Single Technology Appraisal

Rimegepant for preventing episodic migraine [ID6275]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Rimegepant for preventing episodic migraine [ID6275]

Contents:

The following documents are made available to stakeholders:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document**

2. **Comments on the Appraisal Consultation Document from Pfizer**

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. The Migraine Trust
   b. British Association for the Study of the Headache
   c. AbbVie
   d. Teva

4. **Comments on the Appraisal Consultation Document received through the NICE website**

5. **Evidence Review Group critique of company comments on the ACD**

6. **Technical engagement responses and statements from experts:**
   a. Dr Brendan Davies, Consultant Neurologist & Clinical Lead, Midlands Regional Headache clinic, University Hospital of North Midlands – clinical expert nominated by Association of British Neurologists

7. **Clinical expert response to questions from NICE technical team** from:
   a. Dr David Kernick, GP – clinical expert, nominated by Teva UK Limited

8. **Evidence Review Group post-ACM2 response to updated list price**

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

Rimegepant for preventing migraine

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).

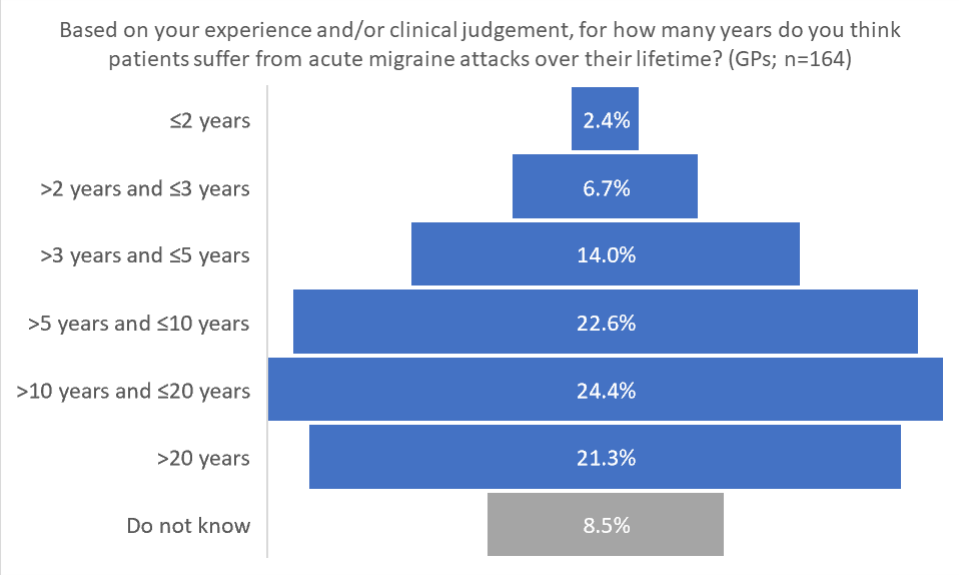
Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help 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..

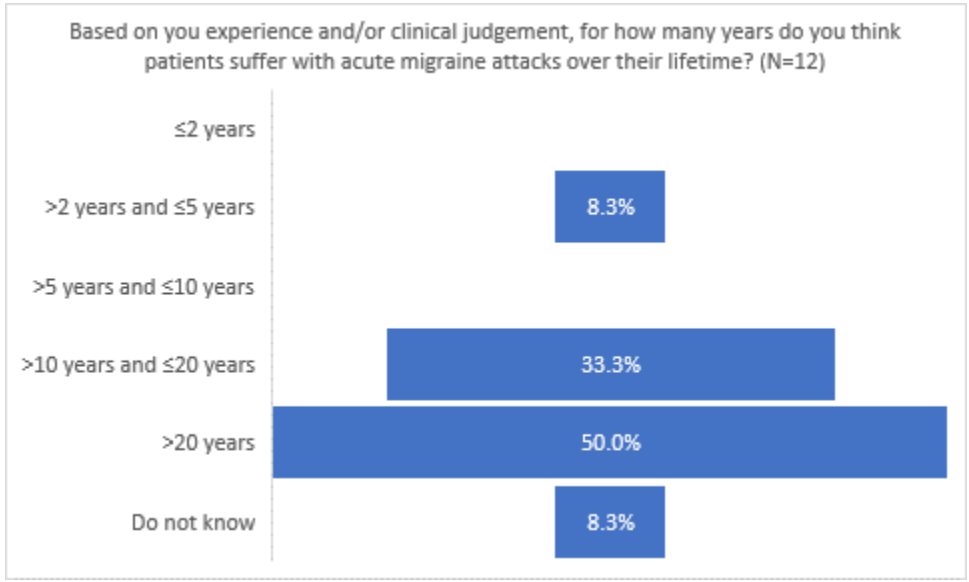
Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal 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	**Time Horizon** Clinical experts, RWE and study data all suggest a time horizon of >10 years is most appropriate in the acute model of migraine. The ACD states 'The committee considered both the 2- and 20-year time horizons but concluded that the costs and benefits of rimegepant as an acute treatment should be reflected in a shorter time horizon than 5 years and more explanation is needed to determine the most appropriate length'. We have provided additional evidence, from clinical experts, trial data and RWE that all suggest a time horizon of >10 years is appropriate. *Clinical experts* Clinical experts support a time horizon of longer than 10 years to properly capture benefits and cost relating to acute treatment of migraine. A survey of general practitioners (GPs) based in the United Kingdom indicate a time horizon of 20-years is appropriate to fully capture a patient's experience with acute migraine and in turn ensure all the associated health outcomes and costs are included in the model. • The Company conducted a survey of 164 GPs to further understand the appropriate time horizon to be included in the acute model. • Recipients of the survey were asked 'Based on your experience and/or clinical judgement, for how many years do you think patients suffer from acute migraine attacks over their lifetime?'. o Of the GPs surveyed, 68% responded >5 years, with the largest percentage selecting the >10 years and ≤20-years category.	Thank you for your comment. For comments relating to rimegepant as an acute treatment of migraine, we will respond separately in ID1539.

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
			○ Figure 1, demonstrates a low confidence in a 2-year time horizon, suggested by the EAG, to capture the outcomes and costs for patients requiring acute migraine treatment. **Figure 1 GP acute treatment time horizon responses**  Further to the above survey, another survey of 12 neurologists with an interest in headache, supported a time horizon of >10 years for the acute model of rimegepant. • Recipients of the survey were asked 'Based on your experience and/or clinical judgement, for how many years do you think patients suffer from acute migraine attacks over their lifetime?' ○ Of the Neurologists surveyed, 83.3% responded >10 years, with the largest percentage (50%) selecting the ≥20-years category.	

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
			○ Figure 2, demonstrates no confidence in a 2-year time horizon, suggested by the EAG, to capture the outcomes and costs for patients requiring acute migraine treatment. **Figure 2 Neurologists acute treatment time horizon responses**  The ACD states 'The clinical experts agreed with the EAG that a 2-year time horizon is more appropriate'. Please note Pfizer believes this statement to be factually incorrect as in the public section of the Appraisal Committee Meeting (ACM) one clinical expert, Dr Brendan Davies, Consultant Neurologist and the Clinical lead for Neurology at the University Hospital of North Midlands, agreed with the 20-year time horizon during the discussions on the appropriate time horizon.	

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
			Extension study data and extrapolation In the long term follow up study (BHV3000-201), patients remained on treatment up to 52 weeks with only a small percentage discontinuing (2.7%). The model extrapolates from the long-term study, BHV3000-201, which shows patients remain on treatment at 20-years, suggesting a 20-year time horizon would be most appropriate to capture all relevant cost and QALY impacts. *Trial demographics show disease duration beyond 20 years* The time horizon assumption of 20-years in the Company's base case acute model is reflective of the disease history of participants enrolled in the clinical studies that is informing the model. Given patients with an average disease history of 20-years had sufficient unmet need to pursue acute migraine medication in clinical trials, this provides sufficient evidence that the need for acute treatments for migraine is long-lasting and thus a 20-year time-horizon is appropriate. In the pivotal clinical trials disease onset was on average 21 years old and average age at enrolment in clinical trials was approximately 39 years of age. • The trial data is supported by the literature whereby Steiner et al. reported onset of migraine in England being 22 years of age and average age at the time of the study was 43 noting patients were suffering from 26 migraines a year, 20 years after onset of migraine.[2] *RWE* Migraine prescription data supports the inclusion of a time horizon longer than 5 years (noting data beyond 5 years was not available). The company conducted a study to understand how long patients with migraine receive prescriptions to better understand the appropriate time horizon to be adopted in the acute model. • The data analysed was from IQVIA OMOP UK Medical Research Data (IMRD) The Health	

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
			Improvement Network (THIN). The registry captured 119,918 patients who were newly diagnosed with migraine between January 1st, 2010, and September 30th, 2017; with prescription data being captured until September 2022. o Of the 29,376 patients with more than one triptan prescription during follow-up, 24.30% (7,150) had ≥ 5 years between their first and last triptan prescription on record. • Using a more stringent approach by defining a 'treatment line' as 2 triptans within 12 months of each other, 23,448 (19.6%) of patients had at least 1 treatment line of triptans o Of which, 15.7% had ≥5 years between the first and last triptan prescription in their first treatment line (i.e., had a gap of no more than 12 months between triptan prescriptions for 5 or more years continuously), suggesting an unmet need with ineffective or poorly tolerated therapy. • It is worth noting, some patients may have exhausted all treatment options and given up on treatment i.e., their migraine has not resolved and would still utilise treatment if more were available. While some patients may buy treatments (e.g., triptans) over the counter (OTC) as it is cheaper than prescriptions. Therefore, the above results should be interpreted as conservative estimates of the length of time patients are receiving acute treatment. *Consistency with preventative treatment of the same condition* • The prevention model adopts a lifetime horizon of 20-years; therefore, it could be deemed illogical to propose a different time horizon for the same disease for the acute treatment model.	
2.		Pfizer	**Reduced monthly migraine days**	Thank you for your comment. For comments relating to rimegepant as

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
			MMD reduction should be included in the acute model. Given the Committee acknowledges 'there is biological plausibility in the suggestion that taking rimegepant as needed may reduce MMDs'. Removing the MMD reduction experienced by patients taking rimegepant PRN has a significant impact on benefit as demonstrated by the change in incremental QALYs in Table 2 when MMD reduction is included in the model. This strongly contradicts the conclusion in the ACD whereby it states, 'removing the assumption from the model 'may be considered as a small, potential uncaptured benefit'. By excluding the reduction in MMDs, the company's updated base case is highly conservative as reflected by the impact of this positive uncertainty seen in Table 2.	an acute treatment of migraine, we will respond separately in ID1539.
3.		Pfizer	**Revised acute base case and scenario analyses** The Company have included the Committee's preferred assumptions in the revised base case and when combined with the lowered list price of rimegepant (as noted in the summary above), Rimegepant is cost-effective under a £20,000 willingness to pay (WTP) threshold, as detailed in Table 2. Given all the committee's preferred assumptions have been included, the degree of certainty around the ICER has substantially increased, suggesting a threshold above £20,000 could be considered more appropriate. In addition, the ICER reduces significantly when the positive uncertainties associated with the MMD reduction with acute Rimegepant (ICER <£12,000 per QALY) and the subgroups relevant to the decision problem are included. The committee also requested further exploration of the time horizons via scenario analysis which are also presented in Table 2. However, even with the most extreme scenario with a 2-year time horizon (which can be consider inappropriate given discussion above), the ICER remains below £30,000 per QALY.	Thank you for your comment. For comments relating to rimegepant as an acute treatment of migraine, we will respond separately in ID1539.

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>Table 2 Changes to the company’s cost-effectiveness estimate in acute
<table>
<tr><th>Scenario</th><th>Incremental QALYS</th><th>Incremental costs</th><th>ICER (£/QALY)</th></tr>
<tr><td>Base case following TE</td><td>0.4117</td><td>£7,307</td><td>£17,521</td></tr>
<tr><td>Company revised base case (20-year time horizon)</td><td>0.1216</td><td>£3,584</td><td>£19,973</td></tr>
<tr><td>Company revised base case (20-year time horizon, probabilistic results)</td><td>0.4261</td><td>£7,397</td><td>£19,158</td></tr>
<tr><td>Time horizon scenarios</td><td></td><td></td><td></td></tr>
<tr><td>15-year time horizon</td><td>0.1714</td><td>£3,444</td><td>£20,100</td></tr>
<tr><td>10-year time horizon</td><td>0.1512</td><td>£3,096</td><td>£20,474</td></tr>
<tr><td>5-year time horizon</td><td>0.1013</td><td>£2,233</td><td>£22,046</td></tr>
<tr><td>2-year time horizon</td><td>0.0408</td><td>£1,187</td><td>£29,109</td></tr>
<tr><td>Positive uncertainty scenarios</td><td></td><td></td><td></td></tr>
<tr><td>Including reduction in MMD with 20-year time horizon</td><td>0.2353</td><td>£2,766</td><td>£11,753</td></tr>
<tr><td>Post-hoc triptan failure subgroup analysis</td><td>0.3644</td><td>£5,549</td><td>£15,226</td></tr>
<tr><td>Prespecified triptan failure subgroup analysis</td><td>0.3513</td><td>£5,536</td><td>£15,761</td></tr>
</table></td><td></td></tr>
<tr><td>4.</td><td></td><td>Pfizer</td><td>Clarification of the difference between the prespecified and post hoc subgroups
The ACD notes ‘In the 3 RCTs, there was a prespecified subgroup of people who had stopped 2 or</td><td>Thank you for your comment. For comments relating to rimegepant as</td></tr>
</table>

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>more triptan treatments because they had not worked. In the company’s submission, a post hoc subgroup analysis was used as its main source of evidence in the economic model. The prespecified subgroup and the post hoc subgroup defined treatment failure differently'. Consequently, the Committee requested clarification of the difference between the prespecified and post hoc subgroups.

Data across the three Phase 3 trials (Study BHV3000-303, Study BHV3000-301, Study BHV3000-302) were pooled to facilitate subgroup analyses of patients who had failed ≥2 triptans. The protocols for these trials included a pre-specified subgroup analysis of triptan non-responders, defined as “any subject that failed 2 or more molecular entities for efficacy reasons. To be considered a failure for a molecular entity, the subject must have failed on all routes of administration that the subject tried for the molecular entity.”

A table summarising the details of the pre-specified triptan non-responder is provided below. The number of patients included in the pooled sample using this pre-specified definition was: rimegepant (n=78) and placebo (n=104).

Table 3 summarises the criteria of the pre-specified triptan non-responder definition (i.e. reason for failure, frequency of reason and number of routes of administration that had to be failed).
<table>
<tr><th>Criteria</th><th>Summary</th></tr>
<tr><td>Failure reason</td><td>Efficacy only. Subject must have provided at least one of the following efficacy reasons for failure:
• Took too long to relieve headache pain
• Couldn’t count on treatment to relieve pain and symptoms every time</td></tr>
</table></td><td>an acute treatment of migraine, we will respond separately in ID1539.</td></tr>
</table>

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

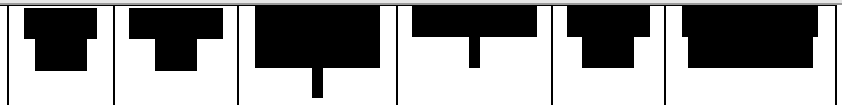
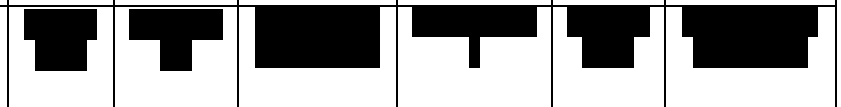
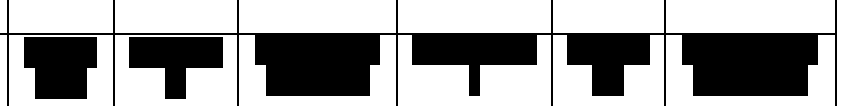
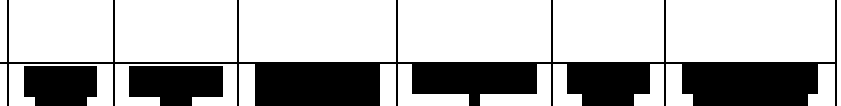
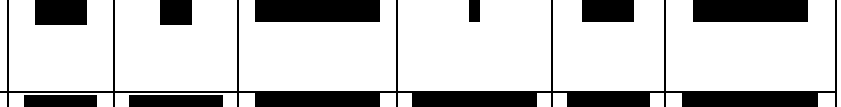
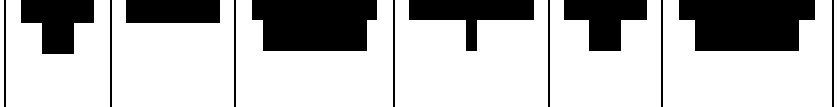
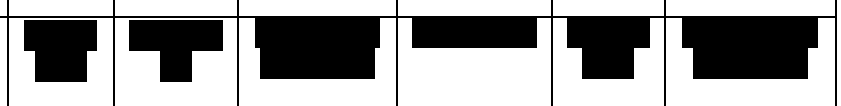
	• Pain returned after it was relieved within 24 hours • Did not relieve other symptoms
Reason frequency	Most or all of the time
Number of routes of administration for a single molecular entity that had to be failed	All routes of administration

Given the strict criteria used for pre-specified definition of triptan non-responder resulted in a relatively small sample size that omitted patients who had failed triptans for reasons of intolerability, a post-hoc analysis was performed that modified this definition to include all patients who reported failure of ≥2 triptans. This post-hoc analysis included those patients that had failed ≥2 previous triptans for reasons of intolerability as well as efficacy. In addition, patients only had to have failed on ≥1 route of administration rather than failing on all routes. This increases the clinical relevance of the post-hoc analysis as adverse events are a common reason for patients discontinuing triptan treatment in clinical practice, and patients do not typically trial all possible routes of administration for a single triptan before trying a different triptan.[3] As seen, in a recent retrospective analysis using the CPRD Aurum dataset, the data shown that only 4.8% of migraineurs have tried more than two different type of triptans for the acute treatment of migraine, suggesting that a third triptan after treatment failure remains relatively uncommon in clinical practice.[4] The results of efficacy analyses for the pre-specified and post-hoc analyses are similar (see Table4, however, the post-hoc definition increased the sample size (rimegepant (n=148), placebo (n=177) and consequently reduced uncertainty in the estimates of treatment effect.

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

Table 4 A comparison of endpoints between prespecified and post-hoc results

	Prespecified pooled analysis; failed ≥2 triptans			Post-hoc pooled analysis of ≥2 triptans		
	RIM n/N (%)	PBO n/N (%)	Risk difference (95% CI) p value	RIM n/N (%)	PBO n/N (%)	Risk difference (95% CI) p value
Primary endpoints						
Pain freedom at 2 hours post-dose	[redacted]	[redacted]	[redacted]	30/148 (20.0)	18/177 (10.2)	9.8 [redacted]
Freedom from MBS at 2 hours post-dose	[redacted]	[redacted]	[redacted]	64/148 (43.0)	38/177 (21.5)	21.5 [redacted]
Secondary endpoints						
Pain relief at 2 hours post-dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Functional disability at 2 hours post-dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sustained pain relief 2 to 24 hours post-dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rescue Medication Use within 24 hours post-dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

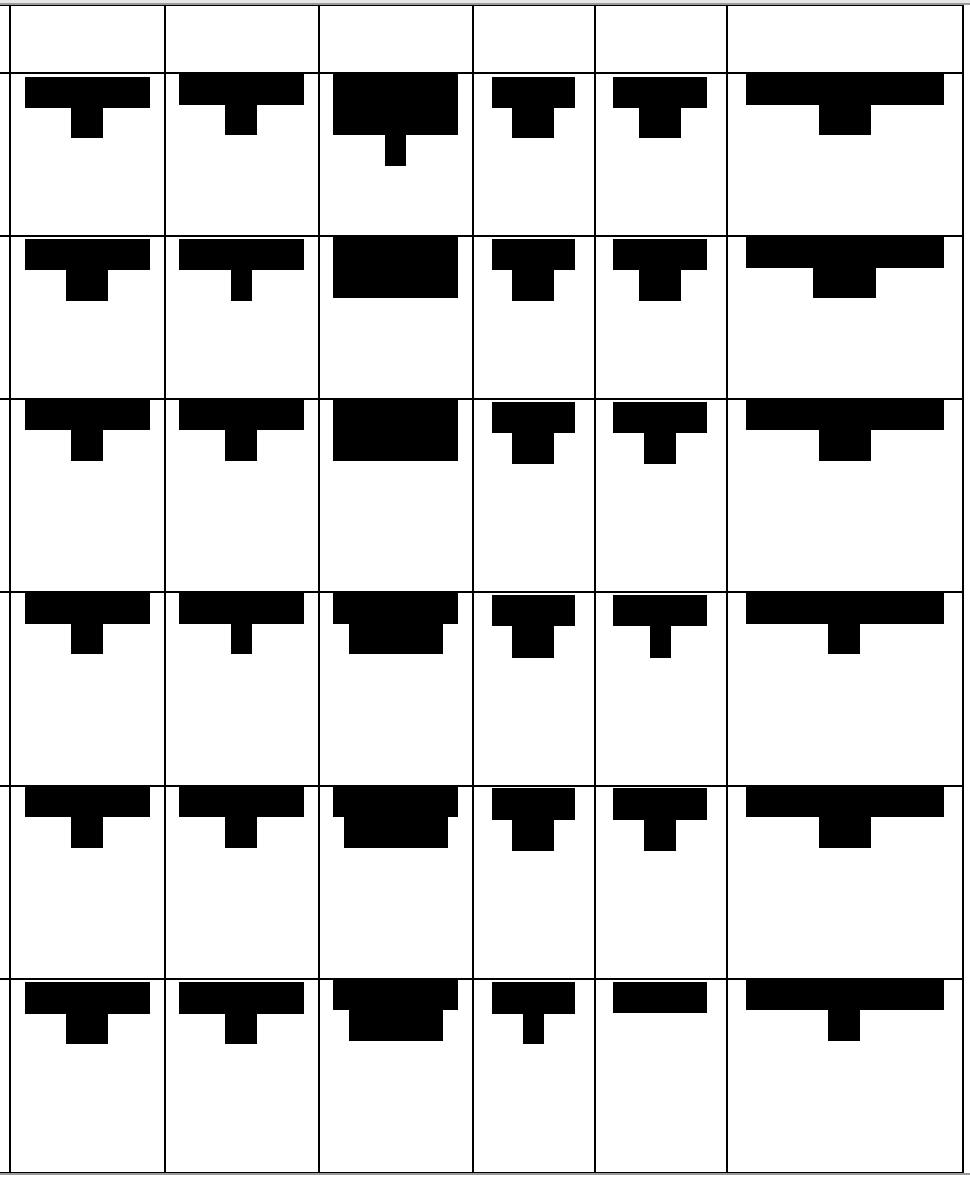
Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Sustained pain relief 2 to 48 hours post-dose  Freedom from photophobia at 2 hours post-dose  Sustained pain freedom from 2 to 24 hours post-dose  Freedom from phonophobia at 2 hours post-dose  Sustained pain freedom from 2 to 48 hours post-dose  Freedom from nausea at 2 hours post-dose  Pain relapse from 2 to 48 hours post-dose 	
5.		Pfizer	**Prespecified subgroup results from the clinical trials BHV3000-301, BHV3000-302, BHV3000-303, for the population who have had 2 or more triptans that have not worked** Table 5 below presents the prespecified subgroup results alongside the pooled mITT results, which are the base case in the model. The prespecified subgroup results from studies 301-303, for the population who have had 2 or more triptan failures is consistent with the post-hoc analysis as	Thank you for your comment. For comments relating to rimegepant as an acute treatment of migraine, we will respond separately in ID1539.

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

previously mentioned, however please note again the prespecified analysis (in Tables 4 and 5) should be interpreted with caution as the risk differences as several endpoints are not significant which is likely due to low sample sizes.

Table 5 Primary and secondary endpoint results, pooled mITT analysis and prespecified pooled analysis who failed ≥2 triptans

	Pooled mITT analysis			Prespecified pooled analysis of ≥2 triptans		
	RIM n/N (%) *stratified risk	PBO n/N (%) *stratified risk	Risk difference (95% CI) p value	RIM n/N (%)	PBO n/N (%)	Risk difference (95% CI) p value
Primary endpoints						
Pain freedom at 2 hours post-dose	[redacted]					
Freedom from MBS at 2 hours post-dose	[redacted]					
Secondary endpoints						
Pain relief at 2 hours post-dose	[redacted]					
Functional disability at 2 hours post-dose	[redacted]					
Sustained pain relief 2 to 24	[redacted]					

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
			hours post-dose 	
			Rescue Medication Use within 24 hours post-dose	
			Sustained pain relief 2 to 48 hours post-dose	
			Freedom from photophobia at 2 hours post-dose	
			Sustained pain freedom from 2 to 24 hours post-dose	
			Freedom from phonophobia at 2 hours post-dose	
			Sustained pain freedom from 2 to 48 hours post-dose	

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
			Freedom from nausea at 2 hours post-dose [redacted] Pain relapse from 2 to 48 hours post-dose [redacted]	
6.		Pfizer	**Economic analyses using the prespecified subgroup results** Rimegepant remains cost-effective using the prespecified subgroup analysis, and therefore, the Company's revised base case is a conservative estimate as demonstrated in Table 2 above. The prespecified subgroup results show a positive uncertainty given the reduction in the ICERs. Here again, the prespecified results are similar to that of the post-hoc analysis.	Thank you for your comment. For comments relating to rimegepant as an acute treatment of migraine, we will respond separately in ID1539.
7.		Pfizer	**Revised prevention base case** Based on willingness-to-pay (WTP) thresholds of £20,000 or £30,000 per QALY, rimegepant is considered cost-effective compared to each mAb as the ICERs are above these WTP thresholds and the incremental net monetary benefits (NMBs) are negative. In the revised base case (Table 6), the monoclonal antibodies (mAbs) are associated with higher costs and higher QALYs than rimegepant. Please note, the revised base case includes the committee's preferred assumption, updated health care resource use (HCRU) costs and the lower list price noted in Table 1 in the summary above. *Secondary care cost savings* Rimegepant is expected to offer cost savings in terms of HCRU compared to the mAbs for migraine	Thank you for your comment. The updated assumptions and cost effectiveness analyses were considered by committee. Please see section 3.13 of the FAD for the committee's discussion on the appropriate healthcare resource use and section 3.15 for the committee's

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
			prevention if predominately managed in primary care, as demonstrated by the total costs presented in Table 6 below**.** Please note, [redacted] The NHS is transforming rapidly with the imminent implementation of recommendations from the Getting It Right First Time (GIRFT) Neurology Report 2021.[5] GIRFT has set out a vision of neurological care closer to home with services provided in a community setting supported by triage systems to empower general practice with efficient advice and guidance. The recently published National Neuroscience Advisory Group (NNAG) headache & facial pain pathway has built on this vision with a template for migraine to be managed in general practice, supported by community-based headache clinics rather than secondary care wherever possible.[6] The Oxfordshire headache pathway has adopted the triage and community headache clinic approach recommended by GIRFT and NNAG with 89% of all headache referrals now triaged away from general neurology, freeing up 979 appointments per annum.[7] The Oxfordshire community clinic approach had benefits beyond freeing up secondary care capacity; prior to their community headache appointment 32% of patients felt able to manage their headache and this rose to 100% after the clinic appointment. In addition, during discussions with clinical experts, it has come to light that rimegepant can provide cost savings in terms of HCRU for patients in the community. Rimegepant has the unique offering of providing the first CGRP-targeted preventative treatment in primary care for patients with migraine. Please note, the revised base case has been updated to explore a more primary care centric approach for migraine prevention care using rimegepant. Additional HCRU scenario analysis have also been presented. Table 6 below.	conclusions on their acceptable ICER.

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>[redacted].

The revised base case includes a one-off initiation cost and a 3-month follow-up cost, with a GP (£39.23 per visit) for rimegepant and with a neurologist (£194.24 per visit) for the comparator mAbs.[8,9] Additionally, a one-off neurologist referral cost has been added to the mAbs costed as one GP visit (£39.23).[8] We believe this to be a conservative approach as monitoring care will likely continue in primary care for rimegepant and secondary for mAbs.
Consequently, a scenario analysis has been provided whereby all rimegepant care (initiation visits, 3-month follow-up and monitoring visits) takes place in primary care for patients using rimegepant.

Rimegepant can offer cost savings in terms of HCRU compared to the mAbs for migraine prevention if predominately managed in primary care as demonstrated by the total costs presented in Table 6 overleaf.

