[redacted]	[redacted]
Pooled mITT population[f] – four studies			
Freedom from pain at 2 h	[redacted]	[redacted]	[redacted]
Pain relief at 2 h	[redacted]	[redacted]	[redacted]

[a]The EAG notes that this is based on the *post-hoc* definition of a triptan failure, described in the company's response to ACD1 as being based on either efficacy or intolerability and no requirement to fail on all routes of administration for a

particular triptan; [b]The EAG notes that this is based on data from studies BHV3000-301, -302 and -303, as data for the ≥2 triptan failure subgroup from BHV3000-310 was not available; [c]The EAG has corrected this from 20.0% - this appears to have led to an incorrect risk difference being calculated ([redacted], when based on percentages in each group this should be [redacted]). [d]The EAG has corrected this from [redacted]; [e]The EAG has corrected this from [redacted]; [f]based on data from studies BHV3000-301, -302, -303 and -310 as per the mITT analysis preferred by the EAG and committee, and used in the EAG and company base case.

Abbreviations: ACD, appraisal committee document; CI, confidence interval; EAG, External Assessment Group; mITT, modified intention to treat.

Table 6. Refractory population scenario analyses – reproduced from Table 3 of the company's ACD2 response

Scenarios	Incremental QALYS	Incremental costs	ICER (£/QALY)
Committee's preferred base case*			
2-year time horizon (committee's preferred base case)	0.0265	£1,167	£43,989
5-year time horizon	0.0624	£2,253	£36,126
10-year time horizon	0.1133	£3,148	£27,788
20-year time horizon	0.1898	£3,655	£19,250
Committee's base case including ≥2 triptan failures (refractory) population			
Indefinite placebo response and 2-year time horizon (committee's preferred assumptions)	0.0637	£1,447	£22,719
5-year time horizon	0.1399	£2,959	£21,147
10-year time horizon	0.2316	£4,424	£19,101
20-year time horizon	0.3417	£5,515	£16,142

**Please note, the analyses use the company-corrected committee's base case as noted in Section 2.1.*

Abbreviations: ACD2, appraisal consultation document 2; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 7. BSC HCRU costs scenario analyses – reproduced from Table 4 of the company's ACD2 response

Scenarios	Incremental QALYS	Incremental costs	ICER (£/QALY)
Committee's preferred base case*			
2-year time horizon (committee's preferred base case)	0.0265	£1,167	£43,989
5-year time horizon	0.0624	£2,253	£36,126
10-year time horizon	0.1133	£3,148	£27,788
20-year time horizon	0.1898	£3,655	£19,250
Committee's preferred base case* + hospital-based services cost			

2-year time horizon (committee's preferred base case)	0.0265	£767	£28,916
5-year time horizon	0.0624	£1,657	£26,581
10-year time horizon	0.1133	£2,392	£21,114
20-year time horizon	0.1898	£2,807	£14,787

**Please note, the analyses use the corrected committee's base case as noted in Section 2.1.*

Abbreviations: ACD2, appraisal consultation document 2; BSC, best supportive care; HCRU, healthcare resource use; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

EAG comment

Using the mITT population

The EAG acknowledges the company's comments about differences in placebo response for the pain relief at 2 h outcome between the mITT population (used in the EAG and company base case, and part of the committee's preferred analysis) and the group with ≥2 triptan failures, as per the *post-hoc* definition (see Table 5 above). The EAG also accepts that it is possible that placebo response differs depending on the number of prior treatment failures and that those with more treatment failures may experience a lower placebo effect, as indicated by the survey performed by the company and feedback from the EAG's clinical experts (as noted in the EAG's original report), and the study cited by the company in its response to ACD2 (although only a non-significant impact was identified in the cited paper).[5] However, the EAG considers that these differences in placebo effect would equally apply to patients taking rimegepant in the trials and, therefore, do not consider the use of the mITT population results from these trials to be conservative.

In addition, the EAG reiterates previously described limitations of the ≥2 triptan failure subgroup analysis in its original EAG report and in its critique of the company's response to ACD1. Of particular relevance to this argument by the company is the fact that baseline imbalances between rimegepant and placebo arms were observed in this subgroup, including a [redacted] proportion in the rimegepant group with severe migraine ([redacted]) at baseline, and a [redacted] proportion with aura in the placebo group ([redacted]), which may bias [redacted]. [redacted] for aura was observed between arms in the overall mITT population (see company response to clarification question A4, Appendix 3), although baseline migraine severity for the two arms in the mITT population is not reported. The EAG is concerned that these differences may contribute to the

[redacted] observed for risk differences between rimegepant and placebo (the benefit of rimegepant [redacted] from [redacted] [depending on whether three or four trials are included] to [redacted] when the ≥2 triptan failure subgroup is used) observed above in Table 5 between the ≥2 triptan failure subgroup and overall mITT population, and subsequently the large impact on the ICER when the committee's preferred assumptions are instead applied to this subgroup. The EAG's clinical experts noted that they could not provide a clinical rationale for this and that, if anything, the opposite would be expected. This difference is likely to be due to a combination of placebo response being [redacted] in the ≥2 triptan failure subgroup compared to the mITT population, but also [redacted] response in the rimegepant group; the latter is something the EAG's clinical experts also noted they would not expect.

The EAG further noted in its report and critique of the company's response to ACD1 that trials were not stratified by triptan failure at randomisation, the full population provides a larger sample size and includes patients for whom triptan treatment was contraindicated and not all patients in the trials had tried a triptan.

In conclusion, while there may be differences in placebo response between groups with different numbers of prior treatment failures, the EAG does not consider that using the response rate from the mITT population is conservative, given differences across these groups in terms of placebo response should apply equally for rimegepant and placebo groups and that the potential impact of imbalances at baseline is a concern for the estimates in the ≥2 triptan failure subgroup.