Table 6 Changes to the company’s cost-effectiveness estimate in prevention
<table>
<tr><th></th><th>Incremental QALYS</th><th>Incremental costs</th><th>ICER (£/QALY)</th><th>NMB (£30,000/ QALY WTP threshold)</th><th>NMB (£20,000/ QALY WTP threshold)</th></tr>
<tr><td colspan="6">Revised base case following technical engagement</td></tr>
<tr><td>Galcanezumab</td><td>0.056</td><td>£6,020</td><td>£160,909</td><td>-£4,330</td><td>-£4,893</td></tr>
<tr><td>Fremanezumab</td><td>0.055</td><td>£5,482</td><td>£99,802</td><td>-£3,834</td><td>-£4,383</td></tr>
</table>
</td><td></td></tr>
</table>

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

Erenumab	0.039	£4,105	£104,919	-£2,931	-£3,323
Revised base case following ACD					
Galcanezumab	0.056	£7,539	£135,082	-£5,865	-£6,423
Fremanezumab	0.054	£6,999	£128,714	-£5,368	-£5,911
Erenumab	0.038	£5,733	£150,269	-£4,589	-£4,970
Revised base case following ACD (probabilistic results)					
Galcanezumab	0.053	£7,288	£136,355	-£5,684	-£6,219
Fremanezumab	0.046	£6,487	£142,143	-£5,118	-£5,574
Erenumab	0.034	£5,375	£156,655	-£4,346	-£4,689
Scenario analysis 1					
Galcanezumab	0.056	£7,576	£135,749	-£5,902	-£6,460
Fremanezumab	0.054	£7,036	£129,398	-£5,405	-£5,949
Erenumab	0.038	£5,771	£151,244	-£4,626	-£5,008

References:

1. The Migraine Trust. NICE has rejected migraine medication Rimegepant for use on

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 NHS in England. 2023 [Available from: https://migrainetrust.org/news/nice-has-rejected-migraine-medication-rimegepant-for-use-on-the-nhs-in-england/ (Last assessed March 2023). **2.** Steiner, T. J., Scher, A. I., Stewart, W. F., Kolodner, K., Liberman, J., & Lipton, R. B. (2003). The prevalence and disability burden of adult migraine in England and their relationships to age, gender and ethnicity. Cephalalgia, 23(7), 519-527. **3.** Shamliyan TA, Choi JY, Ramakrishnan R, Miller JB, Wang SY, Taylor FR, et al. Preventive pharmacologic treatments for episodic migraine in adults. J Gen Intern Med. 2013;28(9):1225-37 **4.** Pfizer. Data on File: CPRD Aurum Analysis. 2022 **5.** Fuller, G. GIRFT Programme National Specialty Report. 2021. [Available from: https://neurologyacademy.org/articles/girft-report-for-neurology (last assessed March 2023)] **6.** National Neuroscience Advisory Group (NNAG). Optimum clinical pathway for adults: Headache & Facial pain. 2023. [Available from: https://static1.squarespace.com/static/5f1021faf6248b39f4c64f5d/t/63dbb10ab1d6657b00247962/1675342095594/04+NNAG+Headache+and+Facial+Pain+Pathway+Final.pdf (last assessed March 2023)] **7.** NICE. Oxfordshire Headache Pathway for the Efficient Diagnostic and Management Support of Headache Disorders.2018. [Available at: https://www.nice.org.uk/sharedlearning/oxfordshire-headache-pathway-for-the-efficient-diagnostic-and-management-support-of-headache-disorders (last assessed March 2023)] **8.** Jones K, Burns A. Unit Costs of Health and Social Care Canterbury (Kent), UK:	

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
			Personal Social Services Research Unit, University of Kent; 2021 [Available from: https://kar.kent.ac.uk/92342/ (last accessed May 2022) NHS Improvement. National Schedule of NHS costs - Year 2019-2020 [Available from: https://www.england.nhs.uk/national-cost-collection/ (last accessed January 2022)	
8.		AbbVie	**Interplay between acute and preventive indications:** As specified within the company submission, rimegepant is under appraisal for the dual indication for both the acute treatment of migraine in adults (regardless of the number of headache days per month), and the preventive treatment of episodic migraine in adults who have at least 4 migraine attacks per month, but fewer than 15 headache days per month. Clinical guidelines published by NICE (CG150; 2021)1 and the British Association for the Study of Headache (2019)2 present acute and preventive migraine treatments as two distinct categories of treatment. As rimegepant is the first treatment licensed for both acute and preventive use, clinical expert opinion indicates that there is currently a lack of clarity in terms of clinical pathway implications for the interplay between acute and preventive treatment following the introduction of a dual indication therapy, given the potential for overlap between indications. Within the company submission, a long-term preventive treatment effect has been claimed when rimegepant is taken as needed for acute treatment based on safety and efficacy data collected in the single arm, Phase 2/3 trial, BHV3000-201. However, as specified in the appraisal consultation document, the committee concluded that there is not enough clinical evidence to support this assumption, and clinical experts advised that patients who experience migraines often enough to have a preventive benefit from an acute treatment should be receiving a preventive treatment. In accordance with clinical opinion and feedback submitted by other stakeholders during the appraisal	Thank you for your comment. The interplay between acute and preventative indications was discussed by committee. Please see section 3.1 of the FAD.

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
			process, AbbVie believe that the practical delivery of rimegepant is an important consideration of this appraisal to ensure that it can be used effectively and safely, as intended by regulatory and HTA authorities. In particular, it will be important to understand the interplay between acute and preventive indications in clinical practice. Given that the dosing form across acute and preventive treatment is identical, there is a potential risk of misuse across the acute and preventive indications; particularly if patients were eligible to receive rimegepant for only one of the two settings. For acute, the recommended dose is a single 75 mg oral dispersible tablet taken as needed once daily. Similarly for preventive, the recommended dose is a 75 mg oral dispersible tablet taken every other day (with a maximum dose per day of 75 mg). Stopping rules are also implemented differently between acute and preventive settings. NICE recommend that preventive treatments available for patients who have experienced three or more treatment failures should be stopped at 12 weeks for monoclonal antibodies (galcanezumab, erenumab, fremanezumab), or at 24 weeks for botulinum toxin type A if a patient has not adequately responded to treatment (as monitored by headache diaries). However, acute treatments are not currently subject to any formal stopping rule for patients who have failed ≥2 triptans, or who are intolerant or contraindicated to triptans. As specified within the appraisal consultation document, this is a source of uncertainty, as the company propose that treatment would be stopped if there was no response to the first dose of rimegepant. However, this stopping rule is not specified within the rimegepant Summary of Product Characteristics (SmPC), nor is it clear how the frequency and duration of dosing is monitored in the acute setting. As such, Abbvie believe that these issues should be considered moving forward as the appraisal continues. References:	

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. National Institute for Health and Care Excellence. CG150: Headaches in over 12s: diagnosis and management. Available at: https://www.nice.org.uk/guidance/cg150/chapter/Recommendations#management-2 2. British Association for the study of headache. National Headache Management System for Adults 2019. Available at: https://headache.org.uk/index.php/bash-guideline-2019	
9.		AbbVie	**Innovation in the preventive treatment setting** In support of clinical expert opinion outlined in the appraisal consultation document, the 'step-change' potential of orally administered calcitonin gene-related peptide inhibitor alternatives to currently available injectable treatments is consistent with feedback received during AbbVie engagement with clinical experts. With these products, there are opportunities to streamline the current clinical care pathway and relieve well-documented NHS-wide capacity issues associated with the management of migraine. As expressed in the company submission and appraisal consultation document, migraine patients eligible for preventive treatment are currently subjected to extensive waiting lists due to difficulties in accessing specialist care, with only a limited number of specialist headache centres in the UK. According to a report published by the Migraine Trust (2021); the average waiting time for patients to access calcitonin gene-related peptide-targeted monoclonal antibodies varies between 3 and 5 months across the UK, and in some cases, it can take up to two years to access specialist headache clinics.1 Orally administered calcitonin gene-related peptide inhibitors will be a welcome alternative for patients to access care quicker and help shorten the NHS waiting list.	Thank you for your comment. The committee discussed innovative nature of rimegepant in the preventative treatment setting. Please see section 3.18 of the FAD.

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
			In line with received clinical opinion, Abbvie agree that the simple to use, oral, well-tolerated nature of oral calcitonin gene-related peptide inhibitors may open doors to novel prescribing pathways which enable the NHS to optimise the delivery of care, and achieve additional efficiencies in terms of saved specialist time. References: 1. The Migraine Trust. State of the Migraine Nation Dismissed for too long: Recommendations to improve migraine care in the UK. Available at: https://migrainetrust.org/wp-content/uploads/2021/09/Dismissed-for-too-long_Recommendations-to-improve-migraine-care-in-the-UK.pdf	
10.		British Association for the Study of Headache (BASH)	It is disappointing that there was no equivalent patient population trial data presented for the respective target population in the UK in line with previous Single Technology Appraisal (STA) assessments to allow indirect comparison. We are unaware that any Rimegepant trials looking at patient failing between 2-4 prior agent for migraine equivalent to the LIBERTY, FOCUS, CONQUER or DELIVER trials in anti-CGRP monoclonal antibodies as the main comparator for either episodic or chronic migraine. There were no data that we are aware and would welcome seeing this for their preventative target population for the UK.	Thank you for your comment. The limitations associated with the indirect evidence presented was discussed by the committee. Please see section 3.7 of the FAD.
11.		BASH	We agree that “post-hoc” analysis on acute use of Rimegepant as effecting migraine frequency may be flawed and would welcome a future appropriately designed clinical trial to evaluate the use of alternative day or daily use preventative nature of oral Rimegepant for migraine in the UK.	Thank you for your comment. For comments relating to rimegepant as an acute treatment of migraine, we will respond separately in

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
				ID1539.
12.		BASH	We note and would like to see future clarification of any uncertainties about repeat dosing of Rimegepant and the reliability of response for acute migraine. We would welcome seeing repeat dosing studies as occurred with Triptans in the past for acute migraine. We are keen to have access to using Rimegepant in the UK for migraine but recognise the need for reliable and robust data to support sustained efficacy both as an acute and preventive therapy in those prescribed this medication.	Thank you for your comment. For comments relating to rimegepant as an acute treatment of migraine, we will respond separately in ID1539.
13.		BASH	BASH agrees that in future Gepants should be available for Primary care prescription after /or following Specialist recommendation to ensure appropriate future efficacious and cost effective prescribing as part of the therapy pathway for migraine sufferers in the UK.	Thank you for your comment. The committee discussed the potential use of rimegepant for in primary care. Please see section 3.13 of the FAD.
14.		The Migraine Trust	Migraine is a painful debilitating disorder for which there is no cure and limited treatment options. Furthermore, people with migraine have for so long been stigmatised and a part of this is due to the lack of understanding, lack of effective treatments and the associated links to productivity at work. Effective targeted treatments are needed to address this. **The ACD reports that, 'clinical trial evidence for acute migraine shows that rimegepant is likely to reduce pain at 2 hours more than placebo'.** Many people are still without an effective acute treatment. Some are at risk of or develop medication overuse headache, which further complicates the condition	Thank you for your comment. This information was included in the ACD but has been amended following comments from other consultees. Pleas see section 3.1 of the FAD.

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
			and adds to its impact and costs. Many people end up in secondary care, A & E or with no effective treatment at all. The personal and economic costs should not be ignored.	
15.		The Migraine Trust	**Costs** We understand that there will always be a degree of clinical uncertainty with new treatments in the context of benefit and cost effectiveness. We would urge you to consider the healthcare costs currently incurred for migraine, particularly for people who have not yet found an effective **acute** and/or **preventive** treatment. A Work Foundation report in 2018 estimated that the UK healthcare costs for migraine are estimated at £1b per year and over £8b in indirect/productivity costs. This data is backed up by pro-bono research the charity received last year which showed the cost of absenteeism and presenteeism was £9b and that by improving the treatment pathway that would reduce frequency / intensity of migraines could enable significant productivity gains - a 10% improvement would save £904m a year and 20% would save £1.8b.	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

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
				methods of technology appraisal.
16.		The Migraine Trust	**Disadvantaged groups** In our submission, we described the disadvantaged group of people with migraine who could derive benefit. This group of people will continue to consult in specialist clinics, primary care and A&E. This imposes significant costs through a lack of treatment for some, poor or inadequate response to current treatments for some and medical contraindications for others. In addition, people with migraine will need to take time off work or be less effective at work and in other aspects of life, incurring indirect costs (absenteeism and presenteeism). If the stated aims of Getting It Right First Time (GIRFT, 2019) are to be realised, there needs to be better treatments to improve the current care for people with migraine.	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.
17.		The Migraine	**The hugely disadvantaged**	Thank you for your

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
		Trust	When considering the options people have for **acute** treatment (CG150): Some cannot use a triptan, NSAID or are unable to restrict them to the recommended number of days to avoid medication overuse. These people are overwhelmingly disadvantaged. Moreover, those for whom these **acute** treatments are contraindicated have no good treatment. Best available care is not an effective option and although we advise against use of opioids in migraine, this may be their only alternative option. Use of opiates will carry its own complications, such as medication overuse headache and dependency, which further compound migraine symptoms and can lead to greater disability for the person with migraine and the subsequent greater use of healthcare resources, including specialist services. Some people use a triptan and have partial relief or side effects, and subsequently cannot treat when needed. Their migraines continue to impact and restrict their work and function. A proportion of these will not consult after a poor response to existing treatments, and resort to self-treatment with OTCs and opioids.	comment. For comments relating to rimegepant as an acute treatment of migraine, we will respond separately in ID1539.
18.		The Migraine Trust	**Do not ignore the advantages to patients and the NHS** 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.	Thank you for your comment. For comments relating to rimegepant as an acute treatment of migraine, we will respond

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
			As an oral treatment with good tolerability, it could provide an excellent opportunity for patients to receive the treatment in the primary care setting, even if it had to be initiated in secondary care in the early stages. In addition to treating acute attacks, this could reduce the number of referrals to specialists and associated costs and waiting times. A treatment that is migraine-targeted without complications of medication overuse headache and is well tolerated should be approved in our view, to meet the treatment need for this disadvantaged group of people for whom the currently recommended triptans and NSAIDs are not an option. We consider it unconscionable to deny this group a treatment option that is more beneficial than placebo.	separately in ID1539.
19.		The Migraine Trust	**Preventive Use** **The ACD states that 'rimegepant might also reduce MMDs. Lack of comparative long term evidence to support this.'** When NICE was reviewing the CGRP mAbs for migraine **prevention**, we were also advised of the lack of data in long term use and in comparisons with botulinum toxin-A (Botox) in preventing migraine. Fortunately, the CGRP mAbs were approved which has been beneficial to many people. A priority group for **prevention** should include the group of people with migraine: who either do not	Thank you for your comment. The committee were aware of the data limitations in the comparator appraisals and recognised that rimegepant could be used for people unable to take current fourth line preventative treatments (see FAD section 3.2).

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
			wish to or cannot tolerate an injection treatment, cannot access cgrp mAbs, or may have tried but not found them effective or tolerable.	
20.		The Migraine Trust	We strongly disagree with the decision to eliminate the option of rimegepant, a migraine-specific (non-repurposed), **acute** and **preventive** treatment. We would urge the committee to reconsider the decision, for a treatment that has the potential to alleviate the disability and negative impact of migraine on people's mental health, emotional well-being, relationships and function at work, particularly for the disadvantaged groups.	The committee recognised that migraine is a highly debilitating disease which can adversely affect quality of life, affecting people's ability to do their usual activities, including work. The wording in the FAD has been adjusted to make this clear (section 3.1)
21.		Teva	Teva believes that in general the ACD provides a good and accurate summary of the evidence submitted to NICE in this appraisal. Teva has only a few comments to make, which are outlined below.	Thank you. Comment noted.
22.		Teva	The main issue that Teva wishes to raise again is the interplay between the two indications for rimegepant. Teva does not feel that this issue has been fully considered within this appraisal so far. There are potential impacts on the cost-effectiveness calculations from this issue, in addition to the clinical practice implications already raised and as outlined below. Importantly, it should be recognised that the two indications (as being considered within this appraisal) represent two distinct patient groups, with only limited crossover, i.e. only a small number	Thank you for your comment. The committee discussed innovative nature of rimegepant in the preventative treatment setting. Please see section 3.18 of the FAD

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
			of patients will have had three preventive therapy failures and two triptan failures; meaning that most patients eligible for rimegepant will have met either the acute or preventive population requirements. In these patients (eligible under one indication only), the combined acute and preventive indications raise the potential for some individuals to start taking the medication for both indications (which may occur for a number of potential reasons). Teva notes that the combined use of rimegepant for both indications is clearly envisaged by the manufacturer, as the long-term safety trial (BH3000-201) includes an arm with combined every other day (EOD) and pro re nata (as needed, PRN) dosing. In addition, despite available safety data for the combined dosing of rimegepant, no efficacy data have been presented for patients using rimegepant as both a preventive and acute treatment. Within the cost-effectiveness calculations, it would be most likely that any misuse of rimegepant in an indication where the patient was not eligible would cause rimegepant to displace another preventive or acute medication. If the patient was not eligible for rimegepant in this indication, then it is likely that the treatment displaced would be more cost-effective in this population (most likely to be less costly and of a similar/greater efficacy). In this case, the use of rimegepant would lead to higher costs with little or no efficacy benefits, thus reducing the cost-effectiveness of rimegepant.	
23.		Teva	Teva retains some concerns around the weaknesses present in the clinical evidence presented to the committee, in particular, regarding the NMA utilised within the appraisal of the preventive indication. Teva notes that in the previous migraine preventive appraisals (TA764, TA682, TA659), the NMAs presented were found by the appraisal committee to have a high degree of uncertainty due to recognised limitations in the analyses. The NMA presented for rimegepant contains all of the same weaknesses as present in these previous appraisals, plus a number of significant additional uncertainties specific to this NMA (exclusion of most relevant patient population, lack of analysis in a defined treatment failure population, differences in endpoint definitions, mixing of patients with chronic	Thank you for your comments. The reliability of the available evidence is considered by the Committee when formulating its recommendations. Please see section 3.7 of the FAD.

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
			and episodic migraine etc).	
24.		Teva	For the appraisal of the acute indication, one additional point has arisen from the clinical expert comments reported within the ACD that Teva feels has not been considered within the cost-effectiveness analyses. This relates to the comment that, "The clinical experts also explained that when triptans are ineffective and the migraine does not respond, it is often because they are not being used properly". The proposed population for the acute indication is "after two or more triptans have not worked" and so improper trials of previous triptans becomes a pertinent factor to the cost-effectiveness analysis for rimegepant, and is one that has not been considered so far in this appraisal. Where triptans are not properly trialled, this would lead to a patient becoming eligible for rimegepant under the proposed criteria (having had two triptans that did not work), when potentially a triptan, when used correctly, may provide effective therapy for them. If a less costly and equally efficacious triptan could provide effective therapy for these patients, this can be seen to reduce the cost-effectiveness of rimegepant by applying an additional cost for no therapeutic gain (when considering the current scenario versus one considering the impact of improper use/trials of triptans and their appropriate reuse). Teva is unaware of any additional evidence that would help to quantify the prevalence of improper use of triptans. It is therefore very challenging to try and quantify the impact of this issue on ICER values. The only additional avenue that Teva can see which could be explored to address this issue is the inclusion of well-defined guidance statements related to triptan use (to define what constitutes an 'acceptable' trial of a triptan) to reduce the impact of this issue. Teva defers to the clinical experts as to what these criteria might include.	Thank you for your comment. For comments relating to rimegepant as an acute treatment of migraine, we will respond separately in ID1539.
25.		Teva	For the appraisal of the acute indication, the committee concluded that a time horizon of less than 5	Thank you for your comment. For

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
			years was preferred. Teva agrees with the committee's rationale on the shortening of the time horizon from 20 years. However, Teva does not find that there was a clear rationale from the committee for choosing a time horizon of less than 5 years rather than the ERG's (also referred to as the EAG in some documents) preferred option of a 2-year time horizon. Teva agrees with the rationale from the ERG that a 2-year time horizon should be sufficient to capture all costs and benefits of the acute treatment of migraine, in particular when this modelling is based solely on efficacy data for the response to a single administration of rimegepant. Teva, therefore, finds that the ERG's conclusion to be more reasonable in the absence of a supporting rationale for extending this to less than 5 years.	comments relating to rimegepant as an acute treatment of migraine, we will respond separately in ID1539.
26.		Teva	For the appraisal of the preventive indication, Teva would like to note one factor that does not appear to have been considered so far. This is that the efficacy inputs for the modelling have included the same reduction in MMDs for all treatments, with the only difference in efficacy modelled for different treatments being the response rate. Whilst this is a necessary limitation based on the data available to the company, it has the potential to underestimate any differences in efficacy between rimegepant and the CGRP pathway antibodies (fremanezumab, erenumab and galcanezumab). This is as the NMA conducted shows that the CGRP pathway antibodies are likely to be superior to rimegepant in terms of both MMD reductions and response rates. This fact has not been included within the economic analyses and therefore should be considered when examining the ICER values produced. This additional benefit for the CGRP pathway antibodies would lead to reduced overall MMDs with these treatments, leading to greater QALYs and lower health-related costs compared to rimegepant.	Thank you for the comment. This information was incorporated into the information for the committee to factor into their decision making.
27.		Teva	For the appraisal of the preventive indication, treatment discontinuation rates appear to have not been fully considered. Teva has raised this issue during the Technical Engagement but it has not been further considered within this appraisal. Therefore, Teva wishes to restate this currently	Thank you for the comment. This information was incorporated into the information for

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
			unresolved issue. The discontinuation rates were raised by the ERG as a potential issue within their report, but this issue has not been considered further. Teva believes that, as the ERG states, there is no reason to expect the same discontinuation rate across such different treatments (CGRP pathway antibodies versus rimegepant). Rimegepant and the CGRP pathway antibodies have different dosing schedules and routes of administration, they have different efficacy profiles (as evidenced by the NMA results), and they appear to have different tolerability profiles (based on adverse events reported in clinical studies and in the absence of head-to-head data). Given these facts, it seems highly unlikely that discontinuation rates would be the same for rimegepant and for the CGRP pathway antibodies. Teva feels that the ERG's suggestion of an imposition of a class effect between CGRP pathway antibodies predicated on the long-term discontinuation rate for erenumab would be the fairest assumption that could be applied in this case.	the committee to factor into their decision making.
28.		Teva	Finally, Teva wishes to reiterate that a number of additional trials for rimegepant are reported to be ongoing that would provide data that are highly relevant to this appraisal and would address some of the current uncertainties surrounding this product (BHV3000-407 [NCT05518123], BHV3000-406 [NCT05509400], BHV3000-309 [NCT05399485]). From the publicly available data on clinicatirals.gov, these trials are due for completion in 2024, with interim results perhaps available sooner.	Thank you for your comment. The Assessment relies on the available evidence submitted to the Institute and that retrieved from the published literature by the assessment group.

Document processed	Organisation name – Stakeholder or respondent	Disclosure on tobacco funding / links	Number of comments extracted	Comments

Theme	Response
Do not agree with the ACD decision to not recommend rimegepant.	Comment noted.
Disease impact	
Highly debilitating/crippling disease causing both psychological and physical pain. Has severe impact on patients' quality of life - 'Around 1/7 people get migraine. Over a billion people worldwide get migraine, and over 10 million in the UK. Migraine is the third most common disease in the world.'	Comment noted. The committee recognised that migraine is a highly debilitating disease with substantially effects on both physical and psychological aspects of quality of life and employment. This information was included in the ACD (see section 3.1 of the FAD).
Impact on employment / education – forced to quit employment (benefits / early retirement), missed attendance, affects the quality of work.	Comment noted. The committee recognised that migraine is a highly debilitating disease which can adversely affect quality of life, affecting people's ability to do their usual activities, including work. The wording in the FAD has been adjusted to make this clear (section 3.1)
Impact on finances – have no entitlement to sick pay, tend to work through the illness and return to work too soon.	Comment noted. The FAD has been amended to reflect this - see FAD section 3.1.
Impact on mental health: depression, fear, no hope, suicidal thoughts.	Comment noted. The committee recognised that migraine is a highly debilitating disease with considerable impact on mental health. The wording in the FAD has been adjusted to make this clear (section 3.1)
Impact on social activities, relationships with family and friends	Comment noted. The committee recognised that migraine is a highly debilitating disease. The wording in the FAD has been adjusted to make this clear (section 3.1)
Impact of family members, in particular kids and partners	Comment noted. The committee recognised that migraine is a highly debilitating disease. The wording in the FAD has been adjusted to make this clear (section 3.1)

Theme	Response
"Invisible disability" – feeling isolated, dismissed and treated as responsible for their condition.	Comment noted. The committee recognised that migraine is a highly debilitating disease. The wording in the FAD has been adjusted to make this clear (section 3.1)
Current treatments	
High unmet need for new treatment options	Comment noted. The FAD has been amended to reflect this - see FAD section 3.2.
Existing treatments don't work for many people and have bad side effects, especially medication overuse headache - 'Overuse is something to be avoided but the point I am making is that sometimes it can't be avoided.'	Comment noted. The FAD has been amended to reflect this - see FAD section 3.2.
Some patients tried 8+ treatments with no pain relief	Comment noted. This information was included in the ACD. Please see section 3.1 of the FAD.
Current treatment options do not directly target migraines	Comment noted. For comments relating to rimegepant as an acute treatment of migraine, we will respond separately in ID1539.
People often have to try alternative 'non-migraine' medications to treat symptoms e.g., anti-depressants and opioids.	Comment noted. The FAD has been amended to reflect this - see FAD section 3.2.
Not all treatments work for everyone – more treatment options needed, especially for acute use where there are no alternatives, particularly for those who cannot take triptans.	Comment noted. The committee recognised that not all current treatments work for every person. For comments relating to rimegepant as an acute treatment of migraine, we will respond separately in ID1539.
No viable treatment options for people who cannot take triptans e.g., older people or people with other health issues as there is an increased risk of taking triptans e.g., cardiovascular problems.	Comment noted. For comments relating to rimegepant as an acute treatment of migraine, we will respond separately in ID1539.
Long waiting lists to access treatments and see specialists. Treatments are not freely available and are limited in dose.	Comment noted. The committee recognised that there is a long waiting lists to see specialists and access treatments. Please see section 3.17 of the FAD.
Current preventative treatments all injectable that need refrigeration and are not suitable for everyone e.g., needle-phobia, homeless patients accessing storing facilities.	Comment noted. The committee recognised that there is a need for alternative oral formulation to current available treatments (see section 3.18).
Experience with rimegepant	
Rimegepant was shown to be effective with few side effects and could support those with medication overuse headache.	Comment noted. The committee concluded that rimegepant appears to be more clinically effective than placebo and associated with a mild adverse event profile (see section 3.5). But it also acknowledged the lack of direct clinical evidence against the comparators (see section 3.7).

Theme	Response
Rimegepant is specifically developed to treat migraine	Comment noted. The committee recognised that rimegepant is a specialist treatment and that current oral treatment options for preventing migraine include drugs that are used to treat other conditions. For comments relating to rimegepant as an acute treatment of migraine, we will respond separately in ID1539.
Rimegepant offers a tablet formulation which is easier to use and preferable to currently available treatments.	Comment noted. The committee recognised that rimegepant could be the first oral calcitonin gene-related peptide preventative treatment (see section 3.13) and that this may be preferred over current injectable treatments.
Further trials needed to: determine the effectiveness of rimegepant in the population that will be eligible to use it; establish benefits in those who cannot use triptans; directly compare against the mAb comparators; determine the extent it reduces medication overuse headache.	Comment noted. The Assessment relies on the available evidence submitted to the Institute and that retrieved from the published literature by the assessment group.
Outcome measures inappropriate. Some treatments take more than 2 hours to provide pain relief.	Comment noted. For comments relating to rimegepant as an acute treatment of migraine, we will respond separately in ID1539.
NMA not appropriate to make conclusion on because there are substantial limitations	Comment noted. The committee acknowledged the limitations associated with the NMA and concluded that they are unresolvable (see section 3.7).
Appropriate to consider rimegepant differently in preventative and acute use.	Comment noted. The Committee recognised considered this comment. See section 3.1 of FAD.
Rimegepant is a last resort for many people.	Comment noted. The committee recognised that there is a high unmet need for new treatment options and that existing treatments do not work for many people. Please see section 3.2.
Wider benefits	
Cost effectiveness analyses should consider the wider impact on economy: health service, education and workdays lost to migraine.	Comment noted. In accordance with the NICE guide to the methods of technology appraisals (sections 5.1.9 and 5.1.10) the committee considered only direct costs to the NHS and personal social services.
Equality	
Affects more women than men – cause them to leave work; cause family issues; often misdiagnosed; hormone element of condition; associated with menstruation.	Comment noted. This information was considered was included in the ACD and has been considered by the committee. Please see section 3.17 of the FAD.
Recommendation discriminates against people with migraine – many of whom are considered having disability.	Comment noted. This information was included in the ACD and has been considered by the committee. Please see section 3.17 of the FAD.

Theme	Response
Available in the US, Europe, UAE and Israel – discrimination on grounds of race and postcode	Comment noted. The Committee cannot speculate about the deliberations of another body. The FAD has been amended to reflect this - FAD section 3.17
The recommendation may discriminate against people on lower incomes who won't afford private prescription	Comment noted. This has been considered by the committee and the FAD has been amended to reflect this - FAD section 3.17
Equality implications of a new medication with easier means of administration and allows people who suffer from cardiovascular disease to be treated.	Comment noted. This has been considered by the committee and the FAD has been amended to reflect this - FAD section 3.17
NHS values, constitution rights and principles	Comment noted. NICE aims to prepare guidance and standards on topics that reflect national priorities for health and care.
The relatively flexible dosing options of rimegepant compared to anti-cgrp-mAb may give pregnant people access to this type of treatment which they would otherwise not have due to gestational/maternal safety considerations of continuous dosing.	Comment noted. This has been considered by the committee and the FAD has been amended to reflect this - FAD section 3.17
It would be discriminatory to not make this medication available to all, particularly those who are unable to take any effective migraine medication e.g., Triptans. Could disproportionately disadvantage those migraine sufferers who are unresponsive to, or unable to use, other interventions (older people or those with other health conditions). You are discriminating against those disabled by not being able to use the existing drugs.	Comment noted. This has been considered by the committee and the FAD has been amended to reflect this - FAD section 3.17
Wording	
Change wording to 'rimegepant when used for acute treatment might also reduce monthly migraine days but there is a lack of comparative long-term evidence to support this'.	Comment noted. For comments relating to rimegepant as an acute treatment of migraine, we will respond separately in ID1539.