HCRU costs for BSC

The company wish for it to be acknowledged that it is not possible to administer a placebo or for a placebo to have an indefinite response with no cost to the NHS and as a result have provided an additional scenario with extra HCRU costs applied to the BSC arm.

The company's additional scenario assumes 20% of BSC patients would be referred to secondary care and 20% of these patients would see HCP over an annual period. This is based on Adelphi data prepared for Pfizer on responder vs inadequate responder patients. [6] This data presents the *"number of times patient seen HCP in last 12 months for migraine (All Migraine Patients)"* and the *"number of times patient seen HCP in last 12 months for migraine (All Migraine Patients Currently Consulting a PCP)"*. No data is available in the document on the number of consultations patients may have whilst on rimegepant. Since the data source used is for all migraine patients the company

have applied this scenario to all BSC patients (including discontinued rimegepant patients), with an option to just apply this BSC-non responders.

As stated in section 4.2.3.1.2 of the original EAG report, the EAG considers the exclusion of treatment costs for BSC to be a conservative assumption, however, this scenario does not seem a reasonable correction. The application of this cost to all BSC patients, including responders, with no evidence of any difference in HCRU for patients on rimegepant is inappropriate.

Previous migraine appraisals

The EAG acknowledges the further rationale described by the company in terms of the duration of placebo response, discussed in more detail in Section 2.1 above. It reiterates that the placebo response lasting no longer than 1 year was based on previous NICE appraisals in migraine prevention, including TA682 and TA764/TA631,[1, 3] and that while ACD2 states that, *"assumptions made in previous preventative migraine treatment appraisals do not necessarily apply"* the company considers them to be indicative. They also highlight evidence from their survey that 10/12 neurologists indicated the placebo response duration for an acute treatment would be shorter than that of a preventative migraine treatment.

The EAG acknowledges these points and notes that they have been covered in Section 2.1. The EAG reiterates that there is no long-term comparative evidence available to demonstrate that there would be a waning of efficacy in the placebo group but not the rimegepant group, as the results for both arms in the short-term comparative trials would include a placebo effect.

2.3 Comment 3. Time horizon.

The company disagrees with the committee's conclusion that a 2-year time horizon is most appropriate for decision making, arguing that it does not adequately reflect the nature of the condition and is unreasonable given the evidence presented. It retains a preference for a 20-year time horizon as patients who remain on treatment for longer periods of time incur both the clinical outcomes and economic costs of migraine from the time they remain on treatment. It also highlights that for patients in the placebo arm who have no alternative treatment, there will be a long-term QALY impact.

The company also notes that placebo response modelling is not the only relevant factor in terms of the model's sensitivity to time horizon. Patients who respond to treatment will remain on treatment and accrue greater benefits than those discontinuing early in the model due to a lack of efficacy. The company notes that as the time horizon extends, it is natural that the higher costs of determining response in the early stage of the model are counterbalanced by ongoing benefit.

Given the following points, the company do not believe that the committee has reached a reasonable conclusion in terms of the most appropriate time horizon to capture all relevant cost and QALY impacts:

- Patient comments in response to ACD1 and trial demographics show disease duration beyond 20 years;
- In the company's response to ACD1, clinical experts support a time horizon of longer than 10 years to properly capture benefits and costs relating to acute migraine treatment;
- Discontinuation data from the extension study and extrapolation support long-term use of rimegepant and with no alternative treatment options, there are important long-term outcome and cost differences to capture long-term outcome and costs;
- Real-world evidence (RWE) in terms of migraine prescription data supports the inclusion of a time horizon >5 years, as described in the company's response to ACD1;
- Consistency with the rimegepant preventive treatment time horizon of the same condition;
- The stopping rule at 12 weeks due to a lack of response applied in the model supports a longer time horizon, offsetting short term costs, while capturing long-term outcomes and costs.
- Differences in results over different time horizons suggest the longer horizon is more appropriate.

EAG comment

The company provides more detail for bullets three and six above and the EAG assumes that the arguments regarding the other points are the same as when raised in response to ACD1; for the latter, the conclusion made by the EAG and the committee was that they acknowledged that patients may experience repeated attacks over many years but that this should not dictate the time

horizon and that a 2-year time horizon should capture the costs and benefits of rimegepant as an acute treatment.

With regards to differences in costs and clinical outcomes, the company notes that rimegepant evidence suggests patients will continue beyond two years, meaning there is an important QALY impact beyond 2 years that should be captured for patients that continue treatment. It notes that an extrapolation of BHV3000-201 (open-label extension study including as needed/*pro re nata* [PRN] rimegepant use) suggests that most patients would be expected to be on treatment beyond 5 years (Figure 3 of the appendix of the company's response to ACD2) and that in the economic model at 5 years, when the committee's preferred discontinuation rate of [redacted] is used, 31% of patients remain on treatment (Figure 2 of the appendix of the company's response to ACD2). The EAG notes that these results appear to be specifically for the group with ≥2 triptan failures in BHV3000-201. Due to this, and the fact that the alternative is to receive no treatment and experience the full detrimental quality of life (QoL) impact of their migraines, the company concludes that it is reasonable to consider there to be significant QALY gains beyond 2 years.

The EAG considers that the points described in the previous paragraph are part of the same argument the company made in response to ACD1, in terms of how many years people will experience acute migraines. Given that the EAG has already acknowledged that this may be correct but that a 2-year time horizon is still appropriate, as when monthly migraine day (MMD) reductions are removed from the model, the differences in costs and health-related QoL relate to a relatively short period (each specific migraine episode), the EAG does not consider there to be any new arguments to change its position on the time horizon. Furthermore, the new EAG base case has relatively little change in ICER with an increased time horizon.

In response to the committee's statement that, *"the Committee said that it understood that migraine is a chronic and lifelong disease, and rimegepant is an acute treatment that could be used repeatedly over many years. It highlighted that these facts were not in any doubt and explained that the issue is the mechanism by which the model produces different cost-effectiveness estimates over different time horizons"*; the company notes that the model is structured with a stopping rule built in, as it assumes patients who do not respond will not continue their treatment beyond their first treatment supply. It considers that this supports the need for a longer time horizon, as patients who are not gaining benefit early in the model move to non-responders but accruing the cost of a full

pack are offset with patients responding long-term, and the average QALY gain improves over time as a result.

The company is correct that the shorter time horizon means the additional cost of rimegepant pack for non-responders will push up costs but this is a relatively small impact. The additional cost of the full pack wasted in the first cycle is £35.85 which has a negligible impact on the incremental costs/ICER.

2.4 Comment 4. Stopping rule.

In response to the committee's request for more information about a stopping rule for rimegepant when used as an acute treatment for migraine, the company notes that the summary of product characteristics (SmPC) does not include a stopping rule, which also applies for other migraine-specific acute treatments. Therefore, the choice to discontinue treatment would be a patient and clinician decision. The company expects that if patients do not respond to rimegepant, they do not continue their treatment beyond their first treatment supply (whole pack of rimegepant, including eight doses), the cost of which is included in the economic model. Patients are also not expected to continue treatment if they are non-responders to two consecutive treatments. However, the company notes that patients are unlikely to persist with treatments that are ineffective and that the model essentially has a stopping rule built in as patients discontinue after one failed response to rimegepant (one dose). It is assumed that rimegepant will be used in clinical practice consistent with the trial design (discontinue after one dose if ineffective) but the company notes that the cost of an entire rimegepant pack is allocated given patients may take multiple doses to determine response and that wastage may occur. The company anticipates that patients would discontinue indefinitely (and not restart at a later date) but considers this would be a patient and clinician decision.

EAG comment

The EAG considers that the company has provided further detail on stopping rules for rimegepant in acute migraine treatment as requested by the committee and confirms that in the economic model, patients who are recorded as non-responders discontinue in the first cycle, with a whole pack costed for.

The EAG notes that this is based on when the company anticipates patients will stop treatment and no formal stopping rules are included in the SmPC for acute rimegepant treatment. The company suggests that rimegepant is likely to be used as in the economic model, where patients discontinue if

they do not respond to one rimegepant dose for a single migraine attack. Given that the EAG's clinical experts and experts in the ACM1 noted that treatments for acute migraine are usually tried for at least three attacks before conclusions about non-response are made, the EAG considers that this may be unlikely. However, the company also acknowledges that this may vary and may be based on a discussion between the patient and clinician, which is why a whole pack has been costed for. The company also mentions that those with non-response on two consecutive treatments are likely to discontinue, but again this is not a formal stopping rule.

2.5 Comment 5. [redacted]

The company highlights

[redacted]

The proportions with ≥30% and ≥50% reduction in MMDs from baseline are presented in Table 8 below.

Table 8. Proportions meeting two MMD reduction thresholds during 12 weeks in BHV3000-201 [redacted] – reproduced from Table 5 of the company's response to ACD2

Trial	≥30% reduction in MMD	≥50% reduction in MMD
BHV3000-201	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: ACD2, appraisal consultation document 2; MMDs, monthly migraine days.

The company acknowledge the committee's statements that, *"there is biological plausibility in the suggestion that taking rimegepant as needed may reduce MMDs"*, and that removing the assumption from the model, *"may be considered as a small, potential uncaptured benefit"* (Section 3.12 of ACD2) but highlight that the impact of removing the MMD reduction from patients taking rimegepant PRN has a considerable impact on QoL benefit.

The company have not reintroduced an MMD reduction for rimegepant to its updated base case but provide scenario analyses to demonstrate the impact. It also highlights that the company's exclusion

of MMD reduction reflects a conservative approach which should be considered by the committee. As indicated in Table 9 below, including the MMD reduction reduces the ICERs for the company's base case as well as the analysis with the committee's preferred assumptions, with values of £13,255 and £26,358, respectively, compared to when MMD reduction is not included (£18,914 and £43,989, respectively) when the company's correction described in Section 2.1 is also applied.

Table 9. Reduction in MMD scenario analyses – reproduced from Table 6 of the company's response to ACD2

Scenarios	Incremental QALYS	Incremental costs	ICER (£/QALY)
Committee's preferred base case* including reduction in MMD			
Indefinite placebo response & 2-year time horizon	0.0367	£966	£26,358
5-year time horizon	0.0818	£1,858	£22,720
10-year time horizon	0.1397	£2,593	£18,564
20-year time horizon	0.2195	£3,009	£13,711
Company's base case including reduction in MMD			
2-year time horizon	0.0505	£925	£18,326
5-year time horizon	0.1197	£1,721	£14,374
10-year time horizon	0.1762	£2,377	£13,495
20-year time horizon	0.2073	£2,748	£13,255

**Please note, the analyses use the company-corrected committee's base case as noted in Section 2.1.*

Abbreviations: ACD2, appraisal consultation document 2; ICER, incremental cost-effectiveness ratio; MMD, monthly migraine days; QALYs, quality-adjusted life years.

EAG comment

The EAG recalls that, in the original CS, MMD reduction was included in the acute migraine model for rimegepant based on evidence from the BHV3000-201 study over 12 months. The EAG's conclusion was that the long-term reductions in MMD with PRN rimegepant are highly uncertain as this is based on a *post-hoc* analysis of an open-label, non-comparative long-term safety study which may suffer from confounding (including but not limited to a possible placebo effect).