Theme	Response
Change wording to ‘Standard treatment for preventing migraine after 3 or more treatments have not worked includes erenumab, fremanezumab or galcanezumab.	Comment noted. FAD updated to reflect this comment.
Change wording to ‘The cost-effectiveness estimates suggest that rimegepant costs more and is less effective than erenumab, fremanezumab and galcanezumab.’	Comment noted. FAD updated to reflect this comment.

NICE National Institute for Health and Care Excellence

Rimegepant for treating or preventing migraine [ID1539]

Consultation on the appraisal consultation document – deadline for comments 5pm on 14 March 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):	Pfizer
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
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.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Rimegepant for treating or preventing migraine [ID1539]

Consultation on the appraisal consultation document – deadline for comments 5pm on 14 March 2023. Please submit via NICE Docs.

Summary

Pfizer are disappointed that NICE have chosen not to recommend rimegepant for the treatment of acute and preventative migraine following the first Appraisal Committee Meeting (ACM) on January 19th, 2023. We strongly agree with the Migraine Trust's statement released after the publication of the Appraisal Committee Document (ACD), which acknowledges the considerable unmet need that remains in the United Kingdom for people suffering with migraine for whom rimegepant can provide an effective alternative treatment option.[1]

The EAG's preferred 2-year time horizon for the acute model is of particular concern as it underestimates the length of time patients, who require acute treatment, suffer with migraine. It is known migraine is a chronic disease and onset occurs during teenage years and continues until a patient reaches their 40s and 50s. Therefore, it is reasonable to assume patients will require acute treatment over the original base case time horizon of 20-years. Furthermore, a longer time horizon has been supported by clinical experts, study data and real-world evidence (RWE).

The Company have included the Committee's preferred assumptions in the revised base case and when combined with the lowered list price of rimegepant (from £20.00 to £13.55 per pill), rimegepant is cost-effective under a £20,000 willingness to pay (WTP) threshold, as detailed in Table 2.

Given all the committee's preferred assumptions have been included, the degree of certainty around the ICER has substantially increased, suggesting a threshold above £20,000 could be considered more appropriate. In addition, the ICER reduces significantly when the positive uncertainties associated with the MMD reduction with acute Rimegepant (ICER <£12,000 per QALY) and the subgroups relevant to the decision problem are included in the model (ICER <£16,000 per QALY) are included.

The committee also requested further exploration of the time horizons via scenario analysis which are also presented in Table 2. However, even with the most extreme scenario with a 2-year time horizon (which can be consider inappropriate given discussion below), the ICER remains below £30,000 per QALY.

The detailed responses to the ACD and the requested information by the committee follow Table 1 overleaf.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Rimegepant for treating or preventing migraine [ID1539]

Consultation on the appraisal consultation document – deadline for comments 5pm on 14 March 2023. Please submit via NICE Docs.

Table 1 EAG and Committee's preferred assumptions and updated 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
Acute			
Trial efficacy data	BHV3000-301 - 303 pooled ≥2 triptan failures	BHV3000-301 – 303 pooled mITT	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 discounting	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
Prevention			
MMD baseline distribution	Empirical	Poisson	Included
Reversion to baseline MMD	Immediate	Gradual	Included
NMA results cycle	Cycle 3	Cycle 1	Included
Response probability	At 12 weeks	Over 12 weeks	Included
Erenumab costs	Monthly regimen assumed for erenumab offered every 30.4 days.	Matching the regimen for erenumab to the regimen reported in the BNF and marketing authorisation, offered every 28 days.	Included
Comparator acquisition	Different acquisition costs	Equating the initial 28-day	Included

Please return to: **NICE DOCS**

costs	in the initial 28-day cycle and subsequent 28-day cycles.	treatment acquisition cost to the ongoing 28-day treatment acquisition cost for all treatments (while the exception of the loading dose for galcanezumab).	

ACUTE

1

Time Horizon

Clinical experts, RWE and study data all suggest a time horizon of >10 years is most appropriate in the acute model of migraine. The ACD states 'The committee considered both the 2- and 20-year time horizons but concluded that the costs and benefits of rimegepant as an acute treatment should be reflected in a shorter time horizon than 5 years and more explanation is needed to determine the most appropriate length'. We have provided additional evidence, from clinical experts, trial data and RWE that all suggest a time horizon of >10 years is appropriate.

Clinical experts

Clinical experts support a time horizon of longer than 10 years to properly capture benefits and cost relating to acute treatment of migraine.

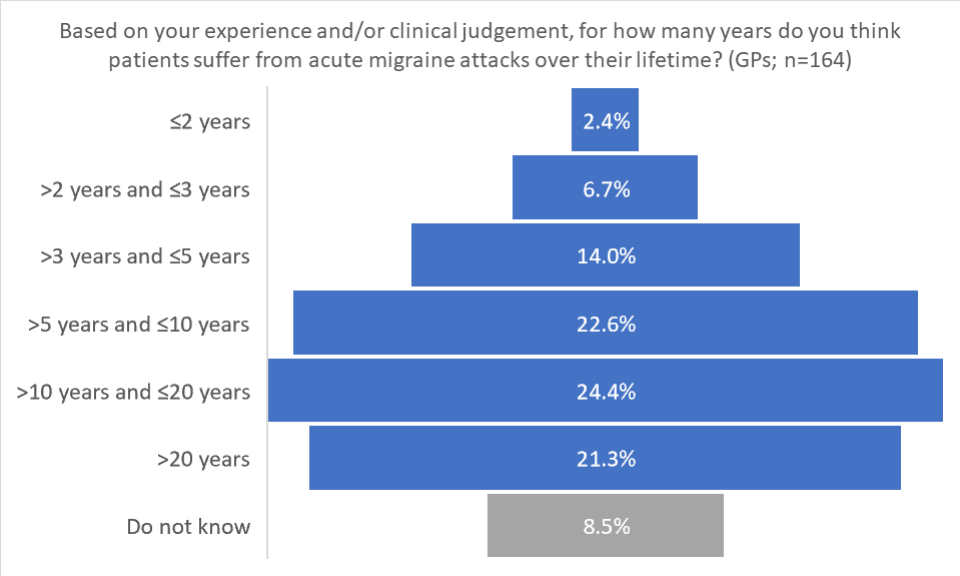
A survey of general practitioners (GPs) based in the United Kingdom indicate a time horizon of 20-years is appropriate to fully capture a patient's experience with acute migraine and in turn ensure all the associated health outcomes and costs are included in the model.

- The Company conducted a survey of 164 GPs to further understand the appropriate time horizon to be included in the acute model.
- Recipients of the survey were asked 'Based on your experience and/or clinical judgement, for how many years do you think patients suffer from acute migraine attacks over their lifetime?'.
    - Of the GPs surveyed, 68% responded >5 years, with the largest percentage selecting the >10 years and ≤20-years category.
    - Figure 1, demonstrates a low confidence in a 2-year time horizon, suggested by the EAG, to capture the outcomes and costs for patients requiring acute migraine treatment.

Rimegepant for treating or preventing migraine [ID1539]

Consultation on the appraisal consultation document – deadline for comments 5pm on 14 March 2023. Please submit via NICE Docs.

Figure 1 GP acute treatment time horizon responses



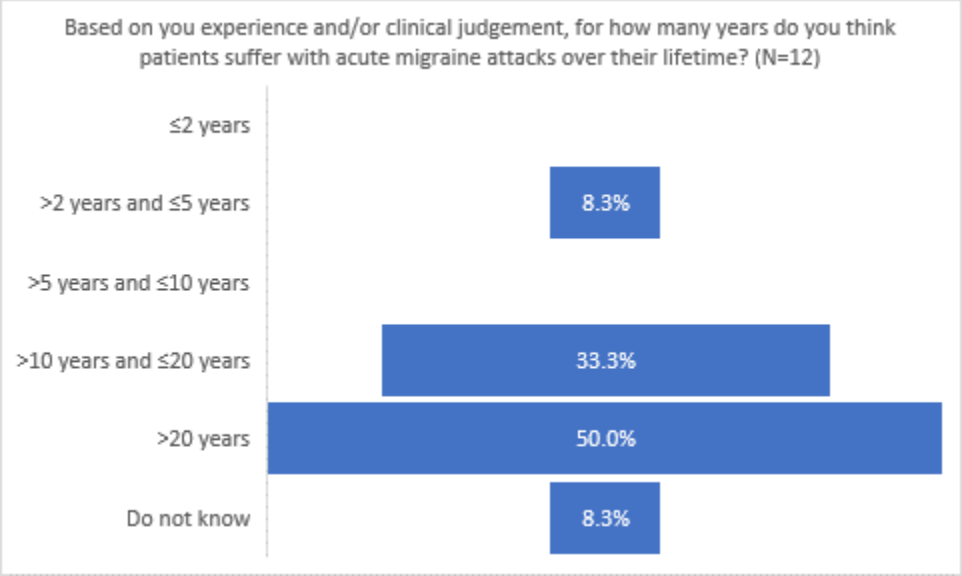
Further to the above survey, another survey of 12 neurologists with an interest in headache, supported a time horizon of >10 years for the acute model of rimegepant.

- Recipients of the survey were asked 'Based on your experience and/or clinical judgement, for how many years do you think patients suffer from acute migraine attacks over their lifetime?'
  - Of the Neurologists surveyed, 83.3% responded >10 years, with the largest percentage (50%) selecting the ≥20-years category.
  - Figure 2, demonstrates no confidence in a 2-year time horizon, suggested by the EAG, to capture the outcomes and costs for patients requiring acute migraine treatment.

Figure 2 Neurologists acute treatment time horizon responses

Rimegepant for treating or preventing migraine [ID1539]

Consultation on the appraisal consultation document – deadline for comments 5pm on 14 March 2023. Please submit via NICE Docs.



The ACD states 'The clinical experts agreed with the EAG that a 2-year time horizon is more appropriate'. Please note Pfizer believes this statement to be factually incorrect as in the public section of the Appraisal Committee Meeting (ACM) one clinical expert, Dr Brendan Davies, Consultant Neurologist and the Clinical lead for Neurology at the University Hospital of North Midlands, agreed with the 20-year time horizon during the discussions on the appropriate time horizon.

Extension study data and extrapolation

In the long term follow up study (BHV3000-201), patients remained on treatment up to 52 weeks with only a small percentage discontinuing (2.7%). The model extrapolates from the long-term study, BHV3000-201, which shows patients remain on treatment at 20-years, suggesting a 20-year time horizon would be most appropriate to capture all relevant cost and QALY impacts.

Trial demographics show disease duration beyond 20 years

The time horizon assumption of 20-years in the Company's base case acute model is reflective of the disease history of participants enrolled in the clinical studies that is informing the model. Given patients with an average disease history of 20-years had sufficient unmet need to pursue acute migraine medication in clinical trials, this provides sufficient evidence that the need for acute treatments for migraine is long-lasting and thus a 20-year time-horizon is appropriate. In the pivotal clinical trials disease onset was on average 21 years old and average age at enrolment in clinical trials was approximately 39 years of age.

- The trial data is supported by the literature whereby Steiner et al. reported onset of migraine in England being 22 years of age and average age at the time of the study was 43 noting patients were suffering from 26 migraines a year, 20 years after onset of migraine.[2]

Rimegepant for treating or preventing migraine [ID1539]

Consultation on the appraisal consultation document – deadline for comments 5pm on 14 March 2023. Please submit via NICE Docs.

	RWE
	Migraine prescription data supports the inclusion of a time horizon longer than 5 years (noting data beyond 5 years was not available). The company conducted a study to understand how long patients with migraine receive prescriptions to better understand the appropriate time horizon to be adopted in the acute model.
	• The data analysed was from IQVIA OMOP UK Medical Research Data (IMRD) The Health Improvement Network (THIN). The registry captured 119,918 patients who were newly diagnosed with migraine between January 1st, 2010, and September 30th, 2017; with prescription data being captured until September 2022.
	  o Of the 29,376 patients with more than one triptan prescription during follow-up, 24.30% (7,150) had ≥ 5 years between their first and last triptan prescription on record.
	• Using a more stringent approach by defining a 'treatment line' as 2 triptans within 12 months of each other, 23,448 (19.6%) of patients had at least 1 treatment line of triptans
	  o Of which, 15.7% had ≥5 years between the first and last triptan prescription in their first treatment line (i.e., had a gap of no more than 12 months between triptan prescriptions for 5 or more years continuously), suggesting an unmet need with ineffective or poorly tolerated therapy.
	• It is worth noting, some patients may have exhausted all treatment options and given up on treatment i.e., their migraine has not resolved and would still utilise treatment if more were available. While some patients may buy treatments (e.g., triptans) over the counter (OTC) as it is cheaper than prescriptions. Therefore, the above results should be interpreted as conservative estimates of the length of time patients are receiving acute treatment.
	
	Consistency with preventative treatment of the same condition
	• The prevention model adopts a lifetime horizon of 20-years; therefore, it could be deemed illogical to propose a different time horizon for the same disease for the acute treatment model.

2	**Reduced monthly migraine days** MMD reduction should be included in the acute model. Given the Committee acknowledges 'there is biological plausibility in the suggestion that taking rimegepant as needed may reduce MMDs'. Removing the MMD reduction experienced by patients taking rimegepant PRN has a significant impact on benefit as demonstrated by the change in incremental QALYs in Table 2 when MMD reduction is included in the model. This strongly contradicts the conclusion in the ACD whereby it states, 'removing the assumption from the model 'may be considered as a small, potential uncaptured benefit'. By excluding the reduction in MMDs, the company's updated base case is highly conservative as reflected by the impact of this positive uncertainty seen in Table 2.

Rimegepant for treating or preventing migraine [ID1539]

Consultation on the appraisal consultation document – deadline for comments 5pm on 14 March 2023. Please submit via NICE Docs.

3

Revised acute base case and scenario analyses

The Company have included the Committee's preferred assumptions in the revised base case and when combined with the lowered list price of rimegepant (as noted in the summary above), Rimegepant is cost-effective under a £20,000 willingness to pay (WTP) threshold, as detailed in Table 2.

Given all the committee's preferred assumptions have been included, the degree of certainty around the ICER has substantially increased, suggesting a threshold above £20,000 could be considered more appropriate. In addition, the ICER reduces significantly when the positive uncertainties associated with the MMD reduction with acute Rimegepant (ICER <£12,000 per QALY) and the subgroups relevant to the decision problem are included in the model (ICER <£16,000 per QALY) are included.

The committee also requested further exploration of the time horizons via scenario analysis which are also presented in Table 2. However, even with the most extreme scenario with a 2-year time horizon (which can be consider inappropriate given discussion above), the ICER remains below £30,000 per QALY.

Table 2 Changes to the company's cost-effectiveness estimate in acute

Scenario	Incremental QALYS	Incremental costs	ICER (£/QALY)
Base case following TE	0.4117	£7,307	£17,521
Company revised base case (20-year time horizon)	0.1216	£3,584	£19,973
Company revised base case (20-year time horizon, probabilistic results)	0.4261	£7,397	£19,158
Time horizon scenarios			
15-year time horizon	0.1714	£3,444	£20,100
10-year time horizon	0.1512	£3,096	£20,474
5-year time horizon	0.1013	£2,233	£22,046
2-year time horizon	0.0408	£1,187	£29,109
Positive uncertainty scenarios			
Including reduction in MMD with 20- year time horizon	0.2353	£2,766	£11,753
Post-hoc triptan failure subgroup analysis	0.3644	£5,549	£15,226
Prespecified triptan failure subgroup analysis	0.3513	£5,536	£15,761

4

Clarification of the difference between the prespecified and post hoc subgroups

The ACD notes 'In the 3 RCTs, there was a prespecified subgroup of people who had stopped 2 or more triptan treatments because they had not worked. In the company's submission, a post hoc subgroup analysis was used as its main source of evidence in the economic model. The prespecified subgroup and

the post hoc subgroup defined treatment failure differently'. Consequently, the Committee requested clarification of the difference between the prespecified and post hoc subgroups.

Data across the three Phase 3 trials (Study BHV3000-303, Study BHV3000-301, Study BHV3000-302) were pooled to facilitate subgroup analyses of patients who had failed ≥2 triptans. The protocols for these trials included a pre-specified subgroup analysis of triptan non-responders, defined as "any subject that failed 2 or more molecular entities for efficacy reasons. To be considered a failure for a molecular entity, the subject must have failed on all routes of administration that the subject tried for the molecular entity."

A table summarising the details of the pre-specified triptan non-responder is provided below. The number of patients included in the pooled sample using this pre-specified definition was: rimegepant (n=78) and placebo (n=104).

Table 3 summarises the criteria of the pre-specified triptan non-responder definition (i.e. reason for failure, frequency of reason and number of routes of administration that had to be failed).

Criteria	Summary
Failure reason	Efficacy only. Subject must have provided at least one of the following efficacy reasons for failure: • Took too long to relieve headache pain • Couldn't count on treatment to relieve pain and symptoms every time • Pain returned after it was relieved within 24 hours • Did not relieve other symptoms
Reason frequency	Most or all of the time
Number of routes of administration for a single molecular entity that had to be failed	All routes of administration

Given the strict criteria used for pre-specified definition of triptan non-responder resulted in a relatively small sample size that omitted patients who had failed triptans for reasons of intolerability, a post-hoc analysis was performed that modified this definition to include all patients who reported failure of ≥2 triptans. This post-hoc analysis included those patients that had failed ≥2 previous triptans for reasons of intolerability as well as efficacy. In addition, patients only had to have failed on ≥1 route of administration rather than failing on all routes. This increases the clinical relevance of the post-hoc analysis as adverse events are a common reason for patients discontinuing triptan treatment in clinical practice, and patients do

not typically trial all possible routes of administration for a single triptan before trying a different triptan.[3] As seen, in a recent retrospective analysis using the CPRD Aurum dataset, the data shown that only 4.8% of migraineurs have tried more than two different type of triptans for the acute treatment of migraine, suggesting that a third triptan after treatment failure remains relatively uncommon in clinical practice.[4] The results of efficacy analyses for the pre-specified and post-hoc analyses are similar (see Table 4, however, the post-hoc definition increased the sample size (rimegepant (n=148), placebo (n=177) and consequently reduced uncertainty in the estimates of treatment effect.

Table 4 A comparison of endpoints between prespecified and post-hoc results

	Prespecified pooled analysis; failed ≥2 triptans			Post-hoc pooled analysis of ≥2 triptans		
	RIM n/N (%)	PBO n/N (%)	Risk difference (95% CI) p value	RIM n/N (%)	PBO n/N (%)	Risk difference (95% CI) p value
Primary endpoints						
Pain freedom at 2 hours post-dose	[redacted]	[redacted]	[redacted]	30/148 (20.0)	18/177 (10.2)	9.8 [redacted]
Freedom from MBS at 2 hours post-dose	[redacted]	[redacted]	[redacted]	64/148 (43.0)	38/177 (21.5)	21.5 [redacted]
Secondary endpoints						
Pain relief at 2 hours post-dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Functional disability at 2 hours post-dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sustained pain relief 2 to 24 hours post-dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rescue Medication Use within 24 hours post-dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sustained pain relief 2 to 48 hours post-dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Freedom from photophobia at 2 hours post-dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sustained pain freedom from 2 to 24 hours post-dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Freedom from phonophobia at 2 hours post-dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sustained pain freedom from 2 to 48 hours post-dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Freedom from nausea at	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Rimegepant for treating or preventing migraine [ID1539]

Consultation on the appraisal consultation document – deadline for comments 5pm on 14 March 2023. Please submit via NICE Docs.

	2 hours post-dose	[redacted]
	Pain relapse from 2 to 48 hours post-dose	[redacted]

5

Prespecified subgroup results from the clinical trials BHV3000-301, BHV3000-302, BHV3000-303, for the population who have had 2 or more triptans that have not worked

Table 5 below presents the prespecified subgroup results alongside the pooled mITT results, which are the base case in the model. The prespecified subgroup results from studies 301-303, for the population who have had 2 or more triptan failures is consistent with the post-hoc analysis as previously mentioned, however please note again the prespecified analysis (in Tables 4 and 5) should be interpreted with caution as the risk differences as several endpoints are not significant which is likely due to low sample sizes.

Table 5 Primary and secondary endpoint results, pooled mITT analysis and prespecified pooled analysis who failed ≥2 triptans

	Pooled mITT analysis			Prespecified pooled analysis of ≥2 triptans		
	RIM n/N (%) *stratified risk	PBO n/N (%) *stratified risk	Risk difference (95% CI) p value	RIM n/N (%)	PBO n/N (%)	Risk difference (95% CI) p value
Primary endpoints						
Pain freedom at 2 hours post-dose	[redacted]					
Freedom from MBS at 2 hours post-dose	[redacted]					
Secondary endpoints						
Pain relief at 2 hours post-dose	[redacted]					
Functional disability at 2 hours post-dose	[redacted]					
Sustained pain relief 2 to 24 hours post-dose	[redacted]					
Rescue Medication Use within 24 hours post-dose	[redacted]					
Sustained pain relief 2 to 48 hours post-dose	[redacted]					
Freedom from photophobia at 2 hours post-dose	[redacted]					
Sustained pain	[redacted]					

Please return to: **NICE DOCS**

Rimegepant for treating or preventing migraine [ID1539]

Consultation on the appraisal consultation document – deadline for comments 5pm on 14 March 2023. Please submit via NICE Docs.

	freedom from 2 to 24 hours post-dose						
	Freedom from phonophobia at 2 hours post-dose						
	Sustained pain freedom from 2 to 48 hours post-dose						
	Freedom from nausea at 2 hours post-dose						
	Pain relapse from 2 to 48 hours post-dose						

6

Economic analyses using the prespecified subgroup results

Rimegepant remains cost-effective using the prespecified subgroup analysis, and therefore, the Company's revised base case is a conservative estimate as demonstrated in Table 2 above. The prespecified subgroup results show a positive uncertainty given the reduction in the ICERs. Here again, the prespecified results are similar to that of the post-hoc analysis.

PREVENTION

7

Revised prevention base case

Based on willingness-to-pay (WTP) thresholds of £20,000 or £30,000 per QALY, rimegepant is considered cost-effective compared to each mAb as the ICERs are above these WTP thresholds and the incremental net monetary benefits (NMBs) are negative. In the revised base case (Table 6), the monoclonal antibodies (mAbs) are associated with higher costs and higher QALYs than rimegepant. Please note, the revised base case includes the committee's preferred assumption, updated health care resource use (HCRU) costs and the lower list price noted in Table 1 in the summary above.

Secondary care cost savings

Rimegepant is expected to offer cost savings in terms of HCRU compared to the mAbs for migraine prevention if predominately managed in primary care, as demonstrated by the total costs presented in Table 6 below**.** Please note,

The NHS is transforming rapidly with the imminent implementation of recommendations from the Getting It Right First Time (GIRFT) Neurology Report 2021.[5] GIRFT has set out a vision of neurological care closer to home with services provided in a community setting supported by triage systems to empower general practice with efficient advice and guidance. The recently published National Neuroscience Advisory Group

(NNAG) headache & facial pain pathway has built on this vision with a template for migraine to be managed in general practice, supported by community-based headache clinics rather than secondary care wherever possible.[6]

The Oxfordshire headache pathway has adopted the triage and community headache clinic approach recommended by GIRFT and NNAG with 89% of all headache referrals now triaged away from general neurology, freeing up 979 appointments per annum.[7] The Oxfordshire community clinic approach had benefits beyond freeing up secondary care capacity; prior to their community headache appointment 32% of patients felt able to manage their headache and this rose to 100% after the clinic appointment.

In addition, during discussions with clinical experts, it has come to light that rimegepant can provide cost savings in terms of HCRU for patients in the community. Rimegepant has the unique offering of providing the first CGRP-targeted preventative treatment in primary care for patients with migraine.

Please note, the revised base case has been updated to explore a more primary care centric approach for migraine prevention care using rimegepant. Additional HCRU scenario analysis have also been presented. Table 6 below.

[redacted].

- The revised base case includes a one-off initiation cost and a 3-month follow-up cost, with a GP (£39.23 per visit) for rimegepant and with a neurologist (£194.24 per visit) for the comparator mAbs.[8,9] Additionally, a one-off neurologist referral cost has been added to the mAbs costed as one GP visit (£39.23).[8] We believe this to be a conservative approach as monitoring care will likely continue in primary care for rimegepant and secondary for mAbs.
- Consequently, a scenario analysis has been provided whereby all rimegepant care (initiation visits, 3-month follow-up and monitoring visits) takes place in primary care for patients using rimegepant.

Rimegepant can offer cost savings in terms of HCRU compared to the mAbs for migraine prevention if predominately managed in primary care as demonstrated by the total costs presented in Table 6 overleaf.

Rimegepant for treating or preventing migraine [ID1539]

Consultation on the appraisal consultation document – deadline for comments 5pm on 14 March 2023. Please submit via NICE Docs.

Table 6 Changes to the company's cost-effectiveness estimate in prevention

	Incremental QALYS	Incremental costs	ICER (£/QALY)	NMB (£30,000/ QALY WTP threshold)	NMB (£20,000/ QALY WTP threshold)
Revised base case following technical engagement					
Galcanezumab	0.056	£6,020	£160,909	-£4,330	-£4,893
Fremanezumab	0.055	£5,482	£99,802	-£3,834	-£4,383
Erenumab	0.039	£4,105	£104,919	-£2,931	-£3,323
Revised base case following ACD					
Galcanezumab	0.056	£7,539	£135,082	-£5,865	-£6,423
Fremanezumab	0.054	£6,999	£128,714	-£5,368	-£5,911
Erenumab	0.038	£5,733	£150,269	-£4,589	-£4,970
Revised base case following ACD (probabilistic results)					
Galcanezumab	0.053	£7,288	£136,355	-£5,684	-£6,219
Fremanezumab	0.046	£6,487	£142,143	-£5,118	-£5,574
Erenumab	0.034	£5,375	£156,655	-£4,346	-£4,689
Scenario analysis 1					
Galcanezumab	0.056	£7,576	£135,749	-£5,902	-£6,460
Fremanezumab	0.054	£7,036	£129,398	-£5,405	-£5,949
Erenumab	0.038	£5,771	£151,244	-£4,626	-£5,008

Rimegepant for treating or preventing migraine [ID1539]

Consultation on the appraisal consultation document – deadline for comments 5pm on 14 March 2023. Please submit via NICE Docs.

References:

1. The Migraine Trust. NICE has rejected migraine medication Rimegepant for use on the NHS in England. 2023 [Available from: https://migrainetrust.org/news/nice-has-rejected-migraine-medication-rimegepant-for-use-on-the-nhs-in-england/ (Last assessed March 2023).

2. Steiner, T. J., Scher, A. I., Stewart, W. F., Kolodner, K., Liberman, J., & Lipton, R. B. (2003). The prevalence and disability burden of adult migraine in England and their relationships to age, gender and ethnicity. Cephalalgia, 23(7), 519-527.

3. Shamliyan TA, Choi JY, Ramakrishnan R, Miller JB, Wang SY, Taylor FR, et al. Preventive pharmacologic treatments for episodic migraine in adults. J Gen Intern Med. 2013;28(9):1225-37

4. Pfizer. Data on File: CPRD Aurum Analysis. 2022

5. Fuller, G. GIRFT Programme National Specialty Report. 2021. [Available from: https://neurologyacademy.org/articles/girft-report-for-neurology (last assessed March 2023)]

6. National Neuroscience Advisory Group (NNAG). Optimum clinical pathway for adults: Headache & Facial pain. 2023. [Available from: https://static1.squarespace.com/static/5f1021faf6248b39f4c64f5d/t/63dbb10ab1d6657b00247962/1675342095594/04+NNAG+Headache+and+Facial+Pain+Pathway+Final.pdf (last assessed March 2023)]

7. NICE. Oxfordshire Headache Pathway for the Efficient Diagnostic and Management Support of Headache Disorders.2018. [Available at: https://www.nice.org.uk/sharedlearning/oxfordshire-headache-pathway-for-the-efficient-diagnostic-and-management-support-of-headache-disorders (last assessed March 2023)]

8. 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 2022)

9. NHS Improvement. National Schedule of NHS costs - Year 2019-2020 [Available from: https://www.england.nhs.uk/national-cost-collection/ (last accessed January 2022)

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Rimegepant for treating or preventing migraine [ID1539]

Consultation on the appraisal consultation document – deadline for comments 5pm on 14 March 2023. Please submit via NICE Docs.

- Please underline all confidential information, and separately highlight information that is submitted under [redacted] and all information submitted under [redacted]. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) 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.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Rimegepant for treating or preventing migraine [ID1539]

Consultation on the appraisal consultation document – deadline for comments 5pm on 14 March 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
Disclosure 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:	[redacted]

Comment number	Comments
	Insert each comment in a new row.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Rimegepant for treating or preventing migraine [ID1539]

Consultation on the appraisal consultation document – deadline for comments 5pm on 14 March 2023. Please submit via NICE Docs.