The EAG notes that [redacted]

[redacted] While the EAG confirms that the 12-week results for proportions with ≥30% and ≥50% reduction in MMDs during 12 weeks [redacted] limited data is provided and it is unclear why the reduction from baseline in MMDs outcome has not been compared in this table instead. Furthermore, results at 12 months [redacted] Even if further comparisons [redacted] had been provided in terms of outcomes and time-points, the EAG considers that [redacted] that led the EAG to conclude that removing the impact of rimegepant on MMD for acute migraine was appropriate ([redacted]).

The EAG also acknowledges that the inclusion of an MMD reduction increases incremental QALYs (0.0367 vs 0.0265 with the committee's preferred assumptions, with the correction described in Section 2.1 applied, and 0.1794 vs 0.2073 with the company's preferred assumptions) and reduces the ICERs but does not consider that further evidence presented is sufficient to change its decision to exclude MMD reduction from the acute model, and that the committee's conclusion that it be considered a potential uncaptured benefit in the model is reasonable.

2.6 Comment 6. Contraindicated and intolerant to triptans subgroup analyses.

In response to the committee's request for clinical and cost-effectiveness analyses in the group that is contraindicated to or intolerant of triptans (Section 3.21 of ACD2), the company provided the information summarised in Table 10 and Table 11 below. The company concludes that when results for this subgroup are used in the model, rimegepant remains cost-effective below £25,000 (ICER of £16,318). The company also states that, *"Given the base case results are similar to the full populations they are deemed representative and support the population for which rimegepant is proposed"*.

Table 10. Freedom from pain and pain relief at 2 h in the triptan refractory, pooled mITT and contraindicated/intolerant to triptans populations from acute rimegepant trials – adapted from Table2 of the appendix of the company's response to ACD2

Outcome	Rimegepant, n/N (%)	Placebo, n/N (%)	Risk difference, percentage points (95% CI) p-value
Refractory population (failed ≥2 triptans, proposed rimegepant population) – three studies[a,b]			
Freedom from pain at 2 h	30/148 (20.3)[c]	18/177 (10.2)	9.8 ([redacted]) p=0.0131
Pain relief at 2 h	[redacted]	[redacted]	[redacted]
Pooled mITT population – three studies[a,b]			
Freedom from pain at 2 h	[redacted]	[redacted]	[redacted]
Pain relief at 2 h	[redacted]	[redacted]	[redacted]
Pooled mITT population[d] – four studies			
Freedom from pain at 2 h	[redacted]	[redacted]	[redacted]
Pain relief at 2 h	[redacted]	[redacted]	[redacted]
Pooled CV contraindicated or intolerant to triptans – three studies[e]			
Freedom from pain at 2 h	[redacted]	[redacted]	[redacted]
Pain relief at 2 h	[redacted]	[redacted]	[redacted]

[a]The EAG notes that this is based on the *post-hoc* definition of a triptan failure, described in the company's response to ACD1 as being based on either efficacy or intolerability and no requirement to fail on all routes of administration for a particular triptan; [b]The EAG notes that this is based on data from studies BHV3000-301, -302 and -303, as data for the ≥2 triptan failure subgroup from BHV3000-310 was not available; [c]The EAG has corrected this from 20.0% - this appears to have led to an incorrect risk difference being calculated ([redacted], when based on percentages in each group this should be [redacted]); [d]Based on data from studies BHV3000-301, -302, -303 and -310 as per the mITT analysis preferred by the EAG and committee, and used in the EAG and company base case; [e]based on data from studies BHV3000-301, -302 and -303, as data from BHV3000-310 was not available for this subgroup.

Abbreviations: ACD, appraisal committee document; CI, confidence interval; CV, cardiovascular; EAG, External Assessment group; mITT, modified intention to treat.

Table 11. Cost-effectiveness results when data from the contraindicated and intolerant to triptans subgroup is incorporated – reproduced from Table 3 of the appendix of the company's response to ACD2

Scenarios	Incremental QALYs	Incremental costs	ICER (£/QALY)
Company's base case	0.1794	£3,394	£18,914
Contraindicated and intolerant subgroup analysis	0.3029	£4,942	£16,318

**Please note, the analyses use the company's correction noted in Section 2.1.*

Abbreviations: ACD2, appraisal consultation document 2; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

EAG comment

The EAG has a number of concerns about the data provided for the new subgroup including those who are contraindicated to or intolerant of triptans, as follows:

- It is unclear if the definition used matches the group described by the committee accurately; it includes those contraindicated due to cardiovascular indications and/or those that discontinued at least one prior triptan due to side effects (with other triptan failures due to efficacy allowed) and the EAG is unsure if this represents a group that would be classed as intolerant in practice;
- While not as substantial as the imbalances for the analysis in the refractory analysis (≥2 triptan failures; discussed above in Section 2.2); there some notable imbalances, one of which may bias in favour of rimegepant.

The company outlined the criteria for inclusion in the contraindicated/intolerant to triptan subgroup, summarised in Table 12 below. The EAG notes that the definition for intolerance is not specific to those that have experienced intolerance to at least two triptans; it allows inclusion of any patient with at least one triptan discontinuation due to intolerance, meaning they might not be considered intolerant to all or multiple triptans. Based on the text in Table 12 below, the EAG initially understood that patients in this subgroup had at least two triptan failures, but only one had to be due to intolerance the others could be due to a lack of efficacy. However, given that the numbers analysed for the contraindicated/intolerant subgroup (n=[redacted] for rimegepant and n=[redacted] for placebo) are higher compared to the refractory subgroup analyses (n=148 for rimegepant and n=177 for placebo), the EAG does consider this to be possible; this would mean the intolerant subgroup is a subgroup of those included in the refractory subgroup definition (as patients failing due to intolerance or lack of efficacy were included in this definition) and the EAG would expect the numbers analysed to be smaller (given the number contraindicated to triptans was fairly small; n=17 for rimegepant and n=12 for placebo). The EAG considers further clarification on the exact group of patients included in this analysis is required, for example, whether this includes all patients with at least one failure due to intolerance (with no requirement for a second failure due to either intolerance or efficacy).

Clinical expert feedback highlighted by the EAG in its original report suggested that multiple triptans would be tried before concluding they are not effective as a whole and that intolerance to one

triptan does not rule out the use of another. Therefore, the EAG is unsure how applicable the subgroup analysis provided is, as there was only a requirement for intolerance to one triptan. If the company confirms that the analysis also did not require a second failure due to either intolerance or efficacy, the EAG considers the subgroup analysis to be even more limited in terms of its applicability to clinical practice.

Table 12. Definitions for inclusion in the contraindicated/intolerant to triptan subgroup (reproduced from the company's response ACD2 following EAG queries)

Group	Definition	Comments
Triptan contraindicated	Patients identified with pre-specified cardiovascular indications as per pre-specified analysis in from pooled mITT of rimegepant acute trials BHV3000-301, BHV3000-302 and BHV3000-303.	As per existing definition in pre-specified analysis. Expect 17 rimegepant and 12 placebo.
Triptan intolerant	Patients who have discontinued 1 or more previous triptans and included a reason of "treatment caused side effects" for at least one triptan with a frequency of either "Most or all of the time" or "Some of the time" from pooled mITT of rimegepant acute trials BHV3000-301, BHV3000-302 and BHV3000-303. Regardless of dose or route of administration.	Patients who also state lack of efficacy in addition to "treatment caused side effects" for the same triptan are included. Includes patients who fail one triptan for "treatment caused side effects" but have failed other triptans for other reasons. For example, a patient who fails first triptan for side effects, but then fails triptan 2 and 3 for lack of efficacy would be classed as triptan intolerant. Provides largest possible population.

Abbreviations: ACD2, appraisal consultation document 2; mITT, modified intention to treat.

The EAG is unsure of the meaning of the following statement by the company: "*Given the base case results are similar to the full populations they are deemed representative and support the population for which rimegepant is proposed*". The EAG's interpretation is that the company is suggesting that as the results of the for the requested subgroup are similar to those used in the company's (and EAG's) base case (mITT population), this means the analyses using mITT can be considered applicable to the group that are contraindicated to or intolerant of triptans. However, the EAG is unsure about this as it notes that in this appraisal, rimegepant has been proposed for the group with ≥2 triptan failures due to efficacy or intolerance (or who are contraindicated), not group of contraindicated or intolerant patients.

Based on the data presented in Table 10 and Table 11 below, the EAG agrees that results for freedom from pain at 2 h are fairly similar across the four analyses; however, there are notable differences across the analyses for pain relief at 2 h outcome (used to define responders in the economic model), including when comparing between mITT and contraindicated/intolerant to triptan groups (risk difference of [redacted] and [redacted], respectively, when studies BHV3000-301, -302 and -303 are included; the EAG's preferred analysis with four studies included had a risk difference of [redacted]). While not as large as the differences when mITT analyses are compared to the refractory group with at least two triptan failures, the EAG does consider there to be differences in the pain relief at 2 h outcome for the contraindicated/intolerant subgroup compared to mITT analyses. . ICERs for this subgroup are similar but slightly lower when applied to the company's base case. The EAG performed this analysis applied to the new base case in section 4.2.

The EAG notes that the initial description of this subgroup analysis and how it has been implemented in the model was very brief but the company clarified that all relevant economic model inputs were updated with data for this subgroup, including baseline characteristics, the percentage experiencing pain relief, time in pain categories, QALH regression and the proportion with moderate/severe event at 24 h.

The EAG notes that there are some imbalances between rimegepant and placebo arms, which may impact the results. These are presented in Table 13 below. While the extent of the difference is smaller than observed for the refractory subgroup (discussed in Section 2.1.1), the EAG notes that there is also a [redacted] proportion of patients with severe migraine in the placebo group compared to rimegepant, which may introduce bias in favour of rimegepant. The EAG considers the imbalance observed for migraine with aura may act in the opposite direction, given [redacted] rimegepant patients have aura. There are also some imbalances in most bothersome symptom (MBS) experienced and the EAG is unclear which direction these may bias results.

Table 13. Baseline characteristics in imbalance for the contraindicated/intolerant to triptan subgroup (adapted from the company's response to ACD2 following EAG queries)

Characteristic	Rimegepant	Placebo
Migraine with aura, n (%)	[redacted]	[redacted]
MBS for treated attack, n (%)	-	-
Photophobia	[redacted]	[redacted]
Phonophobia	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Not reported	-	-

Severe migraine at baseline	[redacted]	[redacted]

Abbreviations: ACD2, appraisal consultation document 2; MBS, most bothersome symptom.

Based on what has been provided by the company, the EAG concludes that clinical expert input is required to determine whether the subgroup presented is applicable to that requested by the committee (i.e., is it acceptable to include those intolerant to only one triptan but may or may not have failed others due to a lack of efficacy). The EAG does not necessarily agree that results for pain relief at 2 h are similar in the contraindicated/intolerant to triptans subgroup presented compared to mITT analyses. Some baseline imbalances exist and may be a concern when this subgroup is used. The EAG's preference for its base case remains the mITT population with four studies included. Based on the results as provided, the EAG confirms that the ICER for this subgroup when applied to the company's base case is similar, with a reduction of ~£2,600; while similar, the EAG notes that this may be an important reduction particularly when ICERs are close to the decision-making thresholds.