	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	Migraine is a painful debilitating disorder for which there is no cure and limited treatment options. Furthermore, people with migraine have for so long been stigmatised and a part of this is due to the lack of understanding, lack of effective treatments and the associated links to productivity at work. Effective targeted treatments are needed to address this. **The ACD reports that, 'clinical trial evidence for acute migraine shows that rimegepant is likely to reduce pain at 2 hours more than placebo'.** Many people are still without an effective acute treatment. Some are at risk of or develop *medication overuse headache*, which further complicates the condition and adds to its impact and costs. Many people end up in secondary care, A & E or with no effective treatment at all. The personal and economic costs should not be ignored.
2	**Costs** We understand that there will always be a degree of clinical uncertainty with new treatments in the context of benefit and cost effectiveness. We would urge you to consider the healthcare costs currently incurred for migraine, particularly for people who have not yet found an effective **acute** and/or **preventive** treatment. A Work Foundation report in 2018 estimated that the UK healthcare costs for migraine are estimated at £1b per year and over £8b in indirect/productivity costs. This data is backed up by pro-bono research the charity received last year which showed the cost of absenteeism and presenteeism was £9b and that by improving the treatment pathway that would reduce frequency / intensity of migraines could enable significant productivity gains - a 10% improvement would save £904m a year and 20% would save £1.8b.
3	**Disadvantaged groups** In our submission, we described the disadvantaged group of people with migraine who could derive benefit. This group of people will continue to consult in specialist clinics, primary care and A&E. This imposes significant costs through a lack of treatment for some, poor or inadequate response to current treatments for some and medical contraindications for others. In addition, people with migraine will need to take time off work or be less effective at work and in other aspects of life, incurring indirect costs (absenteeism and presenteeism). If the stated aims of *Getting It Right First Time* (GIRFT, 2019) are to be realised, there

Rimegepant for treating or preventing migraine [ID1539]

Consultation on the appraisal consultation document – deadline for comments 5pm on 14 March 2023. Please submit via NICE Docs.

	needs to be better treatments to improve the current care for people with migraine.
4	**The hugely disadvantaged** When considering the options people have for **acute** treatment (CG150): Some cannot use a triptan, NSAID or are unable to restrict them to the recommended number of days to avoid medication overuse. These people are overwhelmingly disadvantaged. Moreover, those for whom these **acute** treatments are contraindicated have no good treatment. Best available care is not an effective option and although we advise against use of opioids in migraine, this may be their only alternative option. Use of opiates will carry its own complications, such as medication overuse headache and dependency, which further compound migraine symptoms and can lead to greater disability for the person with migraine and the subsequent greater use of healthcare resources, including specialist services. Some people use a triptan and have partial relief or side effects, and subsequently cannot treat when needed. Their migraines continue to impact and restrict their work and function. A proportion of these will not consult after a poor response to existing treatments, and resort to self-treatment with OTCs and opioids.
5	**Do not ignore the advantages to patients and the NHS** 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, even if it had to be initiated in secondary care in the early stages. In addition to treating acute attacks, this could reduce the number of referrals to specialists and associated costs and waiting times. A treatment that is migraine-targeted without complications of medication overuse headache and is well tolerated should be approved in our view, to meet the treatment need for this disadvantaged group of people for whom the currently recommended triptans and NSAIDs are not an option. We consider it unconscionable to deny this group a treatment option that is more beneficial than placebo.
6	**Preventive Use** **The ACD states that 'rimegepant might also reduce MMDs. Lack of comparative long**

Rimegepant for treating or preventing migraine [ID1539]

Consultation on the appraisal consultation document – deadline for comments 5pm on 14 March 2023. Please submit via NICE Docs.

	term evidence to support this.' When NICE was reviewing the CGRP mAbs for migraine **prevention**, we were also advised of the lack of data in long term use and in comparisons with botulinum toxin-A (Botox) in preventing migraine. Fortunately, the CGRP mAbs were approved which has been beneficial to many people. A priority group for **prevention** should include the group of people with migraine: who either do not wish to or cannot tolerate an injection treatment, cannot access cgrp mAbs, or may have tried but not found them effective or tolerable.
7	We strongly disagree with the decision to eliminate the option of rimegepant, a migraine-specific (non-repurposed), **acute** and **preventive** treatment. We would urge the committee to reconsider the decision, for a treatment that has the potential to alleviate the disability and negative impact of migraine on people's mental health, emotional well-being, relationships and function at work, particularly for the disadvantaged groups.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) 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.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be

unlawful or otherwise inappropriate.

Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Rimegepant for treating or preventing migraine [ID1539]

Consultation on the appraisal consultation document – deadline for comments 5pm on 14 March 2023. Please submit via NICE Docs.

B	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):	[British Association for the Study of Headache (BASH)]
Disclosure 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:	[redacted]

Comment number	Comments Insert each comment in a new row.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Rimegepant for treating or preventing migraine [ID1539]

Consultation on the appraisal consultation document – deadline for comments 5pm on 14 March 2023. Please submit via NICE Docs.

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	It is disappointing that there was no equivalent patient population trial data presented for the respective target population in the UK in line with previous Single Technology Appraisal (STA) assessments to allow indirect comparison. We are unaware that any Rimegepant trials looking at patient failing between 2-4 prior agent for migraine equivalent to the LIBERTY, FOCUS, CONQUER or DELIVER trials in anti-CGRP monoclonal antibodies as the main comparator for either episodic or chronic migraine. There were no data that we are aware and would welcome seeing this for their preventative target population for the UK.
2	We agree that "post-hoc" analysis on acute use of Rimegepant as effecting migraine frequency may be flawed and would welcome a future appropriately designed clinical trial to evaluate the use of alternative day or daily use preventative nature of oral Rimegepant for migraine in the UK.
3	We note and would like to see future clarification of any uncertainties about repeat dosing of Rimegepant and the reliability of response for acute migraine. We would welcome seeing repeat dosing studies as occurred with Triptans in the past for acute migraine. We are keen to have access to using Rimegepant in the UK for migraine but recognise the need for reliable and robust data to support sustained efficacy both as an acute and preventive therapy in those prescribed this medication
4	BASH agrees that in future Gepants should be available for Primary care prescription after /or following Specialist recommendation to ensure appropriate future efficacious and cost effective prescribing as part of the therapy pathway for migraine sufferers in the UK.
5	Rimegepant offers a real way forward in acute migraine management in patients who do not respond to triptans or are unsuitable for triptans (1). 1 - 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.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) 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.
- If you have received agreement from NICE to submit additional evidence with your

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Rimegepant for treating or preventing migraine [ID1539]

Consultation on the appraisal consultation document – deadline for comments 5pm on 14 March 2023. Please submit via NICE Docs.

comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Rimegepant for treating or preventing migraine [ID1539]

Consultation on the appraisal consultation document – deadline for comments 5pm on 14 March 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):	**AbbVie Ltd**
Disclosure 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:	[redacted]

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Rimegepant for treating or preventing migraine [ID1539]

Consultation on the appraisal consultation document – deadline for comments 5pm on 14 March 2023. Please submit via NICE Docs.

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	***Interplay between acute and preventive indications:*** As specified within the company submission, rimegepant is under appraisal for the dual indication for both the acute treatment of migraine in adults (regardless of the number of headache days per month), and the preventive treatment of episodic migraine in adults who have at least 4 migraine attacks per month, but fewer than 15 headache days per month. Clinical guidelines published by NICE (CG150; 2021)[1] and the British Association for the Study of Headache (2019)[2] present acute and preventive migraine treatments as two distinct categories of treatment. As rimegepant is the first treatment licensed for both acute and preventive use, clinical expert opinion indicates that there is currently a lack of clarity in terms of clinical pathway implications for the interplay between acute and preventive treatment following the introduction of a dual indication therapy, given the potential for overlap between indications. Within the company submission, a long-term preventive treatment effect has been claimed when rimegepant is taken as needed for acute treatment based on safety and efficacy data collected in the single arm, Phase 2/3 trial, BHV3000-201. However, as specified in the appraisal consultation document, the committee concluded that there is not enough clinical evidence to support this assumption, and clinical experts advised that patients who experience migraines often enough to have a preventive benefit from an acute treatment should be receiving a preventive treatment. In accordance with clinical opinion and feedback submitted by other stakeholders during the appraisal process, AbbVie believe that the practical delivery of rimgepant is an important consideration of this appraisal to ensure that it can be used effectively and safely, as intended by regulatory and HTA authorities. In particular, it will be important to understand the interplay between acute and preventive indications in clinical practice. Given that the dosing form across acute and preventive treatment is identical, there is a potential risk of misuse across the acute and preventive indications; particularly if patients were eligible to receive rimegepant for only one of the two settings. For acute, the recommended dose is a single 75 mg oral dispersible tablet taken as needed once daily. Similarly for preventive, the recommended dose is a 75 mg oral dispersible tablet taken every other day (with a maximum dose per day of 75 mg). Stopping rules are also implemented differently between acute and preventive settings. NICE recommend that preventive treatments available for patients who have experienced three or more treatment failures should be stopped at 12 weeks for monoclonal antibodies (galcanezumab, erenumab, fremanezumab), or at 24 weeks for botulinum toxin type A if a patient has not adequately responded to treatment (as monitored by headache diaries). However, acute treatments are not currently subject to any formal stopping rule for patients who have failed ≥2 triptans, or who are intolerant or contraindicated to triptans. As specified within the appraisal consultation document, this is a source of uncertainty, as the company propose that treatment would be stopped if there was no response to the first dose of rimegepant. However, this stopping rule is not specified within the rimegepant Summary of Product Characteristics (SmPC), nor is it clear how the frequency and duration of dosing is monitored in the acute setting. As such, Abbvie believe that these issues should be considered moving forward as the appraisal continues. *References:* 1. National Institute for Health and Care Excellence. CG150: Headaches in over 12s: diagnosis and management. Available at: https://www.nice.org.uk/guidance/cg150/chapter/Recommendations#management-2

Please return to: **NICE DOCS**

Rimegepant for treating or preventing migraine [ID1539]

Consultation on the appraisal consultation document – deadline for comments 5pm on 14 March 2023. Please submit via NICE Docs.

	2. British Association for the study of headache. National Headache Management System for Adults 2019. Available at: https://headache.org.uk/index.php/bash-guideline-2019
2	***Innovation in the preventive treatment setting*** In support of clinical expert opinion outlined in the appraisal consultation document, the 'step-change' potential of orally administered calcitonin gene-related peptide inhibitor alternatives to currently available injectable treatments is consistent with feedback received during AbbVie engagement with clinical experts. With these products, there are opportunities to streamline the current clinical care pathway and relieve well-documented NHS-wide capacity issues associated with the management of migraine. As expressed in the company submission and appraisal consultation document, migraine patients eligible for preventive treatment are currently subjected to extensive waiting lists due to difficulties in accessing specialist care, with only a limited number of specialist headache centres in the UK. According to a report published by the Migraine Trust (2021); the average waiting time for patients to access calcitonin gene-related peptide-targeted monoclonal antibodies varies between 3 and 5 months across the UK, and in some cases, it can take up to two years to access specialist headache clinics.[1] Orally administered calcitonin gene-related peptide inhibitors will be a welcome alternative for patients to access care quicker and help shorten the NHS waiting list. In line with received clinical opinion, Abbvie agree that the simple to use, oral, well-tolerated nature of oral calcitonin gene-related peptide inhibitors may open doors to novel prescribing pathways which enable the NHS to optimise the delivery of care, and achieve additional efficiencies in terms of saved specialist time. *References:* 1. The Migraine Trust. State of the Migraine Nation Dismissed for too long: Recommendations to improve migraine care in the UK. Available at: https://migrainetrust.org/wp-content/uploads/2021/09/Dismissed-for-too-long_Recommendations-to-improve-migraine-care-in-the-UK.pdf

NICE National Institute for Health and Care Excellence

Rimegepant for treating or preventing migraine [ID1539]

Consultation on the appraisal consultation document – deadline for comments 5pm on 14 March 2023. Please submit via NICE Docs.

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) 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.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Rimegepant for treating or preventing migraine [ID1539]

Consultation on the appraisal consultation document – deadline for comments 5pm on 14 March 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):	**Teva UK Limited**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	[redacted]

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Rimegepant for treating or preventing migraine [ID1539]

Consultation on the appraisal consultation document – deadline for comments 5pm on 14 March 2023. Please submit via NICE Docs.

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	Teva believes that in general the ACD provides a good and accurate summary of the evidence submitted to NICE in this appraisal. Teva has only a few comments to make, which are outlined below.
2	The main issue that Teva wishes to raise again is the interplay between the two indications for rimegepant. Teva does not feel that this issue has been fully considered within this appraisal so far. There are potential impacts on the cost-effectiveness calculations from this issue, in addition to the clinical practice implications already raised and as outlined below. Importantly, it should be recognised that the two indications (as being considered within this appraisal) represent two distinct patient groups, with only limited crossover, *i.e.* only a small number of patients will have had three preventive therapy failures and two triptan failures; meaning that most patients eligible for rimegepant will have met either the acute or preventive population requirements. In these patients (eligible under one indication only), the combined acute and preventive indications raise the potential for some individuals to start taking the medication for both indications (which may occur for a number of potential reasons). Teva notes that the combined use of rimegepant for both indications is clearly envisaged by the manufacturer, as the long-term safety trial (BH3000-201) includes an arm with combined every other day (EOD) and *pro re nata* (as needed, PRN) dosing. In addition, despite available safety data for the combined dosing of rimegepant, no efficacy data have been presented for patients using rimegepant as both a preventive and acute treatment. Within the cost-effectiveness calculations, it would be most likely that any misuse of rimegepant in an indication where the patient was not eligible would cause rimegepant to displace another preventive or acute medication. If the patient was not eligible for rimegepant in this indication, then it is likely that the treatment displaced would be more cost-effective in this population (most likely to be less costly and of a similar/greater efficacy). In this case, the use of rimegepant would lead to higher costs with little or no efficacy benefits, thus reducing the cost-effectiveness of rimegepant.
3	Teva retains some concerns around the weaknesses present in the clinical evidence presented to the committee, in particular, regarding the NMA utilised within the appraisal of the preventive indication. Teva notes that in the previous migraine preventive appraisals (TA764, TA682, TA659), the NMAs presented were found by the appraisal committee to have a high degree of uncertainty due to recognised limitations in the analyses. The NMA presented for rimegepant contains all of the same weaknesses as present in these previous appraisals, plus a number of significant additional uncertainties specific to this NMA (exclusion of most relevant patient population, lack of analysis in a defined treatment failure population, differences in endpoint definitions, mixing of patients with chronic and episodic migraine *etc*).
4	For the appraisal of the acute indication, one additional point has arisen from the clinical expert comments reported within the ACD that Teva feels has not been considered within the cost-effectiveness analyses. This relates to the comment that, "*The clinical experts also explained that when triptans are ineffective and the migraine does not respond, it is often because they are not being used properly*". The proposed population for the acute indication is "*after two or more triptans have not worked*" and so improper trials of previous triptans becomes a pertinent factor to the cost-effectiveness analysis for rimegepant, and is one that has not been considered so far in this

Please return to: **NICE DOCS**

Rimegepant for treating or preventing migraine [ID1539]

Consultation on the appraisal consultation document – deadline for comments 5pm on 14 March 2023. Please submit via NICE Docs.

	appraisal. Where triptans are not properly trialled, this would lead to a patient becoming eligible for rimegepant under the proposed criteria (having had two triptans that did not work), when potentially a triptan, when used correctly, may provide effective therapy for them. If a less costly and equally efficacious triptan could provide effective therapy for these patients, this can be seen to reduce the cost-effectiveness of rimegepant by applying an additional cost for no therapeutic gain (when considering the current scenario *versus* one considering the impact of improper use/trials of triptans and their appropriate reuse). Teva is unaware of any additional evidence that would help to quantify the prevalence of improper use of triptans. It is therefore very challenging to try and quantify the impact of this issue on ICER values. The only additional avenue that Teva can see which could be explored to address this issue is the inclusion of well-defined guidance statements related to triptan use (to define what constitutes an 'acceptable' trial of a triptan) to reduce the impact of this issue. Teva defers to the clinical experts as to what these criteria might include.
5	For the appraisal of the acute indication, the committee concluded that a time horizon of less than 5 years was preferred. Teva agrees with the committee's rationale on the shortening of the time horizon from 20 years. However, Teva does not find that there was a clear rationale from the committee for choosing a time horizon of less than 5 years rather than the ERG's (also referred to as the EAG in some documents) preferred option of a 2-year time horizon. Teva agrees with the rationale from the ERG that a 2-year time horizon should be sufficient to capture all costs and benefits of the acute treatment of migraine, in particular when this modelling is based solely on efficacy data for the response to a single administration of rimegepant. Teva, therefore, finds that the ERG's conclusion to be more reasonable in the absence of a supporting rationale for extending this to less than 5 years.
6	For the appraisal of the preventive indication, Teva would like to note one factor that does not appear to have been considered so far. This is that the efficacy inputs for the modelling have included the same reduction in MMDs for all treatments, with the only difference in efficacy modelled for different treatments being the response rate. Whilst this is a necessary limitation based on the data available to the company, it has the potential to underestimate any differences in efficacy between rimegepant and the CGRP pathway antibodies (fremanezumab, erenumab and galcanezumab). This is as the NMA conducted shows that the CGRP pathway antibodies are likely to be superior to rimegepant in terms of both MMD reductions and response rates. This fact has not been included within the economic analyses and therefore should be considered when examining the ICER values produced. This additional benefit for the CGRP pathway antibodies would lead to reduced overall MMDs with these treatments, leading to greater QALYs and lower health-related costs compared to rimegepant.
7	For the appraisal of the preventive indication, treatment discontinuation rates appear to have not been fully considered. Teva has raised this issue during the Technical Engagement but it has not been further considered within this appraisal. Therefore, Teva wishes to restate this currently unresolved issue. The discontinuation rates were raised by the ERG as a potential issue within their report, but this issue has not been considered further. Teva believes that, as the ERG states, there is no reason to expect the same discontinuation rate across such different treatments (CGRP pathway antibodies *versus* rimegepant). Rimegepant and the CGRP pathway antibodies have different dosing schedules and routes of administration, they have different efficacy profiles (as evidenced by the NMA results), and they appear to have different tolerability profiles (based on adverse events reported in clinical studies and in the absence of head-to-head data). Given these facts, it seems highly unlikely that discontinuation rates would be the same for rimegepant and for the CGRP pathway antibodies. Teva feels that the ERG's suggestion of an imposition of a class effect between CGRP pathway antibodies predicated on the long-term discontinuation rate for erenumab would be the fairest assumption that could be applied in this case.

NICE National Institute for Health and Care Excellence

Rimegepant for treating or preventing migraine [ID1539]

Consultation on the appraisal consultation document – deadline for comments 5pm on 14 March 2023. Please submit via NICE Docs.

8	Finally, Teva wishes to reiterate that a number of additional trials for rimegepant are reported to be ongoing that would provide data that are highly relevant to this appraisal and would address some of the current uncertainties surrounding this product (BHV3000-407 [NCT05518123], BHV3000-406 [NCT05509400], BHV3000-309 [NCT05399485]). From the publicly available data on clinicatirals.gov, these trials are due for completion in 2024, with interim results perhaps available sooner.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) 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.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

Single Technology Appraisal

Rimegepant for treating or preventing migraine [ID1539]

Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	
Please consider this medicine for use by migraine sufferers. It is so important we have as many options as possible for people with this debilitating condition.	
Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	
Question: Has all of the relevant evidence been taken into account? Response: No **Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Response: No **Question: Are the recommendations sound and a suitable basis for guidance to the NHS?** Response: Absolutely not. **Question: 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** Response: No. Just people who suffer from migraine disease who deserve all the help they can get for such a debilitating disease.	
Name	[redacted]
Organisation	N/A
Conflict	N/A

Notes	N/A
Comments on the ACD:	

Question: 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Response: I can only submit a general response to the decision taken on Rimegepant, based on my experience of suffering frequent migraine throughout my adult life. I am 65 years old and take triptans for acute treatment, but with some trepidation, aware of my increasing risk of developing cardiovascular disease given my age.
Rimegepant would offer myself and others in my age group a viable alternative without the cardiovascular contraindications that triptans have. Therefore I would request that NICE rexamine this decision

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

As someone who has suffered headaches and migraine since childhood (I am now 75) I was really disappointed that NICE haven't approved Rimegepant. I desperately need a good preventative to help stop painkillers and triptans. Please think again.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

As someone who suffers from debilitating migraines and daily tension headache, of which was made worse by medication overuse directed by GP's and non-specialist it upsets me to see why this new drug has been discounted. The preventative medications currently around do not directly target migraine/headache conditions and as a community we are constantly dismissed. I do not want to be taking anti-depressants/ anxiety medications because they indirectly may help my headache condition- please do better for a HUGE community who are suffering in silence and are not being represented in the medical field.

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?
Response: No, please do better for the community of migraine and headache sufferers. We have to use medications not directly used for our conditions. A dismissal of this drug could mean a huge community of people can live their lifes in a normal way and not be suffering from a silent chronic heath condition

Question: 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
Response: Discriminates against chronic heath issues. This drug could help so many people who without it have an incredibly poor quality of life. This is a last resort for many people, and even with the unknown long term issues this would at least allow people to have a better quality of life

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

As a lifelong migraine sufferer who was forced into early retirement by Medication Overuse Headaches caused by “soldiering on” through headaches, trying to earn a living. Now, after 2 years of Botox treatment and a year of Ajovy, I have started to get my life back. With fewer ant generally milder headache days a month, I am able to make plans for the first time in many years.

I still need to take triptans 8 times a month, mostly with a second dose.

As I am 65 this year the triptan option will become progressively more risky. Rimegepant and the other gpant medicines are my only hope of continued recovery. I have been following the progress of these medicines in the US and waiting for them to become available in the UK.

I plead with you to reconsider your decision and make Rimegepant available where triptans are not appropriate.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Comments on Section 1 Recommendations, 1.1:

This is a huge disappointment for people who have not found an effective treatment for migraine control, particularly those who cannot take triptans because of age or other health issues, such as high blood pressure.
like most other migraine treatments, triptans have been adopted by the migraine community from medications initially developed to treat other conditions. it is only relatively recently that specific migraine treatments have become available.
Those of us who use triptans regularly do so with a heavy heart because we are well aware of the risks of medicine overuse headache, and we actually

feel acute guilt at taking them, but often have little alternative in trying to live a reasonably balanced life.
Gepants would have given us the opportunity to achieve this safely and appropriately and now it seems this opportunity is being denied migraine sufferers.
I feel reliance on triptans entrench migraine difficulties, due to their risk of medicine overuse headache and help to create chronic sufferers. every triptan taken increases the need and likelihood of needing to take addition tablets.
Gepants do not appear to cause this rebound effect, and as such would be extremely useful for people such as myself who regularly rely on acute medication to manage their symptoms.
I feel like I have to beg for everything and am being punished for being ill. Clinicians can sometimes view patients as almost responsible for their condition, when the fact is that their condition has been mismanaged due to inappropriate treatment and lack of options.
Now here we have a treatment which again is being denied. Do any of the people making these decisions actually suffer from migraine themselves?

Comments on Section 1 Recommendations, 1.2:

The comment I should like to make here is that the committee were critical of the success rate of Rimegepant in comparison with other injectable drugs, such as fremanezumab. However, I find this galling, and actually irrelevant, because access to these so called superior drugs is also strictly limited and are not freely available. So on the one hand they are being lauded as a more effective treatment, but this hardly matters if the said recommended treatment is also unavailable.
For instance, it is not possible to move from one drug to another in this group. If there is a fail in one, for whatever reason {and in my case it was probable antibody reaction, having worked brilliantly initially} it is not possible to try a sister drug. So comparing it with a treatment that in itself is unavailable seems pointless.
When are migraine sufferers going to be able to stop feeling like beggars or criminals, simply for being ill?
I'm sorry if this is emotive, but when you wake up each day wondering if this is going to be the day that it all becomes too much to bear, with all that might entail, it is difficult to keep things on a purely intellectual level.
I'm 67 years old and have been like this for years and years and I'm just looking for a bit of peace before I die.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Question: Has all of the relevant evidence been taken into account?
Response: No - the evidence is promising but not enough data has been collected

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
Response: No, not enough data has been collected

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?
Response: No, not enough data has been collected

Question: 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
Response: Yes, data should explore the impact for women at different stages of the menstrual cycle

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

The recommendations to not allow rimegepant to be prescribed by the NHS for acute treatment and prevention of migraine is at very least disappointing. I am a migraine sufferer who may well respond to rimegepant as other treatments have not been massively helpful in this dreadful life altering condition. I have progressed from episodic to chronic migraine and still have to hold my job down as an nhs clinician for financial reasons. I already take too many triptans which can be harmful and will likely not be allowed these in 5 years as I will be 65. Rimegepant is available in the US and Europe and it is discriminatory not to authorise this drug for nhs use, particularly for the older population who cannot use triptans. Even for those who use triptans they are limited to 2 days per week which is often not enough. The economic cost of migraine in the workplace is high and migraine is often poorly controlled. Many of the other preventive medications such as amitriptyline and beta blockers have significant side effects which cannot always be tolerated. To buy rimegepant privately would cost at least £400 a month with a private prescription and this is frankly beyond the means of most people in the UK. I am desperate to try this drug having followed its progress in the US and to read that NICE have not approved it is devastating for the migraine population in the UK. I do not imagine everyone will take it as not everyone will respond, so the cost may not be as high as imagined. For those who do respond it could change their lives. It is for these reasons I would like NICE to reconsider use for both acute migraine and prevention.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

As a member of the public who has suffered from migraine with aura for the past 28 years, a condition that has caused me immense physical and psychological suffering, I am saddened and disappointed by this initial decision.

I feel extremely fortunate to have benefitted from specialist neurology treatment. I am on two daily preventative medications and am fortunate to receive NHS monthly erenumab injections. Migraine attacks are still a significant concern for me, can cause me to be unable to work, and reduce my quality of life.

I was so hoping for another possible preventative medication which might be more effective than those I currently take, easier to administer, and with fewer side effects.

For reasons that are probably unclear to most observers, NICE has taken a different view to regulators in the US and EU. I greatly hope that NICE's concerns will be assuaged in further deliberations and this medication approved.

Question: 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Response: The committee seems to acknowledge that migraine has a disproportionate burden on women; but then rather seems to pass over this. Perhaps it should take further into account equality implications of a new medication with an easier means of administration and which allows populations who suffer from cardiovascular disease to be treated.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Question: Has all of the relevant evidence been taken into account?

Response: I think that the fact that you do not consider impact on quality of life for the segment of the population most impacted by migraine - in other words women - means that you have not taken all relevant evidence into account. Women suffer more pain conditions than men and this is another reason why we end up leaving the workforce - in addition to his causing serious family issues. Additionally we are further denied care as we get older - I am now 65 and my GP is pretty much refusing to provide anything for my symptoms (not just migraine) because of my age, just because of my age because I have no other complicating factors. This is especially difficult because despite many visits over many years various, and many, medical

professionals failed to diagnose my migraine and it was only as a result of a fellow migraineur watching me suffer an attack that this was identified when I was already 64. I am fortunate in that I have been able to access care privately and am on Ajovy, but this is not fully effective so I will be asking my specialist neurologist to add another medication - and following recent studies Rimegepant would be my first choice for this. Please do not sentence us to continuing pain, and especially as we get beyond 65 and are denied triptans and other pain reducers. We will have to resort to OTC medications, are you aware of the risks of long-term use of paracetamol, aspirin etc and do you take these into account in your deliberations? And just the suffering .... please think again.

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Response: I question the validity of attributing any sort of cost effectiveness to this - why not allow a 3-month trial per patient and, if the drug us found to be effective, allow that patient to continue to be prescribed it? Given that relief from migraine is not guaranteed for any drug for any one person this should enable targeted relief for those of us who suffer from severe chronic pain. How much value do you put on someone's 24x7 misery and the impact that has not only on them and their overall health and quality of life but everyone they come into contact with? My own life has improved significantly with Ajovy, and I hope to be able to reduce my pain (not just a headache by the way) further by trying another drug in combination with it.

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

Response: No - I do not find them to be sound. Please see my answers to the previous 2 questions.

Question: 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Response: Yes. One in 5 women have migraine and half of them are not even diagnosed and we are therefore untreated for our pain and other symptoms. Many of them have probably been misdiagnosed - for example as having sinus headaches. What is the cost to society of this, at least some of which must be contributing to the level of long-term sickness? And what is the cost to society? Additionally - older people are routinely denied treatment simply due to our age, and given we now live to perhaps age 85 on average this results in having to suffer 20 years of untreated pain. Please do not assume that migraine gets better with age - while it does for some people for others it does not or even gets worse. And here is a drug that could help, with minimal risks even to older people or those with cardiac

issues, and we don't even want to offer it to see if that individual's life might improve? This is not a morally acceptable approach.

Name	[redacted]
Organisation	N/A
Conflict	N/A

Comments on the ACD:

I wonder if any of the evaluation committee are migraine sufferers, like myself who have been trying different migraine treatments since 2019. I have tried at least 3 different oral medications which were not developed specifically for migraines, all of which were unsuccessful, but I had to stay on each of them for 3 months at a time. I also had to withdraw from each of them before I could start afresh. Now we are in 2023, and finally I reached the top if the queue to try Botox injections, which do not work either. I understand I may now, finally, be eligible to try one of the drugs which were actually developed specifically for migraine!!! People like me who cannot work, have a social life, or any quality of life due to chronic migraine, should be at least given a chance to try these drugs. Whatever hope, even slim, is worth having and at the moment, people like me have little. I feel the document did not allow for enough time to be given for this evaluation. Please give people like me a bit of a chance of a decent life.

Question: Has all of the relevant evidence been taken into account?

Response: No, I do not believe so.

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Response: No, I do not believe so

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

Response: No. Use for preventative and acute migraine should certainly be allowed on the NHS for people suffering from medication overuse headaches. Medication overuse headaches are bound to occur when triptans are needed on a frequent basis, and also painkillers, as the triptans do not always work. For people like me, this new drug would be a lifesaver. It would be the only safe alternative to triptans.

Question: 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Response: I believe that being a white female in her fifties means I am frequently discriminated against in favour of other genders, sexual

orientations and nationalities!!! If I was a transgender person I am sure that due to the current rabid political climate, I would be given the new drug!!!!

Name	[redacted]
Organisation	N/A
Conflict	N/A

Comments on the ACD:

I am affected by chronic migraine, and whilst triptans work for me I regularly experience medication overuse headache. This means I have no other acute treatment option to choose from when I am experiencing medication overuse migraines. This drug could help with this. This new treatment option is very much needed.

Unlike other acute treatments such as triptans, non-steroidal anti-inflammatory drugs (NSAIDs), and other painkillers, the gepants don't seem to cause rebound headache (medication overuse headache). This is a really important finding and highlights the importance of having this treatment option for medication overuse migraines. When I am experience medication overuse migraines I have to suffer through a full blown attacked to break the cycle which can last for hours and means I miss out of work and life.

Comment on section 1.3 (recommendations), "The company's evidence for people who have had 2 or more triptans that have not worked"

This does not consider the role of rimegepant in supporting those with medication overuse headaches.

Comment on section 3.1 (details of the condition), "he committee concluded that migraine is a debilitating condition that substantially affects both physical, social and psychological aspects of life and employment."

I agree with this statement

Comment on section 3.2 (treatment pathway), "he committee concluded that for acute treatment, at least 2 triptans should be tried before another treatment is considered."

this does not consider it's role in medication overuse migraines

Comment on section 3.3 (comparators), "Clinical experts agreed that after triptans there are no other treatment options available."

this lack of treatment options for acute use is concerning

Question: Has all of the relevant evidence been taken into account?

Response: It doesn't feel that the use for medication overuse migraines has been properly considered.

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

No. Rimegepant is an important opportunity to help patients like me with medication overuse migraines.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

This is an amazing drug and if triptans do not work it is another drug that can give someone with chronic migraine some hope of pain relief.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Question: Has all of the relevant evidence been taken into account?

Response: With the caveat that I am not an expert in your decision making processes or those of equivalent bodies globally, I would note very broadly that it seems sufficient evidence has been heard by your international counterparts to approve the use of Rimegepant in the US, UAE, Israel and indeed the whole EU now.

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Response: "I do not agree that this interpretation is reasonable when it comes to the use of Rimegepant for acute attacks, although I follow the logic when it comes to prevention. This is because the number and also crucially the diversity of medical options for prevention mean most patients have some option at present. However, for acute treatment, it's triptans or nothing. Rimegepant would change that, which is significant for patients for whom triptans are unsuitable. This is the clinical benefit in the cost benefit analysis which I do not see reflected in this interpretation of the evidence.

The range of treatment options for prevention is reasonably comprehensive, leaving out very few patients. However, if a person does not respond to triptans (a category with various options, but still one category of drug), there is really no other option. The same applies for people who have side effects from triptans or those chronic patients with no option on the 20 days/month ruled out by the risk of medication over use headache. For these people, who cannot use triptans at all or for some of their attacks, there is no other option. This is the argument for treating the case for

Rimegepant differently in preventative and acute use. I see that you are considering these questions separately - I'm very pleased you differentiate. I believe it is reasonable to interpret them differently too.

In terms of cost effectiveness, the cost would be lower with acute use than preventative use. In terms of effectiveness, for prevention, what Rimegepant offers is more choice. Whereas in acute use, it takes a significant group of patients from no treatment at all to some treatment. Going from nothing to something that works is the biggest difference possible. Expressed as a cost-benefit analysis, the argument is quite simply that it brings a benefit where there was none.

To mitigate the risk of inappropriate cost for benefit, or to target the benefit to these currently untreated (or undertreated for those at risk of MOH) group of patients, it would be reasonable to set criteria for their use as you have for preventative CGRP antagonists. It is on the basis of this clear parallel in interpretation and precedent in NICE decision making that I argue it would be a more reasonable interpretation to amend the at the very least the part of the initial decision referring to acute use.

I appreciate the opportunity to describe how my personal situation illustrates this logical argument in practice. Specifically, as a refractive patient for whom no triptans are effective. I have tried all the triptans. Eight or nine I believe. And under the care of my specialist neurologist at UCLH (Queen Square), have thoroughly and rigorously explored various combinations of triptan + antiemetic + painkiller + omeprazole, patiently for years, without success. (Actually, I'm not particularly patient, but I do do as I'm told). And of course any other possible actions that might reduce the length of an attack including endless migraine diary keeping and analysis, lifestyle measures for prevention and mindfulness, yoga, heat, cold and so on for acute attacks. And indeed I now have appropriate prevention (anti-CGRP injections - just amazing). We have done everything possible (including exploring the possibility of other conditions and treating the one other we found). Full differential diagnosis and medical MOT from head almost literally to toe. So, I am a sensible, committed patient under the care of doctors who are as good as they get. And yet, when I get a migraine attack all I can do is try to avoid triggers and wait. I am currently, today, on day 11 of an attack/period of rolling attacks. (And using dictation software to avoid even looking at this screen).

I do know quite a few others in patient forums in the same position. For many of us, there is no more entitlement to sick pay. This month, I will lose at least a third of my salary, maybe more if it goes on longer. (Consider, please, the crushing financial incentive - necessity for most of us - to work through illness, to return too soon, exacerbating migraine in short and long term, even to go to work when infectious with other illnesses - I don't because I am fortunate to live in a two income household, but if our kids' food, heating and home depended on it, believe me, we all would do things that we shouldn't for our health, our communities and our livelihoods). This level of absence from work easily triggers formal absence management

procedures. For me, having no acute treatment option means losing income and may mean well losing my job. Soon. Even at a Disability Confident Three-Tick employer like mine, which is as good as it gets. Pain, we can live with. Ditto vertigo, nausea, weird vision and balance issues. Losing a job or not paying bills, we can't. Our kids and other dependents can't either. For the best of people, in the best of situations, untreated migraine can make life impossible.

In terms of clinical effectiveness, it's reasonable to interpret ""good enough"" for that one drug in terms of the part it plays in a wider picture of treatment options. With migraine, doctors and researchers are always telling us that 50% reduction in severity, duration or frequency in 50% of patients is considered a very good result because it is, in the context of the other migraine drugs available. In this field it really is good, even if patients might think of it as just a coin toss. But the response to that coin landing the wrong way is inevitably ""it's ok, we still have options"". So, for prevention, a given drug with an objectively low-ish efficacy result is a patchy safety net, but at least we have several other patchy safety nets beneath it. It's very rare to fall through every single one. (I nearly did, but when I'd tried every class of drug, something like half a dozen or more over a couple of years, you approved anti-CGRP preventers and I was caught in that one last imperfect but wonderfully life changing safety net. I went back to work and started being a normal mum again. Now, I don't usually need a quiet house and my kids are allowed to listen to music and be a bit raucous when they play like kids should be and I'm reliably well enough in the evenings to take my boy to footy with his friends. So, thank you for Erenumab, thank you.)

So, we know the efficacy of all sorts of migraine drugs are limited - they're patchy safety nets with different sized holes that we know various groups of patients fall through. Currently, the approach to prevention is to layer enough of the best we have, so that one way or another most people get caught at some point. It's not ideal and I'm sure you'd all design a better system with a magic wand, as would the doctors and of course the patients. But this system of layered patchy nets is simply what we can do right now with the science as it stands and one way or another, for prevention, it pretty much works.

But for acute treatments, it's a different picture. Triptans are just one patchy safety net. I'm not arguing that Gepants' efficacy makes them an amazing safety net. Of course Rimegepant is another patchy safety net. I'm arguing that when interpreting the cost benefit of this drug, please consider for those of us falling through one of the three big holes in the triptan net (ineffectiveness, intolerance, medication over use headache), putting another safety net in there.

I would like to conclude that a reasonable interpretation of the evidence would consider acute treatment with a CGRP antagonist (Rimegepant) on an equivalent basis to preventative treatment with a CGRP antagonist. As such, it would be reasonable to interpret the clinical and cost effectiveness

for the use, specifically, in patients for whom triptans are unsuitable. Thank you."

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

"Relevant NHS values: Everyone counts, improving lives, compassion.

Relevant NHS Constitution rights:
- ""You have the right to expect local decisions on funding of other drugs and treatments to be made rationally following a proper consideration of the evidence."" (With thanks, this is what is happening here. For the argument considering whether there are gaps in the 'rational and proper' requirement, please see above)

""You have the right to receive care and treatment that is appropriate to you, meets your needs and reflects your preferences."" (First two of the three clauses here, specifically)

NHS principles: Comprehensive treatment; best value for tax payers money (rimegepant vs sick pay/benefits, for example)."

Question: 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Response: I'm unsure how this is determined in practice although migraine affects women more than men and, due to the hormonal element of the condition, also changes and often requires new management with passing through the life stages associated with ageing (puberty; fertile years including menstruation, pregnancy and breastfeeding; menopause). Chronic migraine often meets the Equality Act definition of a disability. Therefore, it is important to consider the decision with due care to gender and age, pregnancy, maternity and disability.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Question: Has all of the relevant evidence been taken into account?

Response: "Accute treatment in patients who are unable to take triptains, such as those with cardio vascular decease has not been taken into account. There is little here about addressing medication overuse headaches which can in themselves cause misery and lead to more frequent headaches or migraines."

Name	[redacted]
Organisation	Replying as a private citizen via link from The Migraine Trust
Conflict	N/A
Comments on the ACD:	

Question: Has all of the relevant evidence been taken into account?

Response: I am commenting as a mother of a migraine sufferer aged 18 years old and in her first year of university, who struggles with severe migraine attacks which has significantly impacted her education to date and continues to do so. NICE should speak directly to migraine sufferers - the existing medication does not work for a vast majority (including my daughter) the side-effects are damaging. So question how this evidence has been reviewed.

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Response: Can not comment on this. But has this been viewed against the costs to health service, education and work with lost days to migraine.

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

Response: Can not comment on this. But would like details on how NICE has made this consultation.

Question: 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Response: Please NICE review your decision on the availability of this new medication for migraine. This is an invisible long-term condition. There have been no advances in medication available in the UK. This is the medication that so many migraine sufferers have been waiting for and could make a massive different to quality of life (ability to live a productive life). Thank you.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

This is a devastating decision for people living with migraine. I have chronic migraine and have not yet been able to access an effective preventative or acute treatment. Migraine affects my physical and mental health

dramatically. This is exacerbated by medication overuse headache, which is a constant threat and further limits my treatment options. My 9 year old son is already experiencing frequent migraines and I feel very fearful for his future. New treatment options are desperately needed for people with migraine, particularly those who cannot take existing medications or for whom existing medications are not effective. I urge NICE to reconsider this decision.

Question: 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Response: Given that women are more likely to experience migraine, and that women are often particularly affected by migraine during the perimenopause, this is decision is likely to have a significant impact on the protected characteristics both age and gender.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

I have just read that Nice has refused to allow the use of Rimegepant in the UK. I felt very distressed at this news. I have Medication overuse headaches. This means that I can only use 6 triptans a month. If I get a migraine after I have used my monthly allowance it will last approximately 3 days, during which time I am unable to do anything, every movement is extremely painful, sound hurts, wearing my glasses hurts, looking at tv or any other screen is painful. I live in fear of these occurrences.
In addition, I know two people who are unable to use triptans because of other conditions and medications. Their lives are put on hold during bouts of migraine. There must be many thousands of people with similar experiences to myself and my two friends. This drug was going to save us all from these days of extreme pain.
It seems from your document that the main reason for refusing us the use of Rimegepant is because of the areas it has not been tested in. Surely it would be obvious to ask for the drug to be tested in these areas before making this decision.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

I suffer from chronic migraine with aura but can't take medication as I an sensitive to triptans and suffer from medication overuse headaches.

Gepants don't seem to cause rebound headache so would be a life saver for me and around a third of fellow migraine sufferers.

NICE's decision to reject this treatment will also have a devasting impact on people with cardiovascular disease, as unlike another class of acute migraine medication, the triptans, it does not constrict or tighten blood vessels.

Please reconsider your decision.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

I suffer from chronic migraine and have been under the care of a consultant. I have taken sumatriptan for 28 years and frovatriptan for two years. I have been on the fremanezumab injection for nine months. For the first six months it worked very well but has now ceased to work and I am back to having to take sumatriptan every day. I have tried taking nothing for two months and out of 61 days I was only free of pain for 26 - I cannot live like that. I was in bed, in awful pain without relief, vomiting, unable to eat or sleep. My husband became my carer. Even the odd day when the migraine left me I felt hung over and unable to do my normal activities. I have now tried everything and my consultant will only allow me to have eight triptans a month. This means all I have is pain - life becomes unbearable, unliveable - unable to have a holiday, visit family and friends, book or arrange an outing. Pain, dark room, sickness day after day, hour after hour without relief. I do not have a heart condition. Surely our health service is there to help people who suffer like this. If there is something which could help then we should be able to have it - it should not only be available to those who can afford it - for those who can afford to live. I am 76 and have worked and paid taxes all my life.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Question: Has all of the relevant evidence been taken into account?

Response: No: the ACD states 'Rimegepant might also reduce monthly migraine days. But there is a lack of comparative long-term evidence to support this.', so you acknowledge that the required evidence has not been taken into account.

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Response: No: the ACD states ‘Migraine can adversely affect quality of life, affecting people's ability to do their usual activities, including work’; there is no mention of the actual cost to the country of a person being on benefits probably for life, or of the cost of continuing to supply the patient with ineffective medication, that cost will definitely outweigh the cost of the treatment, and that is not mentioned in the review.
No, as GPs/Neurologists usually follow guidelines of try this, then when that fails, try the next on the list, without any reference to a persons genetic makeup; a massive amount of financial waste is incurred, along with a loss of quality of life for the patient.

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

Response: No: there is no mention that alternatives e.g. triptans can have negative health outcomes e.g. for people likely to suffer heart disease or strokes.
No: there has been no widescale mapping between people’s genetics and which medication works; if that was conducted far fewer prescriptions would be issued for medication that was statistically be likely to fail.
No: there is no mention of 'suicide headaches', caused due to lack of treatment.

Question: 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Response: Yes: Gender is not mentioned in the ‘Appraisal consultation document’, the prevalence of migraine varies by gender.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

As there are so few effective treatments for both prevention and acute treatment of chronic migraines, it is disappointing that further trials can’t be performed to determine the true effectiveness of this medication. As migraine is so debilitating it is worth weighing up effective treatments vs time lost at work or reduced productivity caused by migraines.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

I have been a sufferer of chronic daily migraine since I was 13, I am now 47. I have tried Botox, ajovy, nerve blocks, cranial nerve blocks, every

medication you can think of but nothing works. I had high hopes for this medication as I literally suffer every single day all day and cannot remember a day where I have not had a headfree day. It is depressing and debilitating and I want some type of life back. Surely there must be a criteria for people like me who have tried everything that can benefit from this medication? I feel my quality of life has been ruined and I cannot work. Please help me.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

I was very hopeful that Rimegepant could have been an option for me on the NHS due to suffering from debilitating daily migraines. Migraine sufferers need every help they can get including new medications to be available for them. Please make this available to us.

Question: Has all of the relevant evidence been taken into account?

Response: Yes

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Question: Has all of the relevant evidence been taken into account?

Response: No, it's a safe alternative to triptans
NICE’s decision to reject this treatment will also have a devastating impact on people with cardiovascular disease, as unlike another class of acute migraine medication, the triptans, it does not constrict or tighten blood vessels. This makes it a safe alternative to triptans in treating migraine acutely.

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

Response: No, it's a safe alternative to triptans
NICE’s decision to reject this treatment will also have a devasting impact on people with cardiovascular disease, as unlike another class of acute migraine medication, the triptans, it does not constrict or tighten blood vessels. This makes it a safe alternative to triptans in treating migraine acutely

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

As a migraine sufferer for over 30 years, gepant medications are the only medications that have given me any relief. I recently moved to the UK from the United States where these medications have been available for years. Now that I am in the UK, I've experienced intense fear and anguish because I have zero access to medication that allows me to function and which saves me from excruciating pain. I have found the access to treatment in the UK appalling (be it private or NHS) and the lack of treatment options available are truly frightening. Even basic care is so hard to obtain, any further lines of treatment are nearly impossible to access. This decision is incredibly disappointing- I've been following the status of this review since before my arrival in the country. I'm truly left with nothing that eases my pain and steals my time - this condition is so debilitating and people truly seem to dismiss the very real impact it has on our lives. I truly hope you'll consider the impact this medicine has on patients and not just the cost, which I agree is sky high. This decision just leaves me in a country with zero hope for relief on the horizon and it truly scares me.

Name	[redacted]
Organisation	N/A
Conflict	N/A

Comments on the ACD:

Question: Has all of the relevant evidence been taken into account?
Response: I have chronic migraine, which if i told my doctor, they would say it was medication overuse headache even tho it has a clear hormonal pattern. from day before period to 2-4 days after ovulation I get migraines daily, some worse than others. The bad ones always occur within 2 days of each other on the same day each month at times of hormonal change ie day before period, day 2-3, day 8-9, day 10-12, day 14-16, day 22-24. I also get diorrhea on the same days/pattern. There are no treatments that leave me pain free, i struggle through my job most days with brain fog and have given up on socializing much because it drains me of energy which makes my migraines worse. Life is really really hard and noone understands because non migrainers think migraine is just a headache. A migraine is nerve pain - one of the worst and most untreatable pains. I know this because I recently had a herniated disc in my neck and had nerve pain for 3 months. Because of this I was able to take 60mg of codeine every morning and that largely blocked my migraines except for a twinge in the afternoons sometimes when I would take my lower dose tablets. So I had a lovely migraine free and menstrual cramp free 3 months. Then when I stopped the codeine (very easily) over a week, my migraines returned with a vengeance. Now the herniated disc pain in the morning at its worse wasn't that much worse than my bad migraines which I've grown used to putting up with because preventative treatments don't work and have nasty side effects and cause other disorders. The National Migraine Clinic doesn't recommend any of the current migraine preventative treatments because they don't work!! I can confirm this - my migraines came back when I was still taking amyltryptyline for the herniated disc pain. It only works at higher doses and at those doses you are too drowsy to work, it causes depression and other

nasty side effects. I think it also affected my kidneys when I was taking it. No doctors I've spoken to think it's a good drug or that I should take it for pain. I think they've stopped prescribing it so much for pain now. Beta blockers are the other preventative and they cause insomnia, so I'd never take them. Insomnia causes early death due to its effects on the body, they now know . There is no point taking preventative drugs for migraine as none of them work and the side effects are worse than the pain. You have no decent migraine drugs. Triptans and painkillers cause rebound headaches and are dangerous to take long term. But I have no choice as I have to work full time so I ignore the doctors advise and take painkillers regularly because it's the only way I can work and therefore survive. It will shorten my life but at least I eliminate some of my pain.

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Response: I know the NHS has to make difficult decisions but they should research alternative drugs for migraine if this one is too expensive. I would suggest investigating mineral deficiencies due to undiagnosed celiac disease which is about 60% of celiac patients and also melatonin which shows promise for migraines in research. NHS could trial this very easily and I would like to take melatonin but for some reason it's been banned because it's a natural substance that works! I've taken it in the past when you could still buy it on the internet with no side effects though I notice the NHS prescribe double the dose for some reason? Always prescribing drugs at too high doses is what gives patients side effects!! I still have some left though it is out of date but may try it as got no other option from the doctor and wouldn't even go speak to them about my migraines as they have no solutions.

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

Response: I don't think so when you have no other drugs available that don't do harm to the patient!

Question: 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Response: No but chronic migraine is a disability and you currently have no solutions. I lost my last job due to being discriminated against when I asked for a quiet room to work when I had migraines. My boss replied well if your migraines are that bad, maybe you should leave? So, I did!

Name	[redacted]
Organisation	N/A
Conflict	N/A

Comments on the ACD:
I have monthly injections of Fremanezumab which have reduced my migraines. When I do get an attack I use Frovatriptan but this only delays the migraine and it re-appears a day or two later. This results in taking more triptans to get rid of it again. I believe rimegepant doesn't cause rebound headaches, if so, then this would reduce the number of triptans that I would need to take, thus saving money on triptans and a better quality of life for me. For those who can't take triptans, such as those with cardiovascular conditions then rimegepant provides much needed relief, as standard painkillers are often ineffective for migraine. I would struggle without Tripans, although they cause rebound headache issues they are the only drug that stops the migraine. I understand that they shouldn't be taken by those over 65. I am now 65 and so need an effective alternative, I was hoping that rimegepant would be that alternative so I'm disappointed with the decision not to recommend them.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	
Question: Has all of the relevant evidence been taken into account? Response: Need to consider patients who are not allowed access to CGRP medication because they may be having medication overuse headache. It is also an alternative for people with heart conditions.	

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	
I am truly disappointed to hear that this migraine treatment has been rejected. I am a chronic migraine sufferer and currently use botix but this is not an effective treatment in the slightest. I was using ajovy but the NHS has stopped me from using this medication. It was effective for me but not seemed effective enough as I still get migraines, mainly round menstruation. These gepant medication would be a game changer for me as I rely heavily on triptans - zomiltriptan but I need to limit my use as I get rebound headaches. Zomiltriptan is also by no means perfect as the side effects are not pleasant, eg brain fog, neck pain, sore throat, upset tummy, needing to urinate more frequently.	

I would love to have an acute medication with fewer side effects.

No one seems to realise how debilitating migraines are. But without effective treatment I can't work.

The medication might be expensive but it would allow me to be economically active.

For so many years people with migraine have had to put up with treatments that are designed for other illnesses, like antidepressants and epilepsy.

Then when pharmaceuticals create a bespoke medication for migraine it doesn't get approved? It's just not fair.

You gave to understand that we need prophylactic medications that work, like the CGRPs but we also need acute medications that work, like this new class of medications.

Please stop treating migraine as if it is trivial or just a headache. Please rethink this decision.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Can I please urge you to support this migraine treatment.
Migraine is a disabling illness that, when at its worst, is deeply destructive to individuals and their families. Any drug that can support any one person in any way must be viewed as a positive and supported. Some people will try every other treatment available only to find that they don’t work for them for whatever reason. This drug may be their final chance and it would be so desperately sad if that was taken away from them.
Thank you for your consideration
From a lifelong migraine sufferer aged 61.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

I am very disappointed that Nice has decided at this stage to not accept Rimegepant. I have been suffering from migraines since a child and have been taking Triptans for the past 20 years and I am concerned with the long term effects however to date I have been unable to find any alternative treatment. I also suffer medication overuse from the triptans and therefore always looking for an alternative medication. I do hope you will reconsider your decision.
Many thanks

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

I am a 31 year old ex-teacher and have lost much of my life to migraines. Due to cardiovascular risks both present and likely due to hereditary conditions, I cannot take triptans.

Like countless other migraine sufferers, I have other health problems. I have multiple haemangiomas throughout my skeleton that kill the bone and cause me great daily pain in conjunction to my migraines. This, along with medication overuse headache, meant that Rimegepant was one of my final hopes for a treatment that didn't exacerbate or debilitate some other part of my health.

I also have cognitive problems due to a kind of TBI and felt Rimegepant might preserve what little cognitive functioning I have left and belay my suicidal ideation.

This provisional verdict is thoroughly incompassionate and antithetical to the very spirit of NICE and has forsaken a great many people. This medication would save the lives of so many. Without it, they will be devoid of hope and people will die, either due to contraindications, side effects or suicide.

I implore the committee members to meet face to face with acute migraine sufferers and to reevaluate its viability.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

I think that NICE should go ahead with approving this medication as it is the only one that does not give rebound headache and the only thing that works for those that cannot take Triptans or have tried the others.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Comment on section 1.3 (recommendations), “Rimegepant might also reduce monthly migraine days. But there is a lack of comparative long-term evidence to support this.”

without its use more generally, how can the data be collated to assess the cost effectiveness?

Comment on section 1.3 (recommendations):

Owing to a mini stroke I have had to stop the triptan I was successfully able to use to manage my migraines.
I have also had to stop HRT and the combination has resulted in more migraines and my earlier than desired retirement from nursing.
These new drugs were a much anticipated means of managing migraines. Leaving me and others suffering migraines that were previously managed. For me it has resulted in days spent in a darkened room. Misery and unproductivity.

Comment on section 1.3 (recommendations), "Because of the clinical uncertainty, the cost-effectiveness estimates are uncertain. Also, the most likely estimates are above what NICE normally considers to be an acceptable use of NHS resources. So rimegepant is not recommended for acute treatment.":

In my case and others the NHS resources have been diminished because of early retirement or leaving the nursing profession due to depleted health.

Comment on section 1.3 (recommendations), "Standard treatment for preventing migraine after 3 or more treatments includes erenumab, fremanezumab or galcanezumab.":

I have tried monoclonal antibodies with great success in reducing pain. However, I had an adverse reaction to them after a few months, and had to stop using them.

Question: Has all of the relevant evidence been taken into account?

Response: Not enough data of usage to really establish the benefits to those with conditions that cannot use triptans currently available, or other treatments. How many people are in this category like myself, left unsupported, unable to be employed and suffering?

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Response: I do not believe there is enough data.

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

Response: No

Question: 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 race, gender, disability,

religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Response: I would have liked to see evidence for woman and the drug used with a subset of women with menopausal symptoms and migraines who were unable to take the current treatments.

Name	[redacted]
Organisation	N/A
Conflict	N/A

Comments on the ACD:

I have had migraine since I was 5. It became chronic at puberty.I was given Cafergot suppositries at first and was then told these were too dangerous as they constricted blood vessels all over the body. When the Triptans came on the market in the '80's I first had Imigran in injection form and then have used the triptans ever since for the acute attack, Naramig being the most effective.
I attended the Princess Margaret migraine clinic for 10years and then The National Neurological Hospital for another 10 years. During that time I tried every available preventative and acute treatment. The triptans remain the only drug that works for the acute attack.
During an attack I suffer severe pain on one side of my head as well as constant vomiting and many other symptoms. If an attack is not treated with a triptan in time I can be in bed for 3 days with these symptoms.
My migraines are very severe and frequent. I can have anything from 6 -15 migraine days a month. In the past I have had medication overuse headache because I am only supposed to take 6 naramig per month as more causes rebound headaches, but have been desperate to take the pain away. I do limit myself to 6 naramig a month now, but that means I can't treat all my attacks which leads to me spending many days unable to get out of bed.
The level of migraine I have had over the years caused my marriage to break up and meant I had to take early retirement from my job as a teacher. During this time I did overuse the medication just to keep going.
I am now 66 almost 67 and still trying to cope with these debilitating migraines. Naramig is not suitable for women who have been through the menopause or for people over 65 but I have no other choice.
Eight months ago I started to get very strong and frequent ectopic beats. I have had an echocardiogram and a myocardial perf stress and rest scan. I don't have the results yet but I strongly suspect that I will be told Naramig isn't suitable for me. I believe Naramig can even cause heart problems in some cases. To put it bluntly if I can't take naramig my life won't be worth living.
For myself, having had periods of medication overuse and now being 66 with a possible heart problem, Rimegepant would provide a much safer alternative for me as it doesn't constrict blood vessels or cause medication overuse problems.

Question: Has all of the relevant evidence been taken into account?

Response: I don't think enough attention has been given to those people who cannot carry on taking a triptan or who are suffering medication overuse.

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Response: No. The clinical studies are promising. As to the cost,surely it is worth that to help sufferers lead normal lives and not have to give up work.Rimegepant would save older people suffering cardio-vascular problems.

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

Response: No they are not sound as chronic migraine sufferers and older people are overlooked.

Question: 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Response: The recommendations discriminate against chronic migraine sufferers (a very debilitating disability), women(who have been through the menopause) and older migraine sufferers for whom the current available medication isn't safe.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Comment on section 1 (recommendation):

The decision not to approve this drug is devastating. Triptans work but because of the rebound risk migraine sufferers are only allowed 2 triptans a week. I have a migraine every day and could take a triptan every day but instead have to cope with the pain for 5 days every week. The gepants do not have this rebound effect. No one expects an unlimited supply of this drug but even one or 2 extra pain free days a week would be a bonus. This could change lives.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Question: Has all of the relevant evidence been taken into account?

Response: No account has been taken of the possible damage by paracetamol to bodies of those who are unable to take triptans but would have been helped by taking Rimegepant. see https://ard.bmj.com/content/75/3/552 ; nor by aspirin which there are also increasing worries about at the doses needed to control headache pain.

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Response: I do not think you have given enough weight to the cost of not supplying Rimegepant to the patients who need it; both the cost physically of having the migraines, nor the ill effects of the alternative drugs, especially rebound headaches. As an 80 year old who has had severe migraines since I was 8 (with bilious attacks from infancy) I am aware of how the constant migraines resulted in far less exercise than I would have been able to have taken had the pain been controlled. I also got rebound headaches from codeine and paracetamol for many years when their existence was not understood. As I understand it, Rimegepant has not been shown to cause rebound headaches. The knock on effects of having migraines during the reproductive years in the mother's ability to respond to her child/ren means that even a small improvement in the number and severity and total hours of pain would be beneficial for the children.

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

Response: Bearing in mind what I have written in the previous answers, I do not think the right balance has been obtained, bearing in mind the huge cost to the NHS of people with severe headaches, and the cost to the economy from people being unable to work. Even a small advantage over the placebo would have great benefits economically and socially, and that has not been taken into account.

Question: 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Response: Yes, on gender, because more females, especially of reproductive age, than males get migraines, so more women will miss out if Rimegepant is not recommended for use.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Question: Has all of the relevant evidence been taken into account?