2.7 Comment 7. Uncaptured benefit.

The company highlights another two factors that it considers to be conservative in terms of the current modelling for rimegepant in acute migraine:

- The model does not capture medication overuse headache (MOH) induced by other acute migraine treatments. Certain analgesics and front-line abortive medicines, such as triptans, are associated with a greater risk of MOH;[7] however, there is no evidence of MOH occurring with rimegepant in pre-clinical and clinical trials and post-marketing safety data showed 21 cumulative non-serious cases of MOH were reported as of 27 February 2023 (out of a total estimated cumulative post-marketing experience exposure to rimegepant in the EU and rest of the world of ~85 patient-years, and in the USA estimated to be 762,251 patients);[8]
- Chronification due to suboptimal acute migraine management is also not captured in the model.[9]

EAG comment

MOH benefit

The EAG confirms that MOH is not captured in the modelling of rimegepant for acute migraine. The paper cited by the company describes MOH as, *"headache occurring on 15 or more days per month developing as a consequence of regular overuse of acute or symptomatic headache medication (on 10 or more, or 15 or more days per month, depending on the medication) for more than 3 months".*[7] The EAG confirms that this paper highlights the risk of MOH with medications commonly prescribed to treat acute migraine, including analgesics, ergots, opioids and triptans, which the EAG considers may be components of BSC depending on the patient.

The EAG's clinical experts also raised the issue of MOH with regards to current acute migraine treatments, as described in the EAG's original report. While the company notes that there is no evidence of MOH occurring with rimegepant use in patients in pre-clinical and clinical trials, the EAG considers that the evidence available may be too limited to conclude that rimegepant use would definitely reduce MOH incidence. As discussed in the EAG's original report, MOH could not be assessed in the trials for acute migraine as they involved the treatment of a single attack only. The company reported that there was only [redacted] of MOH in the long-term (up to 52 weeks) study (BHV3000-201) used to support rimegepant in the acute setting (see company response to clarification question A15) and [redacted] in the long-term phase (up to 52 weeks) of BHV3000-305 used to support rimegepant in the prevention setting (where every other day [EOD] dosing meant there was a median average exposure of [redacted] tablets per month). However, it is unclear how thorough the identification of possible MOH events was in these studies.

The company has previously highlighted evidence based on real-world data of rimegepant patients in the USA that suggests that the prevalence of MOH is reduced after rimegepant prescription and in its response to ACD2 also highlights 21 non-serious cases of MOH out of ~85 patient-years in the EU and the Rest of the World and ~762,251 patients in the USA.[8, 10] The EAG is unable to comment on how these rates may compare to those for other acute migraine treatments that may comprise BSC.

The EAG acknowledges that preventing or reducing the risk of MOH may represent an uncaptured benefit of rimegepant but that there is currently no comparative evidence to confirm the reduced risk compared to BSC or the extent of any difference.

Chronification of migraine

The EAG also acknowledges that migraine chronification is not captured in the model. The reference cited by the company describes a study that investigated whether ineffective acute treatment of episodic migraine (EM) is associated with an increased risk of the subsequent onset of chronic migraine (CM).[9] The study included patients in the American Migraine Prevalence and Prevention Study that had EM in 2006, completed the Migraine Treatment Optimisation Questionnaire (mTOQ-4; a measure of treatment efficacy rated as very poor, poor, moderate and maximum treatment efficacy) and provided outcome data in 2007. Logistic regression models were used to assess the outcome of transitioning from EM in 2006 to CM in 2007 as a function of mTOQ-4 category, adjusting for covariates.

The EAG confirms that the results of this study indicate that those with very poor and poor acute treatment efficacy may lead to a statistically significantly higher risk of the development of CM in those with EM compared to those reporting maximum efficacy when sociodemographic factors are adjusted for. However, the result for poor efficacy became non-significant when the model adjusted for headache day frequency and disability and the odds ratio for the very poor treatment efficacy group was substantially reduced. The EAG notes that this study may provide some evidence for a link between poor treatment efficacy and subsequent development of CM but that it is not conclusive.[9]

The EAG considers that the issue of poor treatment efficacy and the potential impact on development of CM in EM patients (and any consequences of this in terms of modelling) would apply to any treatment that is not effective, including rimegepant for those who don't respond to it, and not just BSC. However, given that more patients in the economic model respond to rimegepant compared to placebo, the EAG acknowledges that more EM patients on BSC may be at risk of developing CM compared to rimegepant. The extent of any impact were this to be considered an uncaptured benefit is unclear and the EAG notes that the study cited by the company reports fairly small percentages with poor or very poor treatment efficacy transitioning to CM at 1 year (4.4% and 6.8%, respectively), meaning the impacts of CM progression would not apply to all of those not experiencing a response. In addition, the EAG notes that if it were to be considered an uncaptured benefit, this would only apply to EM patients, whereas the proposed use of rimegepant in the acute setting would be for EM and CM patients. ACD2 (Section 3.7) states that, although the acute trials for rimegepant were all in EM, *"the committee accepted that the trial results are generalisable to both populations"*.

The EAG concludes that while it does not dismiss the idea that poor acute treatment efficacy may increase the risk of CM developing in those with EM, and that those on BSC may be at an increased risk of this compared to rimegepant as more patients using rimegepant are responders, it does not consider the current evidence to be conclusive and the extent of any potential benefit is unclear.