Response: No - Rigemapant has only been tested with "indirect" comparisons to erenumab, fremanezumab and galcanezumab. It should be trialled with DIRECT comparisons.

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Response: No, due to both the point I mention in the first question above, as well as the fact that access to treatments for chronic migraine is most definitely not easy to access. The referral process along with the various waiting lists involved before hospital based preventative treatments can be approved, prescribed and delivered, is extremely lengthy - as well as it being a postcode lottery as to who can in fact access those treatments. Therefore a mid-way drug such as Rigemapant, after all other acute meds have been unsuccessful, would be a welcome addition for many chronic migraine sufferers who either have been refused CGRP's and botox, or for whom they are not well tolerated. As well as it being a useful alternative for patients for whom other first-line preventatives have proved ineffective, such as amityryptaline, beta blockers, propanolol and topiramate. Thousands of employment hours are lost every year due to poorly controlled migraine attacks, with many sufferers, such as myself, having to give up work even though there is no 'disability' allowance for the condition, leading to financial hardship for many. Retaining migraine sufferers in the workplace whose episodes are well managed would save many thousands of pounds, which far outweighs the so-called lack of cost effectiveness were Rigemepant to be approved and prescribed.

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

Response: No - for the reasons which I mention above. In addition to which, the range of triptans are wholly ineffective for many migraine sufferers, or in many cases the drug is initially effective but goes on to become ineffective over time. Triptans are not suitable for those with cardiovascular conditions, and even if a patient does not currently suffer with such conditions, it is highly likely that with advancing age they could become a feature, in which case triptans cannot be used - whereas Rigemepant would be an ideal alternative to switch over to.

Question: 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Response: I don't believe so

Name	[redacted]

Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Question: Has all of the relevant evidence been taken into account?

Response: Yes

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Response: No

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

Response: No

Question: 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Response: NO

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Question: 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Response: As a 67 year old who has had migraine for 50 years I need an alternative to triptans which are contraindicated for persons over 60. I need an alternative like rimangepant and am very concerned that this is not an option. It is prescribed in the USA. Why not here? Surely a heart attack or stoke would cost the NHS more if I carry on taking triptans.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

Response: No. It is incorrect to assume that a triptan or other medication is only effective if there is relief after 2 hours. I have used triptans successfully for over 20 years and they take 4 hours to take effect. They then allow me to resume normal life for 10 hours. Without preventative medication of propranolol combined with acute use of triptans for breakthrough attacks, I would have been unable to hold down a job for the last 20 years or look after my children and have normal family life. Please don't evaluate effectiveness on relief within 2 hours as the stomach is slow to absorb medication during migraine, which is a well known fact.
The other comment that triptans don't work because they are not being taken properly is insulting to intelligence and makes me question whether the people reviewing the drug understand migraine at all. I have suffered medication overuse head ache and dread it occurring again. Please consider anything that will assist sufferers, however expensive. Those of us who have had our lives ruined by 40 years of disability and 40 years of dreading the next attack are fed up of being told that medication does not work because we are doing something wrong. This sounds unscientific to me and reminds me of how I was spoken to by the medical profession 40 years ago.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

This is devastating news. Migraine disease has been ignored & dismissed for so long. Around one in seven people get migraine. Over a billion people worldwide get migraine, and over 10 million in the UK.
Migraine is the third most common disease in the world (behind dental caries and tension-type headache). I am currently living on triptans & live in fear of medication overuse headache. This drug had given me hope. Now you've taken that hope away."

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Gepants have the side effects of placebos making them a very safe option for both the acute treatment and prevention of migraines. Triptans which are currently the most commonly prescribed migraine medication in England, do not have a preventative use and are not as safe, particularly for people with cardiovascular conditions. Further, Triptans simply don't work for many migraine sufferers. Gepants offer hope to those people for whom it is not safe to take Triptans or for whom Triptans don't work. Not authorising Rimegepant suggests that NICE do not take seriously migraine which is much more than a headache, it is a disabling neurological disease causing excruciating pain as well as other symptoms. Further, with migraine affecting 3 times more women than men, the refusal to authorise this

treatment could amount to unlawful discrimination under the Equality Act 2010.

Name	[redacted]
Organisation	N/A
Conflict	N/A

Comments on the ACD:

Comment on section 1.3 (recommendations):

The impact on patients unable to tolerate anti-cgrp-mAb is insufficiently considered - for these patients rimegepant is most likely their only remaining clinical option.

Personally, I cannot tolerate triptans (which are also ineffective) and have severe side effects from continuous anti-CGRP-mAb treatment, despite having good clinical effect of the treatment. The more flexible dosing options of rimegepant could allow me to continue to benefit from anti-cgrp treatment whilst avoiding side effects.

Comment on section 3.1 (details of the condition):

This definition of aura is simplistic. Discussing migraine disease in terms of impact on brain function and neurobiology in this guidance is important to increase physicians recognition of the condition as a neurological brain disorder. Migraine disease has a broad and variable range of symptoms and is not simply a headache disorder with a few textbook additional symptoms. A broader list of aura symptoms, clearly indicated as not exhaustive, and relation of these to brain function aberration (e.g. cortical spreading depression) would be an improvement.

Question: Has all of the relevant evidence been taken into account?

Response: Oral cgrp inhibitors such as gepants could be useful in patients unable to tolerate anti-GCRP-mAB due to side effects. Rimegepant could provide greater flexibility in frequency of dosing compared with continuous dosing of mAb (e.g. use for only most disabling attacks, with concurrent reduction in side effects).
The amount of patients impacted by intolerable side effects of anti-CGRP-mAb is not adequately analysed - whilst direct reporting is uncommon, this could be indirectly studied by determining the number of mAb users subsequently prescribed medications associated with anecdotallly recognised side effects (e.g. omeprezole, laxatives, melatonin, anti-anxiety/depression medications etc), as well as local level data on anti-CGRP-mAb cessation, type switches etc. Without this evidence the supposition that anti-cgrp-mAb are able to offer equivalent benefits at lower cost is not justified, as the proportion of patients unable to tolerate anti-CGRP- mAb treatments is not known.

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Response: "Oral cgrp inhibitors such as gepants could be useful in patients unable to tolerate anti-GCRP-mAB due to side effects. Rimegepant could provide greater flexibility in frequency of dosing compared with continuous dosing of mAb (e.g. use for only most disabling attacks, with concurrent reduction in side effects).
The amount of patients impacted by intolerable side effects of anti-CGRP-mAb is not adequately analysed - whilst direct reporting is uncommon, this could be indirectly studied by determining the number of mAb users subsequently prescribed medications assosciated with anecdotally recognised side effects (e.g omeprezole, laxatives, melatonin, anti-anxiety/depression medications etc), as well as local level data on anti-CGRP-mAb cessation, type switches etc. Without this evidence the supposition that anti-cgrp-mAb are able to offer equivalent benefits at lower cost is not justified, as the proportion of patients unable to tolerate anti-CGRP- mAb treatments is not known."

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

Response: Oral cgrp inhibitors such as gepants could be useful in patients unable to tolerate anti-GCRP-mAB due to side effects. Rimegepant could provide greater flexibility in frequency of dosing compared with continuous dosing of mAb (e.g. use for only most disabling attacks, with concurrent reduction in side effects).
The amount of patients impacted by intolerable side effects of anti-CGRP-mAb is not adequately analysed - whilst direct reporting is uncommon, this could be indirectly studied by determining the number of mAb users subsequently prescribed medications assosciated with anecdotallly recognised side effects (e.g omeprezole, laxatives, melatonin, anti-anxiety/depression medications etc), as well as local level data on anti-CGRP-mAb cessation, type switches etc. Without this evidence the supposition that anti-cgrp-mAb are able to offer equivalent benefits at lower cost is not justified, as the proportion of patients unable to tolerate anti-CGRP- mAb treatments is not known.

Question: 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Response: The relatively flexible dosing options of rimegepant compared to anti-cgrp-mAb may give pregnant people access to this type of treatment which they would otherwise not have due to gestational/maternal safety considerations of continuous dosing.

Name	[redacted]

Organisation	N/A
Conflict	N/A
Comments on the ACD:	
I suffer status Migrainous lasting 6 weeks in pain level 10 Migraine patients only have access to 10 days a month of pain medication due to headache overuse These new gepant medications will be life changing for me and my chronic pain When I suffer these long extreme bouts I become suicidal and have to be watched by a family member I just want to die than suffer the pain I'm in not knowing when it will stop Please consider these medications for patients suffering status migrainous that go beyond the 10 day a month	
Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	
I believe that it's important to make Rimegepant available on the NHS in certain cases. For example: chronic migraineurs who have suspected Medication Overuse Headache must cease use of analgesics and triptans for at least one month, This can cause a great deal of suffering (I speak from personal experience) resulting in the loss of days worked and affecting health and wellbeing. Offering Rimegepant as an alternative during this period may provide relief (since Rimegepant has not been shown to lead to MOH). Additionally, monoclonal CGRP inhibitors may not be tolerated in all patients - site reactions have been observed in some, and some are needle-phobic. Given the dearth of migraine-specific treatments (most preventatives having been developed for other conditions) and the disabling effect that migraines can have, I believe that it is important to make Rimegepant (and, for that matter, Lasmiditan) prescribable by specialists to those unable to afford private prescriptions - at least on a short-term basis.	
Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	
Migraine medication for those who suffer acutely is sorely lacking in the NHS. Those medications which do exist cause a whole host of side effects and rebound headaches- it's a constant cycle. New medication should be assessed and side effects weighted over the quality of life it can give a migraine sufferer as it is a truly debilitating condition	
Name	[redacted]
Organisation	N/A
Conflict	N/A

Comments on the ACD:

Question: Has all of the relevant evidence been taken into account?

Response: Lack of options for migraine that doesn't respond to triptans but isn't considered chronic. I have one severe migraine lasting four days every other month, along with milder migraines across the month. My migraines aren't considered chronic, limiting the preventative treatments I can access (eg botox injections) but triptans are no longer effective, eventually just causing medication overuse headache. Being in severe pain, with vomiting and being unable to leave bed for four days has a significant effect on my relationships, mental health, career and ability to live independently yet little help is available. The other CGRP drugs (erenumab, fremanezumab or galcanezumab.) are also out of my reach. It has taken 11 years of this migraine pattern to even be referred to a neurologist. The report mentions that access to specialist migraine support is often limited and I would obviously agree and suggest more options need to be available via GPs.

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Response: I have suffered this severely or worse for 11 years now. Surely £40 every other month isn't too much money for me to regain my life and freedom. My loss of income is significantly more than this from taking around 26 migraine related days of absence a year. Not to mention my inability to contribute to my work or seek other employment opportunities.

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

Response: No, refer to previous statements

Question: 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Response: "Potentially. Migraines overwhelmingly effect women and menstrual migraine tends to be more severe and less responsive to treatment (1, 3). More than half of women notice a link between their migraines and their menstrual cycle (2). Menstrual migraines can only effect people who were born as female and more treatment options need to be available for the menstrual migraine with other migraines pattern: severe monthly migraine lasting a few days, often accompanied by other milder migraines. These types of migraines are susceptible to medication overuse which Triptans are very bad for (3). Providing a medication which doesn't carry this risk for women with menstrual migraine could help prevent the development of medication overuse headache, reduce the need for decades of costly treatments and give women their life back.

(1) - https://migrainetrust.org/understand-migraine/types-of-migraine/menstrual-migraine/
(2) - https://www.nhs.uk/conditions/hormone-headaches/
(3) - Approaching the appropriate pharmacotherapy of menstrual migraine - Paolo Martelletti & Martina Guglielmetti - https://www.tandfonline.com/doi/full/10.1080/14737175.2020.1693265"

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

As a woman who has cardiovascular disease and who has had severe migraine since age 14 I am horrified to hear we are to be denied this new treatment. I used to get relief from triptans but these are now sadly contraindicated. I believe there is ample evidence from the USA that this treatment is effective and safe.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

So disappointed that Rimegepant is not recommended. I take triptans which are quite successful for me but at the age of 76 and having suffered from medication over use headaches and concerns about cardiovascular disease, I would have welcomed an alternative.

Considering the years of migraine knowledge and the number of sufferers, I find it strange that this is only the second medication to have been produced specifically for migraines. If Rimegepant was recommended it would help to save many lost hours and relieve the agonising suffering of many migraineurs.

Thank you.

Name	[redacted]
Organisation	Medicines optimisation team, Centre for Guidelines, NICE
Conflict	N/A
Comments on the ACD:	

Comment on section 1.3 (recommendations), "Why the committee made these recommendations":

See comments made on selected text in the why the committee made these recommendations section.

Comment on section 1.3 (recommendations), "Rimegepant might also reduce monthly migraine days. But there is a lack of comparative long-term evidence to support this.":

Under why the committee made these recommendations acute treatment section, last 2 sentences of second paragraph:
These statements are confusing as they are currently written. Can they be rewritten so that it is clear what you mean. That is, that you mean rimegepant when used for acute treatment might also reduce monthly migraine days but there is a lack of comparative long-term evidence to support this. Otherwise, it could look like the statements are referring to rimegepant use for preventative treatment.

Comment on section 1.3 (recommendations), "Standard treatment for preventing migraine after 3 or more treatments includes erenumab, fremanezumab or galcanezumab.":

Under why the committee have made these recommendations preventing migraine section, first sentence:
For clarity, can this say '.....for preventing migraine after 3 or more treatments have not worked....'

Comment on section 1.3 (recommendations), "The cost-effectiveness estimates suggest that rimegepant costs more and less effective than erenumab, fremanezumab and galcanezumab.":

Under why the committee have made these recommendations preventing migraine section:
Typo 'and is less...'

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Your decision to reject this treatment will also have a devasting impact on people with cardiovascular disease, as unlike another class of acute migraine medication, the triptans, it does not constrict or tighten blood vessels. As a migraine sufferer for whom is suffering from the side effects of Triptans allowing This medication as a safer alternative to triptans in treating migraine acutely is hugely important

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Question: Has all of the relevant evidence been taken into account?

Response: Please consider those individuals who are unable to take Triptans or other migraine medication due to health reasons and this is the only medication that we are able to take that helps chronic migraine. Without this lives would be changed dramatically for the worst and involve inability to be a functioning part of society.

Question: 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Response: It would be discriminatory to not make this medication available to all, particularly those who are unable to take any effective migraine medication eg Triptans. In excluding this medication you would affect a large number of chronic migraine suffers who would not be able to continue to work. Will then need additional NHS support for chronic pain. It would severely affect and damage many peoples lives affect working life, well-being and family relationships. As without this medication you lead a half life, and one that is almost not worth living.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Question: Has all of the relevant evidence been taken into account?

Response: Probably not - individual experiences with existing GEPANTS have not been considered.

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Response: Cost benefit calculations are usually fatuous; data are never collected prospectively and much of them are guesstimates, fabrications or wishful thinking. I have had data published as such myself.

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

Response: No. There is no good reason to deny the small proportion of the population that are allergic to the licenced SC Gepants access to alternative drugs.

Question: 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Response: You are discriminating against those disabled by not being able to use the existing drugs.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Question: Has all of the relevant evidence been taken into account?

Response: The network meta-analysis comparing Rimegepant with erenumab, fremanezumab, galcanezumab contains substantial limitations. This includes using studies with patients with chronic migraines, which is not part of the licensing application of Rimegepant, therefore it is not necessarily appropriate to make a conclusion that Rimegepant is less effective than other treatments.
Rimegepant doesn't cause rebound headaches. People with heart conditions, or over 60 years of age can't use triptans, which is the only acute medication available. There are very few migraine clinics in the UK and patients don't receive the treatments they should receive. There are no other choice for acute medicine than triptan, which can't be taken by many patients or is inefficient.

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Response: Migraine has a significant impact on society as a whole, with higher rates of absence from the workplace and reduced productivity. Therefore, ineffective treatments for migraine sufferers has economic consequences at every level of society. Drawing conclusions solely based on estimated QALY is not a good measure in assessing migraine treatments due to the nature of the condition. The social isolation caused by migraine has a cost on its own.
Cost on society is higher with no adequate treatment especially since the delivery of/access to care is very low and there is currently no medications available except Triptans, which can't be taken by many sufferers.

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

Response: The recommendations are not a sound and suitable basis for guidance because the existing guidance to treat migraines is insufficient to help people who have very debilitating episodic attacks, which then lead to chronic migraines because of the lack of acute medication. There is no readily accessible migraine clinics or specialists.

Question: 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 race, gender, disability,

religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Response: There are aspects of discrimination in the recommendations against people over the age of 60 and people with heart conditions as they can't take triptans. The same goes for women in general because they represent up to 75% of sufferers, and almost 20% of the female population suffer from migraines at some stage in their life. It goes against pregnant women because they can't take preventive medication and if the existing acute medication is ineffective. It discriminates against people who live in areas where there is no access to a migraine clinic or specialist.

Name	[redacted]
Organisation	N/A
Conflict	N/A

Comments on the ACD:

Question: Has all of the relevant evidence been taken into account?

Response: I don't believe so. I have suffer migraines all my life, and they have had a massive negative affect on my life and career, despite me gaining a degree in Computer Science and Psychology. Yet a few years ago I started taking a Triptan preventative medication, which has changed my life for the better. However, recently out of the blue I suffered a heart attack due to the tightening of my blood vessels. If one has led to the other, where is the cost saving? I now require more medication, more NHS care than I ever did.

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Response: No. As stated above, the damage that can be caused by the side effects of the other medications can in the long run cost more. Also we should be future looking, migraine will not go away, the cost of these new measures will only go down if they are used and utilised, we need to think of the future as well as today.

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

Response: Of course not, they are purely financial. Heath care with a foundation on economics is a very unstable structure. The wellbeing of the people it was designed to protect become second or even third in importance, which is a very poor state of affairs to be in.

Question: 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 race, gender, disability,

religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Response: I think we have gone way past unlawful discrimination.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Question: Has all of the relevant evidence been taken into account?

Response: The NICE response does not provide any detail about the comparisons it has made or the evidence it has reviewed so it is not possible to answer this question.

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Response: See my answer to the question above. Without sight of the evidence, it is not possible to answer this question.

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

Response: No. see answers to questions above. Without sight of the evidence, it is not possible to accurately and objectively answer this question. Subjectively, it appears that NICE is saying that there is insufficient evidence to establish whether Rimegepant is cost-effective. It does not state that the drug is ineffective or unsafe. On this basis, it would seem sensible to recommend that the NHS uses it on a trial basis in order to gather more evidence. For those migraine sufferers who have not responded to, or are unable to use, other drugs such as triptans or CGRP inhibitors, all interventions so far have been a waste of resources yet the NHS is happy to continue using them. Therefore, why not use the Gepant group of drugs in case it DOES make a measurable difference to those groups of patients? The cost of not doing so far outweighs the cost of the drugs in terms of further use of NHS resources, lost productivity of working age patients, lost time in education of school age patients and continued reduction in quality of life.

Question: 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Response: This decision could disproportionately disadvantage those migraine sufferers who are unresponsive to, or unable to use, other interventions. This will include those patients who suffer from medication

overuse headaches. All these groups, by the nature, frequency and severity of their condition are highly likely to fall with the scope of the Equality Act 2010 and, therefore, be regarded as having a disability.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

It is really disappointing that NICE have not approved the use of this drug. Migraine sufferers are in desperate need of options - many of the medications are archaic and come with significant side effects, access to newer drugs is limited and the migraine world summit (just been with worldwide expert leading neurologists) have identified that it is not necessarily one drug that does the job in chronic migraine sufferers. Overuse headache is a real issue and it is OK for advisers to say don't take NSAIDs or Opiods if you are in severe daily pain - this drug is an option and alternative that can be used for preventing or acute treatment for an attack - why would you not give this the chance it deserved to give migraine patients a chance.

Personally, I am a 33 year old lady, recently married and I am a Solicitor. I am unable to work, my social life is non-existent and I am struggling to cope. We should be able to have access to anything that can possibly help us and America have approved this drug and patients are finding great benefit. I urge you to watch the migraine world summit please!

Question: Has all of the relevant evidence been taken into account?

Response: Yes

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Response: No this is unsatisfactory

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

Response: no

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

I rely on triptans to treat chronic migraine, not just to prevent up to 48 hours of pain, lack of sleep and disruption to my life but also for the peace of mind provided by knowing I have a fall-back if necessary, as other pain-relief medication has no effect. However, triptans are not recommended, as I am

73, and I worry what will happen if I am prevented from taking them for other health reasons. Rimegepant seems to offer a promising alternative to triptans, as well as to the preventative medications that I also take. I am disappointed that it will not be available, at least to those for whom triptans are not an option.

Question: Has all of the relevant evidence been taken into account?

Response: More research needed.

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Response: Not for those unable to take triptans.

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

Response: Not at present, as more research is needed, especially into rimegepant's effectiveness as an acute treatment for those unable to take triptans, but also to compare rimegepant with other preventative treatments, given it's potential for dual use.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

For people like me who can't use triptans and no other medication tried deters migraine attacks I'm very disappointed in this.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

I am a sufferer of migraines and regular headaches, for the past 8 or 9 years. I have tried endless treatments, drug related and otherwise. The most effective to date has been Aimovig which seemed to reduce the intensity of the pain but not the frequency of the episodes. I still experience headaches 50% of the time, mostly but not always, waking with one in the middle of the night. These vary in pain level from bearable to a lot of pain with occasional intense migraines which cause me to vomit and I can barely move around. Even though the Aimovig has helped to a point, it hasn't changed the frequency. Its close cousin, Emgalaty seems to be making matters worse. I rarely get an unbroken good night's sleep. I try to carry on with a normal life and am a busy volunteer, so I do use Sumatriptan 50mg (or 100mg) if necessary, especially if I have an important day coming up. Sumatriptan usually works for the less intense headaches. I am well aware of the problems of overuse and do my best to limit my use of

Sumatriptan to less than 10 a month. Sometimes, if I have a very hectic schedule, I have gone over that number and then have to spend many sleepless, painful nights trying not to take any medication. Overuse is something to be avoided but the point I am making is that sometimes it can't be avoided. To have a drug like Rimepant which could help get through those unavoidable over-use times would be invaluable.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Unlike other acute treatments for migraine like triptans, NSAIDs, even paracetamols, the gepants don't seem to cause medication overuse headaches (MOH). As one who has had migraines since the age of 11 and therefore took acute treatments for many years I have found for some time that I cannot take any painkillers, even paracetamols, as they give me medication overuse headache. Not only has this affected my quality of life but it has caused me to miss many working days and if I have worked while having a migraine attack I have made many mistakes due to inability to concentrate and the need to vomit frequently. I know other migraineurs whose experience is the same. We miss more working days due to migraines and MOH than for other illnesses. Loss of working days affects productivity and the economy. There is a stigma attached to migraine and many think it is 'just a headache'. When you are lying in bed with sharp stabbing pains usually on one side of the face, vomiting constantly, noise and light sensitivity, you wish you could die. Surely the more treatments available for health practitioners to prescribe to patients the better.

Comment on section 2.3 (information about rimegepant), price:

There are other gepants either available in other countries or being developed like Ubrogepant and Atogepant. With more companies developing the drug and the more it is prescribed the more the price will lower.

Comment on section 3.2 (committee discussion), treatment pathway:

Triptans cause blood vessels to tighten and contract so are not suitable for people with cardiovascular disease or those over 60 due to the risk of a heart attack.

Taking 2 triptans once a week over several years can cause medication overuse headache. Gepants do not seem to cause this.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

As an American, I was able to receive Rimegepant from my GP. Since moving to London, I no longer have this option. It is an amazing drug option for migraine sufferers. My sister also suffers from migraine and swears by her use of Rimegepant and how it has helped her with her migraine attacks. You denying this medication to millions of migraine sufferers is not fair.

Comment on section 1.3 (recommendations), "Rimegepant might also reduce monthly migraine days. But there is a lack of comparative long-term evidence to support this.":

This should be enough! If it's able to reduce monthly migraine days, that is amazing for migraine sufferers.

Comment on section 1.3 (recommendations), "Clinical trial evidence for preventing migraine shows that rimegepant reduces monthly migraine days more than placebo. It has not been directly compared in a trial with erenumab, fremanezumab or galcanezumab, but indirect comparisons suggest that it is less effective than these":

There have been no trials. How can you be 100% sure this is the case? It clearly reduces the monthly migraine days more than a placebo. That should be a strong enough case to prove that this drug is worth it for migraine sufferers.

Question: Has all of the relevant evidence been taken into account?

Response: Yes

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Comment on section 1, recommendations:

Migraines are debilitating and impact so many lives. My daughter has 4 to 5 migraines a month, she is about to graduate from university and worries about how her condition will impact her future career. Having a heathy workforce with less sickness and higher productivity can only be more beneficial for society . The cost to the NHS and the government would be outweighed by improving the Heath of a huge number of the population who suffer from this condition and have their lives and careers impacted .

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

I am a chronic migraine sufferer who constantly has to manage the risk of medication overuse headache, this medical would be life changing for me. I have 17 attacks a month and my neurologist says I can only take triptans 10 days a month, so I am already in agony and experiencing medication overuse headaches. This medication could give me my life back.

Name	[redacted]
Organisation	N/A
Conflict	N/A

Comments on the ACD:

This is a very sad day for all of us who suffer daily from chronic Migraines, those who had hope on this medication, very sad to hear that the UK is trying to save money on one of the must horrible disease around, getting behind on the must promises medication at the moment, we know this medication have been rulings in the USA SINCE 2021 WITH HUGE SUCCESS among sufferers. has been approve in Europe last year and now commercialize as Vydura , as Pfizer bought the patents from BIOHAVEN, . we were waiting so desperate for this moment and now NICE decide is to expensive , it doesn't worth it , I feel ashamed this Agency is thinking money instead of wellbeing.

Question: Has all of the relevant evidence been taken into account?

Response: no

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Response: no

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

Response: no

Question: 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Response: no

Name	[redacted]
Organisation	N/A
Conflict	N/A

Comments on the ACD:

Question: Has all of the relevant evidence been taken into account?

Response: "Gepants have been approved and safely used for some time in USA and so on what medical grounds have NICE rejected their use in UK Triptans are contraindicated in the older patient for the treatment of migraine attacks and if no other alternative has worked for those patients Gepants would seem to be the safer option to try"

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

This is disappointing news for older migraine sufferers who cannot take Triptan medications due to the effect on blood vessels.
I have had migraines since 15 years old and am now 70 years old & I cannot take Triptans.
New effective medication for older people is desperately needed.
Please research more and review the decision.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Comment on section 1.3 (recommendations), "Standard treatment for preventing migraine after 3 or more treatments includes erenumab, fremanezumab or galcanezumab.":

Many patients still face significant difficulties in accessing these 'standard' treatments across the UK.

They are also not suitable for patients who are needle-phobic - chronic migraine patients deserve access to decent alternatives that work.

The impact of migraine on quality of life is SIGNIFICANT, not to mention the cost to the economy through absenteeism from chronic migraine patients.

With the cost of living crisis, it also needs to be considered that injectable medications need to be kept refrigerated - and with government warnings of power cuts, £1000's of medication could potentially go to waste which would not be more cost effective.

Working for the NHS myself with biologics, there are also difficulties and a significant amount of extra work that goes into providing homecare-only injectable medication for homeless patients - these patients also deserve easy access to the best medications that will suit their needs.

Question: Has all of the relevant evidence been taken into account?

Response: No. The current 'standard' treatments are all injectable.

Injectable medications are not suitable for everyone - because of needle-phobia, the cost of running a fridge in a cost-of-living crisis, and the issues that homeless patients face in accessing injectable medications that require storage in a fridge.

Migraine patients deserve access to a variety a medications that suit their needs - there are an abundance of high cost treatments available for other conditions - such as eczema and psoriasis - migraine is incredibly disabling, and migraine patients have once again been done a massive disservice by being denied access to newer/better treatments.

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Response: No - I don't believe NICE appreciate how significant an impact migraine has on a person's life - migraine is DISABLING.

Migraine patients want to be actively involved - in work, in our social lives and in our communities - and by denying access to newer/better treatments, we are once again being let down, left behind, and left out of contributing to society to our full potentials.

The cost to the economy by us NOT being able to contribute is far greater than the cost of this medication.

Question: 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Response: As above, not approving this medication potentially discriminates against those on lower incomes who cannot afford to store the refrigerated injectable medications which are currently the 'standard' treatments available.

It also discriminates against, and makes it much harder for homeless patients to access these same treatments.

As migraine predominately effects women, the lack of access to good migraine care and decent treatments also potentially discriminates against women.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Disappointing not to have Rimegepant as an acute treatment for migraine. I have suffered with migraines for 23 years that have changed from episodic to chronic in the last 18 months, triptans are no longer effective and I am unable to take NSAIDs. The research suggests Rimegepant would have been an ideal treatment, and in fact the only potential acute treatment for my migraines.

Name	[redacted]
Organisation	N/A
Conflict	N/A

Comments on the ACD:

As someone who has suffered from medication over user headache and swung between episodic and chronic migraine I was disappointed to see that the purported reduced risks of medication overuse headache compared to triptans do not appear to have been considered as a relevant factor to the recommendation of Rimegepant as an acute treatment.

If there is deemed to be insufficient data in this area as to the extent of the problem of MoH or the instances of MoH with respect to treatment with Rimegepant, I would hope that an ongoing trial would be recommended.

Comment on section 1.3 (recommendations), "The company proposed rimegepant for acute treatment to be used after 2 or more triptans have not worked, or if people cannot have triptans":

This part of the case is very important there is a whole group of people who cannot take triptans and whom this drug could help in a way for which there is no current alternative.

Question: Has all of the relevant evidence been taken into account?

Response: I cannot see any mention of analysis of the comparative effects of medication overuse headache with acute treatment.

This would be especially at the upper end of what is considered to be episodic migraine and chronic migraine when the number of attacks per month exceeds the number of days triptans and conventional pain killers can be taken.

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Response: I think they are too generalised and not enough evidence has been taken into account with regard to specific clinical need groups.

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

Response: I feel that some important factors have been undervalued and a whole group of patients effectively left with no effective acute treatment option so no.

Question: 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Response: It seems that people with cardiac conditions are being denied access to an effective acute treatment for migraine, but I do not know if this fits the lawful definition of a disability.

Name	[redacted]
Organisation	N/A
Conflict	N/A

Comments on the ACD:

Question: Has all of the relevant evidence been taken into account?

Response: I recently had treatment by a neurosurgeon who said that I needed to see a neurologist regarding my migraines as I'm not currently on any specific medication and having to take tablets that can cause rebound migraines. I'm in pain most of the time. Rimegepant was the medication that he believed I needed. I can't take tryptans, so there isn't anything else that could help me.
I don't think that people like me have been taken into consideration.

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Response: I don't think so

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

Response: No

Question: 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Response: As in my first answer. My headaches render life unbearable for me. I spend most of my time in bed, in the dark. This isn't life. I had to ask my GPs to refer me to neurosurgeon, they wouldn't have realised there was anything to help me. When the neurosurgeon told me that there was medication available now that would be suitable, I just cried. It's because of

him that my gps have now referred me to neurologist. In Cornwall there's a 20 month wait. Not much better in Plymouth but hopefully they will read report from surgeon.
To think that there is medication that could help but you're now planning to remove it, seems like torture o me.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

This medication has such potential for those of us with chronic migraine. High use of triptans is inevitable for this condition, and a drug that does not lead to overuse is vital. Also the cvs side effects are of concern to those of us who are older. Triptans do not work as an acute treatment for all migraine sufferers, and this is a promising option. So disappointing that the large number of migraine sufferers , with significant disability, are being ignored again.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

As someone who suffers from chronic migraine I would simply say that it is important for people like me to have choices in treatment. By rejecting this option you are effectively taking away a chance for thousands of us to be more productive in our lives; perhaps being able to work or function for many more days. I am also a nurse and can attest to having missed many days of work due to inadequate treatment options. Thank you.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Question: Has all of the relevant evidence been taken into account?

Response: It doesn't appear that there has been sufficient consideration given to people like me:
I'm 72 and have suffered migraine on and off for more than 50 years. I suffered a TIA in 2014. In recent years this has become worse and I now have significant head pain on about 20 days a month.
I have been advised to avoid:
- NSAID medication and Aspirin while on Clopidogrel due to bleeding risk.
- Codydramol because of risk of overuse headaches. I only took them occasionally as they were not effective but stopped altogether in January 2022

- Triptans are contra-indicated due to previous TIA
The only pain medication remaining to me is Paracetamol and this is ineffective.
I sometimes experience severe pain lasting more than 24 hours.
I was looking forward to the arrival in the UK of Gepants as an appropriate treatment.

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Response: I don't know about this

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

Response: It is to be regretted if Rimegepants is not made available in the UK

Question: 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Response: Not that I'm aware of

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Comment on section 1.1, recommendations:

My migraines (in a specific area on the left side of my head) were infrequent and managed with Zolmitriptan. After about 5 years they became more frequent but still manageable with the Triptan.
Recently, after 10 years, they are now more frequent and much more intense.. added to this, exceptional pain over all my head and neck.
I am now 71, and have been advised NOT TO TAKE ANYMORE TRIPTAN.. due to the dangers of Triptans with the elderly.
Triptans no longer work for the excruciating all-over head pain.
THIS NEW DRUG would be the answer for 1000s of people like me.
NB
The pain is so severe that I have come close to ending my life.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Comment on section 1.3 (recommendations), “which is narrower than the marketing authorisation”:

This is not an accurate representation of those who cannot tolerate triptans. The report does not qualify the reasons WHY people 'cannot have triptans' which vary from medical interactions, to intolerance of side effects. It should also be noted that there is a significant difficulty in obtaining sufficient triptans for chronic migraine sufferers, as they are only prescribed in small amounts in order to prevent medication overuse headache. This is not a risk with Rimegepant, which would change the game for migraine sufferers.

Comment on section 1.3 (recommendations), “cost-effectiveness”:

Whilst I recognise the need to look at cost-effectiveness, this does not take into account the economic impact that migraine has on the workforce for those who suffer with it, resulting in countless days, if not weeks, of missed work and reduced productivity.

Comment on section 3.32 (acute treatment), “recognised the substantial burden that migraine has on quality of life and day to day functioning”:

With respect, without experiencing for oneself how this can impact daily life, it's clear to see why this has not been recommended for approval. A tablet is preferable over an injectable and this would change lives across the UK.

Comment on section 3.34 (preventative treatment), “erenumab, fremanezumab and galcanezumab”:

Again, these are all injectables - a tablet form would be revolutionary.

Question: Has all of the relevant evidence been taken into account?

Response: No, the experience of being reliant on injectables has not been taken into account. The ease and convenience of a tablet form of preventative treatment cannot be overstated. This would benefit thousands of sufferers across the UK.

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Response: It seems incorrect to compare the cost-effectiveness of a tablet against that of an injectable, as it is very much an apples to oranges comparison. If there was an existing tablet on the market, then this would be acceptable, but this is a revolutionary treatment - the first of its kind in the UK - and to deny sufferers access to it on a false comparison is irresponsible, misguided, and ultimately unacceptable.

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

Response: No.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

I am 52 and have suffered with migraine from being 9 years old. Over the last few years the migraines have gone from being episodic to chronic. I have tried 6 preventative medications which had no effect, Botox which had limited effect and also take triptans which sometimes reduce pain for a short time but do not eradicate the other symptoms. Since Christmas (it is now March) I have had a total of only 10 days with no migraines. I work for the NHS and on most days I have to struggle through the working day and go to bed as soon as I finish. I take the maximum number of triptans that I am allowed to - 8 in a month - but that still leaves me with a high level of symptoms for most of the month. I love my job in the NHS but without relief from a different type of medication I will have no option but to either go on sick leave or leave my job altogether. I would strongly ask you to reconsider your decision on Rimegepant as it is discriminatory against people such as myself whose lives are blighted by having this neurological condition

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Acute treatment:
There are people who do not respond to triptans +NSAID, and some of these will respond to rimegepant, as CGRP antagonist, so it should be available. However it appears that the price being asked of the NHS is too high. Such a high price is unethical and not required by pharma to manufacture the drug and we know that R&D costs are not the explanation for high drug costs. The pharma company should agree a reasonable price with NICE.
Prevention:
As for acute treatment it should be available on the NHS but the pharma company should negotiate a reasonable lower price.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Question: Has all of the relevant evidence been taken into account?

Response: Are NICE considering the use of this ,as an acute medicine ,in conjunction with eg Frenebubab /Ajovy ? I use Frenemebab,great reduction in intensity of migs and reduced frequency fair amount. But due to Triptans MOH and restricted use to 8 a month .I still have to suffer 8 to 10 days a month ,with no drugs at all. This is where the gepants would help me ,as don't give you MOH,so I could use for every migraine . Would still need Ajovy though .Suffering migraines with drugs is bad enough ,but the 8 to 10 days with none at all is gruelling and I feel inhumane .You wouldn't leave an animal in pain for so long with no acute meds to help .The disability is overwhelming and severely depressing.

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Response: Have NICE considered ,the percentage of migraineurs that get MOH and benefit to NHS in long term and patient being able to contribute 100 % to economy ,by total effective work, or even to be able to go to work. I haven't been able to work for 3 years and can never see myself managing a job again ,with 16 to 18 migs a month .Gepants could help me return

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

Response: Why are they using them in America ,if no good ?Has all the evidence really been considered ,or it more about cost and state of NHS at present ?Migraine is a hidden, unrecognised disability ,with poorly funded research .If more men suffered ,than women, this would be a different story .Migraine is a stigma of 'just a headache ' or ' just a sickie day 'or 'she was ok yesterday '.Lifelong battle trying to make people understand how you feel ,with a defunct brain.

Question: 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Response: "Have NICE really considered ALL the research .If so ,can more research not be done, and soon. Reading my previous comment ,I feel women are discriminated against ,in case of
Migraine Disorder ,as they are highest proportion of sufferers .So give gepants a try ."

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

I am 75 years old and a chronic migraine sufferer who has had this disease since I was 21. As time has gone by the migraines have become so severe

they are almost daily and completely ruin my life. Unfortunately I have failed all the traditional preventative medications my Headache Specialist/GP has tried me on, mainly because I haven't been able to tolerate anything but the lowest dose which makes them ineffective. I still find I get some side effects on the lowest dose of Nortriptylene but I stick with it as it gives me some relief but makes me extremely sleepy so all I can do is to rest.

As an informed patient I have followed the annual Migraine summit from the US for the past 10 years and have been very excited to learn about the developments of the CGRP class of medications which I know are now allowed in the UK but only in the form of injectables which have to be done monthly. The problem for me with this approach is that I am so sensitive to medications that I could get side effects which could go on for a month as this happened when my Headache Specialist gave me Botox for migraine prevention. I reacted within 10 minutes of the 40 injections and had a terrible month with more migraines than normal plus severe dizziness at times that caused some insomnia. This has obviously made me very aware of possible issues over a monthly injection of a CGRP medication.

However I would love to try a Gepant like Rimegepant which is taken daily, both as an acute treatment but also can be used frequently as a preventative which would be brilliant for me.

I should mention that the triptans help me deal with the actual bad migraines but they cause rebounds so I have been very careful, by way of a migraine diary to only take no more than 2 a week and basically suffer at other times with ineffective medication like paracetamol. I don't doubt I have ended up with Medication Overuse Headaches but have tried so hard to go without but end up feeling like giving up in general.

On rereading my email I realise I forgot to point out that the European Medicines Authority have passed the use of the Gepants and Ditans in chronic migraine sufferers from this year so it would seem extremely unfortunate that here in the UK this is not the case. I shouldn't mention the B word but had we still been in the European Union we could now access these drugs which I believe could change so many sufferers' lives!

Name	[redacted]
Organisation	N/A
Conflict	N/A

Comments on the ACD:

This treatment is needed so much for people who can't take the current preventative treatments available for Migraine. My migraines were triggered after having the Astra Zenneca COVID vaccine, this is my third year now of 15 to 17 severe migraines per month, my GP and now my Consultant Neurologist have tried me on so many of the currently available preventative treatments. I have just had to stop AJOVY treatment, as I have reacted to this also. It was a life changer for me as I went from 17 migraine per month

to 9, and they were less severe, I felt like I my life was coming back. I am just one of many thousands of migraine sufferers who desperately need a treatment to cope with this debilitating condition. Please help us and pursue this treatment further and give it approval for use here in the U.K.

Name	[redacted]
Organisation	N/A
Conflict	N/A

Comments on the ACD:

I am desperately disappointed to see you have rejected a gepant. I am 82 and have constant migraine headaches but also high blood pressure. I have been waiting for gepants to be approved as there appears to be nothing else safe and that would help. Please reconsider.

Name	[redacted]
Organisation	
Conflict	N/A

Comments on the ACD:

Question: Has all of the relevant evidence been taken into account?

Response: We consider that evidence could have been included in the appraisal that would have painted a very different picture of the clinical effectiveness, disease burden, and potential for advancement of NICE's stated goals of reducing health inequalities in the UK.
Migraine's impact on the individual, on society and the economy, on emergency services and primary care, is ubiquitously underestimated by the general public and non-specialist healthcare professionals. It is thought of as a 'bad headache' with some flashing lights. Anyone reading the committee report would not easily be disabused of this notion.

The following evidence is relevant:

Migraine's disease burden

- At an individual level, chronic migraine causes disability on a par with paraplegia, blindness and dementia according to the WHO. Lower frequency migraine still costs may people their jobs due to high levels of absence.

- Migraine is the second leading cause of disability.

- It is the leading cause of disability in young women.

- 'No other disease, communicable or non-communicable, is responsible for more years of lost healthy life in young women.'

- It most affects women's working and reproductive years. It blights capacity for parenthood and work, and widens both the gender pay gap and the 'gender pain gap'.

Further relevant evidence will be discussed under the questions to which it pertains.

Reference:

- Steiner, T.J., Stovner, L.J., Jensen, R. et al. Migraine remains second among the world's causes of disability, and first among young women: findings from GBD2019. J Headache Pain 21, 137 (2020). https://doi.org/10.1186/s10194-020-01208-0

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Response:

Migraine's economic burden

- The most recent UK estimated cost to the economy (released in 2018) in healthcare and lost productivity is £8-10 billion.
- Each year, approximately 2.5% of patients with episodic migraine develop new-onset chronic migraine (ie, chronification).
- The cost of treating chronic migraine is 84% higher than treating episodic migraine.
- A major cause of chronification is inadequate timely treatment of episodic migraine.
- Medication overuse headache (MOH) is a major contributor to this inadequate treatment and chronification.
- MOH due to migraine alone has a global prevalence of 83,755.8 thousand, and years lost to disability (YLD) of 9,166.1 thousand. For comparison, epilepsy has a total prevalence of 27,288.3 and YLD of 8,561.9.
- Until now MOH has been difficult to treat, once established, with challenges of detoxification a major obstacle.
- Data on the efficacy of anti-CGRP monoclonal antibodies indicates that MOH patients treated with these medications may not need to be detoxified in order to successfully treat MOH.
- This makes MOH a modifiable risk on a completely new scale, where previously it was fraught with challenges to action (requiring nationwide GP education and implementation).
- The NHS spends £1 billion on migraine. This suggests, given breakdown above, somewhere in the region of £25,000,000 of this money is spent on new-onset chronic migraine, much of which could be prevented with effective treatment that avoids MOH.

Future burden

- Migraine is one of several conditions know to begin or worsen following SARS-CoV-2 infection so the rate of new cases can be expected to have been increasing rapidly since 2019.
- As noted above, migraine is under-recognised as a progressive disease and a major cause of this progression is lack of prompt

effective treatment, and lack of adequate education at primary care about MOH.
- This makes the rapid increase in new-onset migraine a potentially avoidable 'ticking time bomb' for NHS spending, and for the UK economy.

Present treatment options

As noted in the appraisal document, triptans are the only acute migraine treatment option without tertiary referral. The document recognises there are too few headache specialists relative to need, especially in more deprived parts of the country, and waiting lists are long. This wait is decisive when prompt, effective treatment plays a major role in preventing chronification and/or MOH. Without specialist input, patients are to be offered nothing if triptans fail.

It is worth noting that, in a setting where migraine patients report frequent dismissive treatment at GP level, but know game-changing drugs like rimegepant exist, being offered 'nothing' is less equivalent to a placebo, and closer to a nocebo, for many patients facing disablement without treatment.

- Triptans are contraindicated in one in five patients.
- Triptans are ineffective in one in three patients.

By contrast

- Rimegepant is not contraindicated for the major patient groups excluded from triptans, namely cardiovascular conditions and all patients over 65.
- Rimegepant has comparable efficacy but because there is no correlation with triptans in terms of which patients it helps, having both options will **significantly increase the number of patients** who can be successfully treated in primary care.
- Unlike triptans, which are powerfully implicated in disease progression for this reason, Rimegepant has not been associated with MOH, and shows profound promise for treatment of MOH itself. Even daily use seems to reduce attacks.
    - 'It not only didn't seem that the frequency of headache becomes greater over the course of the clinical trials, but two recent trials have shown that using them daily actually reduces headache frequency. There is a very good chance that they're not going to cause medication overuse headache […] We always limit treatment, so sometimes a person comes in to see us and they're having 10 to 12 attacks a month and it's difficult for the patient to hear you might not be able to treat every attack[…]To be able to instruct a patient that the minute they feel symptoms of a migraine to take their medicine and not be concerned about medication overuse headache is revolutionary and could potentially change the disease course itself'

    - Dr. Jessica Ailani, director of the MedStar Georgetown Headache Center in Washington, D.C, quoted at Gepants and Ditans Therapies | American Migraine Foundation.
- Rimegepant's safety against MOH is supported not only by the data but also by the pathophysiology of MOH, since MOH is itself caused by repeated exposure to existing acute medications' suppression of endogenous antinociceptive systems leading to up-regulation of the calcitonic gene-related peptide (CGRP) system. Since by contrast, rimegepant is a CGRP blocker, it is not surprising that it would not cause this to happen.
- Rimegepant has a lower overall side effect burden, and unlike triptans, it is not more safe and effective in one sex than the other (see Q4. below).

A note on section 3.2 of the consultation document ('Treatment Pathway') and the NHS RightCare Headache and Migraine Toolkit

The committee heard 1. that there is disagreement among neurologists about how many triptans should be trialled and 2. 'when triptans are ineffective and the migraine does not respond, it is often because they are not being used properly. They said that if people have no response to between 2 and 4 triptans, it is unlikely they will have response to any more triptan treatments'.

Medication 'often not being used properly', at first glance, faults patients. This is in keeping with the idea that migraine is a minor complaint, and not a condition we might as patients care to treat right. At second glance, GPs might seem to blame. They could educate their patients and they often do not. Indeed admirable efforts have been ongoing to train GPs on MOH, and personalising triptans to symptoms. This enormous, systemic change will take a long time to implement.

As patients we want improved triptan outcomes and we would hope that as this education programme progresses, it will become profitable to trial more triptans before moving on to rimegepant. Guidance could be updated at that point. But until then, unless rimegepant is offered now, more patients – and given the pandemic, likely more patients than before, will develop MOH, remain ill, and progress to chronic, and the opportunity will be lost to reduce the individual, economic and healthcare burdens this creates.

References:

- Manack AN, Buse DC, Lipton RB. Chronic migraine: Epidemiology and disease burden. Curr Pain Headache Rep 2011;15(1):70–78. doi: 10.1007/s11916-010-0157-z.
- Stokes M, Becker WJ, Lipton RB, Sullivan SD, Wilcox TK, Wells L, Manack A, Proskorovsky I, Gladstone J, Buse DC, Varon SF, Goadsby PJ, Blumenfeld AM. Cost of health care among patients with chronic and episodic migraine in Canada and the USA: results from the International Burden of Migraine Study (IBMS). Headache.

2011 Jul-Aug;51(7):1058-77. doi: 10.1111/j.1526-4610.2011.01945.x. PMID: 21762134.
- GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392(10159):1789–858. doi: 10.1016/S0140-6736(18)32279-7.
- Sun-Edelstein, C., Rapoport, A.M., Rattanawong, W. et al. The Evolution of Medication Overuse Headache: History, Pathophysiology and Clinical Update. CNS Drugs 35, 545–565 (2021). https://doi.org/10.1007/s40263-021-00818-9
- Dismissed-for-too-long_Recommendations-to-improve-migraine-care-in-the-UK.pdf (migrainetrust.org)
- de Boer I, Verhagen IE, Souza MNP, Ashina M. Place of next generation acute migraine specific treatments among triptans, non-responders and contraindications to triptans and possible combination therapies. Cephalalgia. 2023 Feb;43(2):3331024221143773. doi: 10.1177/03331024221143773. PMID: 36739516.
- Sun-Edelstein, C., Rapoport, A.M., Rattanawong, W. et al. The Evolution of Medication Overuse Headache: History, Pathophysiology and Clinical Update. CNS Drugs 35, 545–565 (2021). https://doi.org/10.1007/s40263-021-00818-9
- E.g. Rimegepant 75 mg Demonstrates Safety and Tolerability Similar to Placebo With No Effects of Age, Sex, or Race in 3 Phase 3 Trials (1609) Jack Schim, Susan Hutchinson, Richard Lipton, Elyse Stock, Alexandra Thiry, Charles Conway, Christopher Jensen, Beth Morris, Vladimir Coric, Robert Croop Neurology Apr 2020, 94 (15 Supplement) 1609.

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?

Response: The evidence suggests to us that the recommendations presently understate the burden of migraine for the patient, the economy, and the NHS. It further shows that the benefits of rimegepant have not been captured in the appraisal. The opportunities for preventing and treating MOH – and the scale of the cost in not doing so. The scale of disability, on a par with paraplegia, that could be averted when early effective treatment stops progression. The increased capacity for headache management in the community, and reduced need for referrals to specialists. The potential gain to the UK's economy through reduced absences and disablement. The chance to reduce health inequalities for women, older people, people with cardiovascular illness, and people from low-income backgrounds. We hope all of this can be front of mind when the committee meets.

Question: 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Response:

Women
The reason women experience more migraine is partly biological. But in 2023, it is also a result of decision making around healthcare.

Migraine has been profoundly and consistently underfunded in both research and healthcare provision relative to its disease burden. The reason for this over decades has been sexism and misconceptions stemming from it. It is the leading example among many conditions disproportionately affecting women that have poorer care due to underfunding, stigma and disinterest.

Sex differences in current best treatment
At present, triptans, as the only acute medication option, mean women have worse outcomes than men.

- **Men benefit more from triptans** than women.
- Triptans cause **more adverse events in women.**
- Triptans cause **more headache reoccurrence in women.**
- Women's attacks are more likely to be more severe and frequent, putting them at **more risk of MOH** and chronification.

By contrast, **rimegepant has equal safety and effectiveness in both sexes.**
When triptans were the only available effective treatment, this disparity was acceptable. Now that equal treatment is possible, it should be offered, or else it is an active choice to offer worse care to women than men.

Maternity
The demographic must affected by migraine is women in their reproductive years. Women in our group have shared their experiences of difficult choices (or 'loss of choice') around starting a family. This has frequently been as a result of inadequate early treatment leading to MOH and chronification such that they were too disabled to cope with pregnancy and motherhood. Others have shared the burden of caring for young children when debilitated by migraine, unable to tolerate light, sound, or being out of bed. Others shared their anxiety about their children's wellbeing, and about burden placed on young carers. The impact on mothers, given migraine is the leading cause of disability in young women, is both vast and disproportionate.

Age
All migraine patients over the age of 65 are presently *without any acute treatment option* as triptans are contraindicated. The decision to provide Rimegepant disproportionately affects older people, and now that we have the opportunity to provide more equal treatment for all ages, this must be taken into account. Age is also a key variable for cardiovascular conditions, so a larger proportion of older patients under the age of 65 would now needlessly be denied any treatment if they cannot be offered rimegepant.

Gender reassignment
Sex-based differences in migraine treatment response are partly a result of hormone differences, and partly related to other sex-specific biology. However, it has been shown that use of cross-sex hormones results in increased risk of some of the same adverse events found in biological females in response to triptans, due to relationship of estrogen with serotonin 5-HT1B.[1]

Socio-economic status
The disparity in provision of specialist care for migraine at tertiary level in the UK is extremely marked. In particular, there is a lack of headache services in Northern England. There is a very strong association between risk of chronic migraine and low socio-economic status. It is not difficult to identify the direction of causality, or to recognise that inequitable provision of tertiary care is driving progression to chronic for people who already face additional barriers to access healthcare. When one in five cannot be offered triptans, and one in three are not helped by them, patients in more deprived areas of the country are at greater risk of becoming disabled by migraine, of losing their jobs, and falling into severe financial hardship. Until the disparity in headache provision is resolved, denying rimegepant widens economic inequalities, and means better healthcare is offered to people who are better off.

References:

- Migraine prevalence in male to female transsexuals on hormone therapy Tamara Pringsheim, Louis Gooren Neurology Aug 2004, 63 (3) 593-594; DOI: 10.1212/01.WNL.0000130338.62037.CC

Rimegepant for treating or preventing migraine (ID1539)

EAG response to company ACD comments

March 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 (ACD) produced by the National Institute for Health and Care Excellence (NICE) for the appraisal of rimegepant for treating or preventing migraine (ID1539).

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 0 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 EAG response, as well as reference to which section they are discussed in more detail.

Table 2 below summarises the EAG's preferred assumptions within the EAG report, committee preferences/comments from the ACD and the company's updated base case assumptions following ACD.

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

Comment in company ACD response		Relevant sections of ACD	Company response	EAG comment
1	Acute migraine - time horizon.	3.12, 3.15	Further rationale (based on clinical expert feedback, real-world evidence and study data) provided to explain why a time horizon of >10 years is appropriate for the acute model of migraine.	The EAG acknowledges the rationale put forward by the company and the idea that patients may experience acute migraine attacks for much longer than 2 years; however, this does not impact the EAG's decision with regards to appropriate time horizon as this was based on the modelled benefits and costs of treatment being short term and acute. (see Section 2.1)

2	Acute migraine – reduced MMDs	3.12, 3.15	Argument against excluding MMD reduction from the acute model provided.	Argument previously addressed at TE, the EAG retains its position. (see Section 2.2)
3	Acute migraine – revised acute base case and scenario analyses	3.15	Company's base case revised to include committee's preferred assumptions in Section 3.15 of the ACD. Rimegepant discontinuation was also increased from 9.7% to 13.5% (note this was erroneously labelled discounting in the company ACD response).	The EAG maintains that 2 years is the most appropriate time horizon, given the costs and benefits are acute and the long-term benefit relies on assumptions surrounding BSC response. (see Section 2.3)
4 to 6	Acute migraine – prespecified and post-hoc subgroup analyses	3.5, 3.33	As requested by the committee, further clarification on differences between prespecified and post-hoc subgroup analyses were provided. Results for prespecified analyses were also provided with these explored as a scenario in the model.	The company has provided the additional information requested by the committee. Results between subgroup definitions are similar and when used in the model, ICERs are similar for both definitions. The EAG's position on the mITT population being preferable in terms of informing response in the model has not changed. (see Section 2.4)
7	Migraine prevention – revised base case	3.24, 3.29, 3.31, 3.34	Company's base case said to be revised to include committee's preferred assumptions in Section 3.29 of the ACD.	The company's revised base case model includes all EAG and committee preferred assumptions.

			Amendments in terms of reversion to baseline MMD, erenumab costs and comparator acquisition costs also mentioned.	Other amendments mentioned by the company are those that were made in response to TE rather than since the ACD. The EAG is uncertain whether these amendments should be accepted so have presented results with and without these new costs. (see Section 2.5).

Abbreviations: ACD, appraisal consultation document; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; mITT, modified intention to treat; MMDs, monthly migraine days; NMA, network meta-analysis; TE, technical engagement.

Table 2. List of assumptions and preferences following the EAG report and ACD

EAG preferred assumptions	Committee preference / comments	Revised company base case assumptions
Acute		
Trial efficacy data- BHV3000-301 – 303 pooled mITT	EAG assumption	EAG assumption
Trial efficacy data include Asian study - Include BHV3000-310	EAG assumption	EAG assumption
Trial population characteristics- BHV3000-301 – 303 pooled mITT including BHV3000-310	EAG assumption	EAG assumption
Rimegepant discontinuation- 13.5%	EAG assumption	EAG assumption
MMD baseline distribution - Poisson	EAG assumption	EAG assumption
Discontinue rimegepant pain trajectory - Revert to placebo all comers	EAG assumption	EAG assumption
MMD reductions - Exclude	EAG assumption	EAG assumption
Time Horizon - 2-years*	EAG assumption/Committee undecided	20 years

Prevention		
MMD baseline distribution - Poisson	EAG assumption	EAG assumption
Reversion to baseline MMD - Gradual	EAG assumption	EAG assumption
NMA results cycle - Cycle 1	EAG assumption	EAG assumption
Erenumab costs - Matching the regimen for erenumab to the regimen reported in the BNF and	EAG assumption	EAG assumption
Comparator acquisition costs - Equating the initial 28-day treatment acquisition cost to the ongoing 28-day treatment acquisition cost for all treatments (while the exception of the loading dose for galcanezumab).	EAG assumption	EAG assumption
Rimegepant response probability - over 12 weeks	EAG assumption	EAG assumption
Regression used to predict MMD distributions during the assessment period - Option 2 (alternative regression with specific coefficients)	EAG assumption	EAG assumption**

Abbreviations: ACD, appraisal consultation document; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; mITT, modified intention to treat; MMDs, monthly migraine days; NMA, network meta-analysis; PRN, *pro re nata*; TE, technical engagement.

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

**note this was not stated in the company's updated response document but was included in the updated model

2 EAG's critique of company response to ACD

2.1 Comment 1. Acute migraine – time horizon.

In its response to the appraisal consultation document (ACD), the company provides feedback from clinical experts, and refers to study data and real-world evidence (RWE), to support their argument that a 2-year time horizon (as preferred by the EAG in its base case when a reduction in monthly migraine days [MMDs] is not included) is not appropriate for modelling acute migraine treatment

with rimegepant. The EAG notes that these arguments centre around the idea that people with migraine experience acute attacks, and would therefore need acute treatment with rimegepant, for much longer than 2 years.

In terms of clinical expert feedback, a total of 164 general practitioners (GPs) and 12 neurologists with an interest in headache were asked, *"based on your experience and/or clinical judgement, for how many years do you think patients suffer from acute migraine attacks over their lifetime?"*. From these responses (summarised in Figures 1 and 2 of the company's response to ACD), the EAG notes the following:

- of GP respondents (n=164), most believe the answer to this question is >2 years, with the most common answers being >5 to ≤10 years (22.6%), >10 to ≤20 years (24.4%) and >20 years (21.3%);
- all neurologist respondents (n=12) believe the answer to this question is >2 years, with the most common answer being >20 years (50%), followed by >10 to ≤20 years (33.3%).