2.8 Comment 8. Risk to new innovative medicine.

As touched on in Section 2.1, the company raises concerns about highly conservative assumptions included as part of the committee's preferred analysis. It notes that this may risk discouraging innovation in acute migraine, an area in which there is a considerable unmet need in terms of new treatments. It notes that it has lowered the list price considerably and increased certainty in the model by accepting seven of the nine committee-preferred assumptions and taking an overall conservative modelling approach. It highlights that the lowered list price of rimegepant (£12.90 per pill) is significantly lower than some triptans currently available on the market (Table 7 of the company's response to ACD2) and is cheaper than 42.2% of triptans prescribed, which may be a conservative estimate if redosing (a common requirement with triptan use) is considered.

The company highlights that there has been limited innovation in acute migraine in recent years, with no new treatments approved in the UK in over 20 years. It reiterates that rimegepant would not be cost-effective at £0.00 over time horizons of ≥10 years. The company concludes that the committee's preferred assumptions threaten future innovation within the acute migraine space and may create inequalities for acute migraine patients who have already lost out on access to new innovations, such as lasmiditan which is not launching in the UK despite being reimbursed elsewhere in Europe.[11]

EAG comment

The EAG has commented on the company's points around costing rimegepant at £0.00 and other assumptions favoured by the company in the previous sections. The EAG acknowledges the reduced list price for rimegepant since the original CS and the unmet need in terms of acute migraine treatments but does not consider these to be points that the EAG can provide any further insight on. The EAG highlights that similar risks to the NHS exist in terms of resources if medicines that are not cost-effective are recommended.

2.9 Comment 9. Revised acute model and scenario analyses.

The company provides an overview of the company's and the committee's preferred base cases, including the new lowered list price of rimegepant (from £20.00 to £12.90 per pill; from £160 to £103.20 per 8-pack). The company notes that based on its base case, rimegepant is cost-effective with an ICER less than £25,000. It concludes that the committee's preferred assumptions represent an overall conservative approach and provides an overestimation of the ICER. In addition, the company notes that the value of rimegepant in the NHS is also greater than that reflected in the company's base case. The company's base case incorporates seven of the nine committee-preferred assumptions, which the company states has reduced uncertainty in the model and increased ICERs, which has been offset by reducing the list price of rimegepant. Cost-effectiveness results and scenarios are summarised in below in Table 14.

Table 14. Cost-effectiveness results and scenario analyses – revised acute migraine model – reproduced from Table 8 of the company's response to ACD2

Scenarios	Incremental QALYS	Incremental costs	ICER (£/QALY)
Committee's preferred base case*			
Indefinite placebo response & 2-year time horizon	0.0265	£1,167	£43,989
5-year time horizon	0.0624	£2,253	£36,126
10-year time horizon	0.1133	£3,148	£27,788
20-year time horizon	0.1898	£3,655	£19,250
Company's base case by time horizon			
2-year time horizon	0.0408	£1,126	£27,621
5-year time horizon	0.1013	£2,325	£20,889
10-year time horizon	0.1512	£2,932	£19,391
20-year time horizon (Company's preferred base case)	0.1794	£3,394	£18,914
20-year time horizon (Company's preferred base case PSA)	0.1214	£2,235	£18,444
Company's base case including ≥2 triptan failure (refractory) population			
2-year time horizon	0.0786	£1,412	£17,958
5-year time horizon	0.1845	£2,837	£15,375
10-year time horizon	0.2870	£4,216	£14,690
20-year time horizon	0.3629	£5,238	£14,432
Company's base case including reduction in MMD			

2-year time horizon	0.0505	£925	£18,326
5-year time horizon	0.1197	£1,721	£14,374
10-year time horizon	0.1762	£2,377	£13,495
20-year time horizon	0.2073	£2,748	£13,255
Company's base case including ≥2 triptan failure (refractory) population and reduction in MMD			
2-year time horizon	0.0887	£1,237	£13,955
5-year time horizon	0.2047	£2,475	£12,095
10-year time horizon	0.3161	£3,674	£11,623
20-year time horizon	0.3974	£4,562	£11,478

**Please note, the analyses use the company-corrected committee's base case as noted in Section 2.1.*

Abbreviations: ACD2, appraisal committee document 2; ICER, incremental cost-effectiveness ratio; MMD, monthly migraine days; QALYs, quality-adjusted life years.

3 Company updated results

The company's base case incorporates most of the EAG/committee preferred assumptions aside from the shortened time horizon and the turning off of the placebo response loss. The only change from the previous ACM that impacts the company base case is a decrease in price per pill of rimegepant from £13.55 to £12.90. The updated company base case is shown in Table 15.

Table 15. Company updated base case

Results per patient	Rimegepant	BSC	Incremental value
Revised base case			
Total costs	£5,420	£2,026	£3,394
Total QALYs	8.93	8.75	0.18
ICER (£/QALY)	—	—	£18,914

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

Most relevant scenarios around the company's base case can be found in the company's analysis in Table 14. However, two alterations to the model allowed for additional scenarios around the discontinuation of BSC responders over time and the incorporation of additional HCRU costs for BSC patients. The company only ran these in comparison to the EAG/Committee base case, therefore these scenario results can be found in Table 16.

Table 16. Company base case cost-effectiveness scenarios

Scenario	Incremental QALYs	Incremental costs	ICER (£/QALY)
Discontinuation of BSC responders			
20-year time horizon	0.18	£3,390	£18,738
10-year time horizon	0.15	£2,928	£19,179
5-year time horizon	0.10	£2,112	£20,552
2-year time horizon	0.04	£1,122	£26,566
BSC HCRU cost scenarios (All BSC patients)			
20-year time horizon	0.18	£2,547	£14,193
10-year time horizon	0.15	£2,176	£14,391
5-year time horizon	0.10	£1,520	£15,013
2-year time horizon	0.04	£726	£17,809
BSC HCRU cost scenarios (BSC non-responder patients)			
20-year time horizon	0.18	£2,763	£15,395
10-year time horizon	0.15	£2,479	£16,391
5-year time horizon	0.10	£1,779	£17,562
2-year time horizon	0.04	£870	£21,338
Contraindicated and intolerant subgroup analysis			
20-year time horizon	0.30	£4,942	£16,318
10-year time horizon	0.24	£3,975	£16,712
5-year time horizon	0.15	£2,678	£17,773
2-year time horizon	0.06	£1,342	£22,049

Abbreviations: BSC, best supportive care; HCRU, healthcare resource use; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life years.

4 EAG preferred assumptions

4.1 Correction to the EAG base case

Following ACM2, the committee recommended that the placebo response stop at 12 months be turned off. The EAG has accepted this change by committee and incorporated this as part of the EAG base case. In order to ensure that this placebo response working long-term does not lead to artificially higher BSC outcomes when compared to discontinued rimegepant patients, both the EAG and the company have made adjustments to the model. The resulting EAG base case transformation is found in Table 17. The PSA results are found in Table 18.

Table 17. EAG's revised base case results (acute migraine treatment)

Results per patient	Rimegepant	BSC	Incremental value
Original EAG/committee base case			
Total costs	£1,351	£169	£1,182
QALYs	1.27	1.25	0.02
ICER (£/QALY)	—	—	£58,486
Company correction (parity for rimegepant QALH assumptions when placebo waning is turned "off")			
Total costs	£1,351	£169	£1,182
QALYs	1.27	1.25	0.02
ICER (£/QALY)	—	—	£56,125
Revised base case (Treatment non-responders QALH of placebo-all comers)			
Total costs	£1,293	£169	£1,124
QALYs	1.28	1.25	0.04
ICER (£/QALY)	—	—	£29,833

Abbreviations: BSC, best supportive care; EAG, External Assessment Group; ICER, incremental cost effectiveness ratio; QALH, quality-adjusted life hours; QALY, quality adjusted life years.

Table 18. EAG updated probabilistic base case

Results per patient	Rimegepant	BSC	Incremental value
Revised base case			
Total costs	£860	£111	£749
QALYs	1.36	1.34	0.0256
ICER (£/QALY)			£29,281

Abbreviations: BSC, best supportive care, EAG, External Assessment Group; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life years.

4.2 Scenarios around the EAG base case

Scenarios around the EAG base case are shown in Table 19. The EAG has attempted to show all scenarios provided by the company vs the new base case. However, the validity of many of these scenarios is disputed as covered in previous sections.

The EAG considers that the subgroup analysis provided for those contraindicated/intolerant to triptans may not match what was requested by the committee and may lack applicability to clinical

practice, and also notes that there are baseline imbalances between rimegepant and placebo within this subgroup that might impact results. This is covered in Section 2.6.

The EAG does not consider the HCRU cost a plausible scenario given the lack of data provided/available on rimegepant patients use of these services as covered in section 2.2.

The EAG does not consider the discontinuation of BSC responders an appropriate scenario as discussed in section 2.1.1.

As discussed in the EAG report and at technical engagement the EAG does not consider including the reduction in MMDs in the base case appropriate.

Table 19. Cost-effectiveness results and scenario analyses – revised acute EAG migraine model

Scenarios	Incremental QALYs	Incremental Costs	ICER (£/QALY)
EAG's preferred base case*			
Indefinite placebo response & 2-year time horizon	0.04	£1,124	£29,833
5-year time horizon	0.07	£2,165	£29,327
10-year time horizon	0.10	£3,018	£29,115
20-year time horizon	0.12	£3,486	£28,925
Contraindicated and intolerant subgroup analysis			
2-year time horizon	0.06	£1,369	£24,499
5-year time horizon	0.12	£2,807	£24,324
10-year time horizon	0.17	£4,233	£24,451
20-year time horizon	0.22	£5,371	£24,843
EAG's base case including hospital-based services cost (all BSC patients)			
2-year time horizon	0.04	£724	£19,218
5-year time horizon	0.07	£1,570	£21,265
10-year time horizon	0.10	£2,262	£21,819
20-year time horizon	0.12	£2,639	£21,895
EAG's base case including hospital-based services cost (BSC non-responder patients)			
2-year time horizon	0.04	£868	£23,037
5-year time horizon	0.07	£1,828	£24,762
10-year time horizon	0.10	£2,564	£24,737
20-year time horizon	0.12	£2,854	£23,686
Discontinuation of BSC responders			
2-year time horizon	0.04	£1,109	£25,703

5-year time horizon	0.10	£2,089	£20,530
10-year time horizon	0.19	£2,793	£15,055
20-year time horizon	0.31	£2,961	£9,486
EAG's base case including ≥2 triptan failure (refractory) population			
2-year time horizon	0.07	£1,414	£19,676
5-year time horizon	0.15	£2,883	£19,434
10-year time horizon	0.22	£4,290	£19,293
20-year time horizon	0.28	£5,298	£19,116
EAG's base case including reduction in MMD			
2-year time horizon	0.05	£923	£19,311
5-year time horizon	0.09	£1,770	£18,985
10-year time horizon	0.13	£2,463	£18,938
20-year time horizon	0.15	£2,840	£18,919
EAG's base case including ≥2 triptan failure (refractory) population and reduction in MMD			
2-year time horizon	0.08	£1,240	£15,094
5-year time horizon	0.17	£2,521	£14,917
10-year time horizon	0.25	£3,748	£14,854
20-year time horizon	0.31	£4,622	£14,780

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

5 References

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