Further evidence from trial data or RWE are also mentioned by the company in terms of supporting a disease duration that is longer than 2 years:

- the company notes that in the long-term study BHV3000-201, patients remained on treatment up to 52 weeks with only 2.7% discontinuing. The economic model extrapolates from this study and shows patients remain on treatment at 20 years. The EAG was unable to validate the figure of 2.7% discontinuation in the clinical study report (CSR) for this study and believes this value may instead refer to the proportion discontinuing due to adverse events across all three groups (those with 2-8 migraine attacks per month receiving *pro re nata* [PRN] rimegepant, those with 9-14 migraine attacks per month receiving PRN rimegepant and those receiving every other day rimegepant for prevention in addition to PRN rimegepant as needed) included in this long-term study, but notes that the mean duration in the long-term phase of this trial was [redacted] weeks for those with 2-8 migraine attacks per month and [redacted] weeks for those with 9-14 migraine attacks per month receiving PRN rimegepant. The EAG notes that [redacted] of patients remain on treatment at the start of year 20 in the model;

- the company highlights that in studies used to inform the economic model, the average age of onset was ~21 years and the average age at enrolment in the trials was ~39 years, indicating a disease duration substantially longer than 2 years. The EAG was unable to validate this in the CSRs for the randomised controlled trials (RCTs) or the long-term study;
- an external telephone survey study is cited by the company, which reports that patients included in this study were experiencing a mean of 26 migraines per year, 20 years after the onset of migraine. The EAG notes that these figures are specifically for males but similar (24 migraines per year) was observed for females;[1]
- the company analysed RWE on migraine prescriptions from the IQVIA OMOP UK Medical Research Data (IMRD) The Health Improvement Network (THIN). This included 119,918 patients newly diagnosed with migraine between January 2010 and September 2017, with prescription data available until September 2022. Using various definitions for people with more than one triptan prescription during this period, the company highlight that ~16 to 24% had a ≥5-year period between the first and last prescription, suggesting an ongoing unmet need in terms of acute migraine treatments. They also note that some patients may exhaust all treatment options and give up on treatment but would still utilise treatment if more were available, or they may buy them over the counter.

In conclusion, the EAG notes the following:

The EAG acknowledges the additional evidence provided in the company's response, which supports the idea that acute migraine attacks may affect patients for much longer than 2 years. However, while this may be true, this does not dictate the appropriate time horizon length and the EAG's justification for the appropriateness of a 2-year time horizon was that, once the reduction in MMDs is removed, the treatment costs and consequences are modelled as short-term and acute. The EAG considers this to be in line with the National Institute for Health and Care Excellence (NICE) reference case stating, "A time horizon shorter than a patient's lifetime could be justified if there is no differential mortality effect between treatment options, and the differences in costs and health-related quality of life relate to a relatively short period (for example, in the case of an acute infection which has no long-term sequelae)". With the removal of MMD reductions the differences in costs and health-related quality of life relate to a relatively short period; each specific migraine episode.

A short-term time-horizon is favoured in this situation as it removes long-term uncertainty while capturing all relevant costs and consequences. It should be noted that the reason the treatment is more cost-effective in the model over a longer period is almost exclusively due to placebo patients assumed loss of response at 12 months. This assumption results in worse relative health outcomes for patients in the best supportive care (BSC) arm for all subsequent years.

The EAG does not consider any of the additional rationale put forward by the company in response to the ACD to be a reason for the EAG's position on the appropriate time horizon to change.

2.2 Comment 2. Acute migraine – reduced monthly migraine days (MMDs)

The company reiterated their justification for the reduction in MMDs to be included in the cost-effectiveness analysis due to acknowledgement from clinical experts and the committee that it is clinically plausible. The company considers removing the benefit highly conservative as the ACD acknowledges that this may result in a potential uncaptured benefit.

Since no additional arguments or data has been provided, the EAG position remains unchanged from appraisal committee meeting 1 (ACM1). The company has excluded MMD reduction from the updated base case.

2.3 Comment 3. Acute migraine – revised acute base case and scenario analyses

The company incorporated all the committee's preferred assumptions aside from the time horizon. However, the company has provided scenario analysis exploring alternate time horizons, in line with the committee's request. Further scenarios explored inclusion of MMD, *post-hoc* triptan failure subgroup analysis and prespecified triptan failure subgroup. These are all scenarios the company still maintains should be in the base case but they have excluded them in line with EAG and committee recommendations. Results can be found in Section 3.

2.4 Comments 4 to 6. Acute migraine – prespecified and *post-hoc* subgroup analyses

Comments 4 to 6 in the company's response to the ACD relate to the committee's request (Section 3.33 of the ACD) for:

- clarification of the difference between the prespecified and *post-hoc* subgroups;
- prespecified subgroup results from the clinical trials BHV3000-301, BHV3000-302 and BHV3000-303, for the population who have had 2 or more triptans that have not worked;
- and economic analyses using the prespecified subgroup results.

In terms of the differences between the prespecified and *post-hoc* subgroup definitions, the EAG presents the two definitions alongside each other in Table 3 below. The EAG notes these data are only based on three randomised controlled trials (RCTs; BHV3000-301, -302 and -303) given the fourth (BHV3000-310) did not have data for a ≥2 triptan failure subgroup. The company states that the rationale for changing this definition *post-hoc* was based on the small sample size identified for the original definition and to allow inclusion of those failing based on intolerability. The company notes that adverse events are a common reason for patients discontinuing triptan treatment in clinical practice and that patients do not typically trial all possible routes of administration for a single treatment before trying a different triptan; the EAG acknowledges that patients may discontinue triptans due to adverse events, which may be important to capture, but notes that feedback from experts at ACM1 suggests that it would not be unusual to try different routes of administration for the same triptan before moving on to a new triptan (Section 3.2 of the ACD).

The company concludes that results from the two analyses are similar for primary and secondary trial endpoints (Table 4 of the company's response to ACD), with uncertainty being slightly reduced in the *post-hoc* analysis due to a higher sample size. The EAG broadly agrees with this conclusion but notes that the risk differences are [redacted] in the *post-hoc* analysis, suggesting [redacted] for rimegepant vs placebo for all outcomes when compared to the risk differences obtained in the prespecified subgroup analysis. The EAG notes that for the key efficacy outcome used in the economic model to inform response (pain relief at 2 h), risk differences vs placebo are similar (a difference of [redacted] and [redacted] between rimegepant and placebo in prespecified and *post-hoc* analyses, respectively; Table 4). The EAG notes that the prespecified subgroup analysis is similar to the *post-hoc* analysis in terms of the extent that the risk difference for the pain relief at 2 h outcome differs compared to results in the overall modified intention to treat (mITT) population from these three studies, with the risk difference being [redacted] when the ≥2 prior triptan failures subgroup is focused on (Table 4).

As requested by the committee, the company has also performed a scenario analysis using the results of the prespecified analysis to inform treatment response for rimegepant and placebo. This is

presented in Section 3 and the results indicate that the difference between these subgroup definitions has limited impact on the incremental cost-effectiveness ratio (ICER).

While the EAG considers the company has addressed requests from the committee regarding these subgroup definitions, the EAG's preference remains for the overall mITT population, with the addition of the BHV3000-310 study, to be used in the base case of the economic model (which is now also reflected in the company's revised base case). This is based on limitations already described in the EAG's report and summarised below:

- although it was a prespecified subgroup analysis, the trials were not stratified by prior triptan failure at randomisation, meaning that randomisation is broken in the subgroup analysis;
- the full trial population provides a larger sample size and includes patients for whom triptan treatment was contraindicated;
- not all patients in the trials had tried a triptan, meaning that some classified in the 'no history of triptan discontinuation' subgroup might have been eligible for one of the two triptan discontinuation categories (one triptan failure or at least two triptan failures) had they been used;
- while baseline characteristics for rimegepant and placebo arms could not be compared by the EAG for the prespecified ≥2 triptan failure subgroup, the EAG notes that given randomisation was not stratified, it is possible that similar imbalances reported for the *post-hoc* analysis in the EAG's report ([redacted] proportion in the placebo group with aura and a [redacted] proportion in the rimegepant group with severe migraine [redacted] at baseline) would be observed. [redacted] for aura was observed between arms in the overall mITT population (see company response to clarification question A4, Appendix 3), though baseline migraine severity for the two arms in the mITT population is not reported;
- although for the *post-hoc* definition there is a [redacted] for the outcome used in the economic model to identify responders (pain relief at 2 h) between the group that had discontinued at least two triptans and those with no triptan discontinuations ([redacted] with rimegepant vs placebo in those with at least two discontinuations, see Tables 20 and 21 of the company submission [CS]), the EAG's clinical experts note that there is not a plausible clinical rationale to explain this result (although prior treatment failure status should not have a large effect on efficacy with a new drug if it

is a different class of drug to those used previously, if there was to be a difference, [redacted] would be expected in the group with [redacted]).

Table 3. Criteria for prespecified and post-hoc definitions of triptan non-responders (adapted from Table 3 of the company's response to the ACD and Table 17 of the CS)

Criteria	Prespecified triptan non-responder definition	*Post-hoc* triptan non-responder definition
Failure reason	Based on efficacy only. Subject must have provided at least one of the following efficacy reasons for failure: ● took too long to relieve headache pain; ● could not count on treatment to relieve pain and symptoms every time; ● pain returned after it was relieved within 24 h; ● did not relieve other symptoms.	Based on either efficacy or intolerability. The EAG assumes subjects needed to have at least one of the criteria described in the adjacent column for the prespecified definition. No further details about criteria for failure based on intolerability are provided.
Reason frequency	Most or all of the time.	This is not reported by the company, but the EAG assumes this is the same as described in the adjacent column for the prespecified definition.
Number of routes of administration for a single molecular entity that had to be failed	All routes of administration.	Subjects did not need to fail on all routes of administration (i.e. analysis was failure per product, not per molecular entity).
Number meeting the criteria for ≥2 triptan failures	Across the three trials, n=78 for rimegepant and n=104 for placebo.	Across the three trials, n=148 for rimegepant and n=177 for placebo.

Abbreviations: ACD, appraisal consultation document; CS, company submission; EAG, External Assessment Group.

Table 4. Comparison of pain relief at 2 h post-dose across different analyses presented by the company in acute migraine – adapted from Tables 5 and 6 of the company's response to the ACD

Outcome	Prespecified analysis, ≥2 triptan failures			*Post-hoc* analysis, ≥2 triptan failures			Overall pooled mITT analysis		
	RIM n/N (%)	PBO n/N (%)	RD (95% CI) p-value	RIM n/N (%)	PBO n/N (%)	RD (95% CI) p-value	RIM n/N (%)	PBO n/N (%)	RD (95% CI) p-value
Pain relief at 2 h post-dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ACD, appraisal consultation document; CI, confidence interval; EAG, External Assessment Group; mITT, modified intention to treat; PBO, placebo; RCTs, randomised controlled trials; RD, risk difference; RIM, rimegepant.

Based on pooling of all patients in the overall mITT populations of BHV3000-301, -302 and -303 RCTs or only those within these RCTs with ≥2 triptan treatment failures according to post-hoc or prespecified definitions of ≥2 triptan failures.

2.5 Comment 7. Migraine prevention – revised base case

The revised base case prevention model accepted all of the EAG recommended model changes; use of the random-effects baseline risk adjusted network meta-analysis (NMA), rimegepant responsibility to be defined as over 12 weeks and use of the recommended regression used to predict MMD distributions during the assessment period (although this update to the MMD distributions regression was not referenced in the text of the company response).

[redacted]. As a result, a revised base case has been produced to explore the primary care centric approach for migraine prevention. The revised base case includes a one-off initiation cost and a 3-month follow-up cost, with a GP (£39.23 per visit) for rimegepant and with a neurologist (£194.24 per visit) for the comparator mAbs. Additionally, a one-off neurologist referral cost has been added to the mAbs costed as one GP visit (£39.23).

The company suggest this is a conservative approach as monitoring care will likely continue in primary care for rimegepant and secondary for mAbs. Consequently, a scenario analysis has been provided whereby all rimegepant care (initiation visits, 3-month follow-up and monitoring visits) takes place in primary care for patients using rimegepant.

[redacted]. As a result, the EAG is not convinced by the company's updated costings as the committee previously identified that rimegepant would require a referral to a specialist, a specialist diagnosis before use, then treatment to be managed by a specialist, although it could eventually be used in primary care (Section 3.31 of the ACD).

3 Company updated results

3.1 Acute migraine treatment

The company's base case incorporates all EAG/committee preferred assumptions aside from the shortened time horizon. The only changes from the EAG base case model are a time horizon increase from 20 years to 2 years and the use of the total pooled acute mITT population to inform baseline patient characteristics (aside from MMD distribution). Base case results can be found in Table 5 and changes/scenario analysis can be found in Table 6.

Table 5. Company updated base case

Results per patient	Rimegepant	BSC	Incremental value
Revised base case			
Total costs	£5,611	£2,026	£3,584
Total QALYs	8.93	8.75	0.18
ICER (£/QALY)	-	-	£19,973

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

Table 6. Changes to the company's cost-effectiveness estimate in acute

Scenario	Incremental QALYs	Incremental costs	ICER (£/QALY)
Base case following TE	0.4117	£7,307	£17,521
Company revised base case following ACM1 (20-year time horizon)	0.1794	£3,584	£19,973
Company revised base case (20-year time horizon, probabilistic results)	0.4261	£7,397	£19,158
Time horizon scenarios			
15-year time horizon	0.1714	£3,444	£20,100
10-year time horizon	0.1512	£3,096	£20,474
5-year time horizon	0.1013	£2,233	£22,046
2-year time horizon	0.0408	£1,187	£29,109
Company scenarios			
Including reduction in MMD with 20- year time horizon	0.2353	£2,766	£11,753
Post-hoc triptan failure subgroup analysis	0.3644	£5,549	£15,226
Prespecified triptan failure subgroup analysis	0.3513	£5,536	£15,761

Abbreviations: ACM1, appraisal committee meeting 1; ICER, incremental cost effectiveness ratio; MMD, monthly migraine days; QALY, quality adjusted life years; TE, technical engagement.

3.2 Migraine prevention

The company have implemented all EAG assumptions into their updated base case.

The company have adopted updated costings which includes a one-off initiation cost and a 3-month follow-up cost, with a GP (£39.23 per visit) for rimegepant and with a neurologist (£194.24 per visit) for the comparator mAbs. Additionally, a one-off neurologist referral cost has been added to the mAbs costed as one GP visit (£39.23). The base case is shown in

Table 7. Company updated base case (prevention)

.

The company has also adopted a scenario analysis where all rimegepant care takes place in the primary care setting; shown as part of

Table 8.

Table 7. Company updated base case (prevention)

Results per patient	Ere (4)	Gal (3)	Fre (2)	Rim (1)	Incremental value		
					(1-4)	(1-3)	(1-2)
Total costs	£22,660	£24,466	£23,926	£16,927	-£5,733	-£7,539	-£6,999
QALYs	9.036	9.053	9.052	8.997	-0.038	-0.056	-0.054
ICER (£/QALY)	-				£150,269*	£135,082*	£128,714*
NHB £20,000/QALY					0.249	0.321	0.296
NHB £30,000/QALY					0.153	0.195	0.179

*SW quadrant ICER
Abbreviations: EAG, External Assessment Group; Ere, erenumab; Fre, fremanezumab; Gal, galcanezumab; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

Table 8. Changes to the company's cost-effectiveness estimate in prevention (incremental results presented with rimegepant as the comparator treatment and mAbs as the intervention)1

Treatment	Incremental QALYS*	Incremental costs*	ICER (£/QALY)	NHB (£30,000/ QALY WTP threshold)*	NHB (£20,000/ QALY WTP threshold*
Revised base case following technical engagement					
Galcanezumab	0.056	£6,020	£160,909	-0.145	-0.245
Fremanezumab	0.055	£5,482	£99,802	-0.128	-0.219
Erenumab	0.039	£4,105	£104,919	-0.098	-0.166
Revised base case following ACD					
Galcanezumab	0.056	£7,539	£135,082	-0.195	-0.321
Fremanezumab	0.054	£6,999	£128,714	-0.179	-0.296
Erenumab	0.038	£5,733	£150,269	-0.153	-0.249
Revised base case following ACD (probabilistic results)					
Galcanezumab	0.053	£7,288	£136,355	-0.189	-0.311
Fremanezumab	0.046	£6,487	£142,143	-0.171	-0.279
Erenumab	0.034	£5,375	£156,655	-0.145	-0.234
Scenario analysis 1					
Galcanezumab	0.056	£7,576	£135,749	-0.197	-0.323
Fremanezumab	0.054	£7,036	£129,398	-0.181	-0.298
Erenumab	0.038	£5,771	£151,244	-0.154	-0.251

*Note that the company presents these incremental results using the mAbs as the intervention and rimegepant as the comparator
Abbreviations: ACD, appraisal committee document; ICER, incremental cost effectiveness ratio; NHB, net health benefit; QALY, quality adjusted life years; WTP, willingness to pay.

4 EAG preferred assumptions

4.1 Correction to the EAG base case

4.1.1 Acute migraine treatment

The EAG base case for acute migraine has adopted one change since the previous iteration used for ACM1. This is the use of the total pooled acute mITT population to inform baseline patient characteristics (aside from MMD distribution). This was included in the EAG's base case submitted with the report but removed at TE as the EAG accepted the company's argument. This change has a minimal impact on the ICER, reducing it from £29,111 to £29,109. The only remaining divergence from the company base case is with the preferred time horizon.

The EAG base case results are shown in Table 9 and probabilistic results are shown in

Table 10. Note that there is significant deviation between the EAG's deterministic and probabilistic results because the PSA does not allow for the 201-migraine event distribution method. This method involves rerunning the model multiple times with different baseline migraine event numbers and then distributing the results using the BHV3000-201 trial data. For the PSA iterations the mean migraine attacks was used from the mITT data (including BHV3000-310).

Table 9. EAG updated deterministic base case

Results per patient	Rimegepant	BSC	Incremental value
Revised base case			
Total costs	£1,412	£225	£1,187
QALYs	1.27	1.22	0.04
ICER (£/QALY)	-	-	£29,109

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

Table 10. EAG updated probabilistic base case

Results per patient	Rimegepant	BSC	Incremental value
Revised base case			
Total costs	£940	£148	£792
QALYs	1.35	1.32	0.03
ICER (£/QALY)	-	-	£28,655

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

4.1.2 *Migraine prevention*

The company have implemented all EAG assumptions into their updated base case and have updated initiation and follow-up costs.

The EAG has not accepted the costing changes to initiation and follow-up for prevention put forward by the company in response to ACD; the only update to the EAG base case from TE is the reduced list price cost for rimegepant. The results are shown deterministically, in Table 11, and probabilistically, in Table 12.

Table 11. EAG deterministic base case (prevention)

Results per patient	Ere (4)	Gal (3)	Fre (2)	Rim (1)	Incremental value		
					(1-4)	(1-3)	(1-2)
Total costs	£22,237	£24,042	£23,502	£16,848	-£5,388	-£7,194	-£6,654
QALYs	9.036	9.053	9.052	8.997	-0.038	-0.056	-0.054
ICER (£/QALY)	-				£141,220*	£128,896*	£122,364*
NHB £20,000/QALY					0.231	0.304	0.278
NHB £30,000/QALY					0.141	0.184	0.167

*SW quadrant ICER
Abbreviations: EAG, External Assessment Group; Ere, erenumab; Fre, fremanezumab; Gal, galcanezumab; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

Table 12. EAG probabilistic base case (prevention)

Results per patient	Ere (4)	Gal (3)	Fre (2)	Rim (1)	Incremental value		
					(1-4)	(1-3)	(1-2)
Total costs	£22,333	£24,246	£23,445	£16,959	-£5,374	-£7,286	-£6,486
QALYs	9.024	9.043	9.035	8.990	-0.034	-0.053	-0.046
ICER (£/QALY)	-				£156,287*	£136,226*	£141,795*
NHB £20,000/QALY					0.234	0.311	0.279
NHB £30,000/QALY					0.145	0.189	0.170

*SW quadrant ICER
Abbreviations: EAG, External Assessment Group; Ere, erenumab; Fre, fremanezumab; Gal, galcanezumab; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

4.2 Scenarios around the EAG base case

4.2.1 Acute migraine treatment

In order to demonstrate that the time horizon is only indirectly influencing the cost effectiveness the EAG ran two scenarios. One is a 20-year time horizon with no loss of placebo response in the BSC arm, shown in

Table 13. The second is a 1-year time horizon in which placebo response is lost immediately, shown in

Table 14. It is notable that the 1-year time horizon becomes more cost-effective than the company base and the 20-year time horizon becomes less cost-effective than the EAG base case, demonstrating that the cost-effectiveness of rimegepant is highly dependent on the assumed benefit from the loss of placebo response in the comparator arm.

Table 13. EAG scenario 20 years no loss of placebo response (acute)

Results per patient	Rimegepant	BSC	Incremental value
Total costs	£5,611	£1,241	£4,370
QALYs	9.01	9.03	-0.02
ICER (£/QALY)	-	-	Rimegepant dominated

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

Table 14. EAG scenario 1 year with immediate loss of placebo response

Results per patient	Rimegepant	BSC	Incremental value
Total costs	£776	£144	£632
QALYs	0.64	0.61	0.03
ICER (£/QALY)	-	-	£19,453

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

4.2.2 *Migraine prevention*

The EAG has no new scenarios to provide regarding prevention treatment as there has been no significant change from the previous iteration.

The company has provided scenario analysis whereby all rimegepant care (initiation visits, 3-month follow-up and monitoring visits) takes place in primary care for patients using rimegepant. In order to validate the company's results the EAG has reproduced this scenario, using the company's primary care costs relating to initiation and follow-up. Results for this are shown in Table 12.

Table 15. EAG reproduced company scenario 1

Results per patient	Ere (4)	Gal (3)	Fre (2)	Rim (1)	Incremental value		
					(1-4)	(1-3)	(1-2)
Total costs	£22,660	£24,466	£23,926	£16,890	-£5,771	-£7,576	-£7,036
QALYs	9.036	9.053	9.052	8.997	-0.038	-0.056	-0.054
ICER (£/QALY)	-				£151,244*	£135,749*	£129,398*
NHB £20,000/QALY					0.250	0.323	0.297
NHB £30,000/QALY					0.154	0.197	0.180

*SW quadrant ICER
Abbreviations: EAG, External Assessment Group; Ere, erenumab; Fre, fremanezumab; Gal, galcanezumab; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

5 References

1. Steiner TJ, Scher AI, Stewart WF, Kolodner K, Liberman J, Lipton RB. The prevalence and disability burden of adult migraine in England and their relationships to age, gender and ethnicity. *Cephalalgia* 2003; **23**: 519-27.

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Rimegepant for treating or preventing migraine [ID1539]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report (section 1.1). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Clinical expert statement

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **Wednesday 19 October**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

Clinical expert statement

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating migraine and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Brendan Davies
2. Name of organisation	Association of British Neurologists
3. Job title or position	Consultant Neurologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with migraine? ☐ A specialist in the clinical evidence base for migraine? or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for migraine? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To reduce the impact of migraine related symptoms such as head pain, nausea/vomiting and any associated functional impairment and any resultant functional impairment that affects daily functioning both due to a migraine attack and/or by reducing the frequency of migraine attacks and associated symptoms.

9. In your clinical practice, what do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	There are several measures dependent on whether assessing "migraine attack treatment" or "preventative treatment". Migraine attack treatment – Pain free within 2-4 hours or able to function after acute treatment; Duration of benefit before migraine recurrence should be at least 24 hours and ideally longer Migraine prevention -This depends on the migraine subtype 30-50% reduction in monthly migraine day frequency or severe monthly migraine day (MMD) frequency is clinically significant. The lower figure is more acceptable with chronic migraine and 50% for episodic migraine but change in HIT-6 status by at least 6 points and ideally a change to less than 60 if there is no change in MMD suggest that although there may not have been an overall change in frequency the functional impact is significant.
10. In your view, is there an unmet need for patients in migraine?	Yes • Unmet needs in relation to acute migraine abortive treatment in Triptan non-responders or Triptan intolerant patients. • Unmet needs in terms of vascular or other contraindications to Triptans e.g. drug interactions if on multiple drugs affecting serotonin antagonism e.g. SSRIs, SNRIs • Unmet needs in relation to migraine prevention with repurposed anti-migraine drugs and tolerability as well as efficacy. • Unmet needs in terms of contraindications to new possible contraindications to long half-life mono-clonal antibody therapies • Unmet needs in terms of non-responders to anti-CGRP mono-clonal antibody therapies • Unmet needs in terms of ease of timely access to diagnosis and even more issues with widespread access to new injectable therapies and their provision (e.g. Botox clinics, Anti-CGRP monoclonal antibody services) • Unmet needs in terms of ease of prescription of new therapies & administrative prescription barrier logistics (Bluetec forms, Homecare

	services) • Unmet need for migraine sufferers in relation to primary care knowledge about the recognition and diagnosis of Migraine let alone knowledge about effective treatments
11. How is migraine currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	British Association for the Study of headache UK National Guidelines 2019 and online access via Home (headache.org.uk) for England & Wales SIGN Guidelines for Scotland Pharmacological management of migraine (sign.ac.uk) 2021-2022 NICE Guideline CG 150 (2012 & 2016) - needs revisitation & revision. Migraine is largely managed by GPs and other HCPs in the community with patients with high frequency migraine/chronic migraine +/- Medicagion koveruse headache, patients failing on at least 2-3 oral preventatives for migraine, patients with complex comorbidities or contraindications to conventional therapies being referred to secondary care. There is considerable variation across the UK about the threshold for referral and how the clinical pathway is delivered and by whom determined often by geographical area and dependent on primary care services, local resources, specialist headache services or general Neurology services across England as well as local & regional headache pathways. The new therapies are delivered by a variety of models of care across the UK since their introduction. This new technology might make it easier to treat more people more easily as oral agents are easier to prescribe, do not require refrigeration but compliance may be worse.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care?	In general, probably not. The only way it may be used in the same way is in patients with triptan non-response or intolerance to multiple triptan or other migraine acute abortive agents. This depends on if it used only as an acute abortive or as a preventative. It would add a new option.

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) •	Primary care prescription following recommendation by secondary care or specialist headache services/clinics (GPwSI run) would probably be the optimum clinical pathway to ensure the most clinically effective/appropriate and cost-effective therapy options are utilised first. This technology could then be prescribed in primary care on recommendation as primary care would need guidance given there will total unfamiliarity with this class of drugs. Prescribing directly from secondary care or specialist headache clinics/services only would introduce barriers to care.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes – It would certainly increase health-related quality of life more than current care for cohorts of patients who currently cannot access current migraine targeted therapies due to medical contraindications or intolerances
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There are groups where it would be appropriate rather than more or less effective. See Box 10 above
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Easier as process of oral prescription is logistically easier. I hope there will not be use of blutech process
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No formal or informal start or stop criteria for use in clinical practice in the UK have so far been suggested over and above the licence - I do not envisage additional monitoring or testing.
17. Do you consider that the use of the technology will	Certainly oral medication will ease usage but the frequency of usage may lead

result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	to worse adherence compared to a monthly injection and personal anecdotal experience with monthly monoclonal antibody therapies has shown excellent adherence and preference over more frequent oral therapies contrary to my intuition.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Innovative in terms of providing a new "oral formulation" with a short half live making it theoretically safer in patients with perceived increased medical risk with anti CGRP based therapies when compared to Long half-life Monoclonal antibody therapies. If the data is truly correct that alternate day preventative therapy has efficacy as well as usage as an effective abortive therapy then it would add a novel therapy option (the data is less robust than I would like) Offers unmet need in specific patient populations as an acute abortive therapy
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Unclear – at this time
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No – not entirely Triptans are used for at least 3 attacks to gauge efficacy reliability - not one The preventative data does not include CM patients with more than 16-18 headache days, Patients seen in most secondary care and specialist headache clinics have CM with higher frequency migraine & headache burden. Acute migraine attack response at 2hours and 24 hours I have insufficient experience using this technology to answer the adverse effects question.

21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence (e.g., clinical trial evidence) since the publication of NICE technology appraisal guidance Galcanezumab [TA659], Erenumab [TA682] and Fremanezumab [TA764] for preventing migraine?	No new clincal trial data on the 3 mentioned drugs but new data on Eptinezumab and a NICE STA – just about to be published (Jan 16th 2023)
23. How do data on real-world experience compare with the trial data?	Not aware of any large data publication
24. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population	I am not immediately aware of any

• lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Acute migraine	
Exclusion of chronic migraine (CM) patients from acute randomised controlled trials (RCTs) and extrapolating evidence from episodic migraine (EM) patients *The RCTs included to support rimegepant use in acute migraine treatment (EM or CM patients) excluded those with CM.* *Would you expect similar*	The response to acute abortive therapy in my experience is less in chronic migraine especially if very high frequency more than 20-22+ days per month or with daily pain at least with Triptans. Patient report worsening efficacy - shorter, less effective, needing more when compared with lower frequency episodic migraine. I am not aware of any observational or clinical trial that has reported a reliable differential response in EM and CM apart from anecdotal clinical observation but Medication overuse is often postulated with Triptans that may be a confounding factor It is probably not correct to exclude CM patients and then extrapolate acute abortive efficacy into this population without studying them

efficacy of an acute treatment between people with EM and CM in clinical practice? *In your opinion is it appropriate to extrapolate evidence from the included acute RCTs to the CM population?* *Are you aware of any evidence comparing the effectiveness of acute migraine treatments in EM and CM patients?*	
Cost-effectiveness results based on the orally dispersible tablet (ODT) formulation trials	I agree with the ERG
Using response to the first migraine attack to inform response to subsequent migraine attacks *The RCTs included to support rimegepant use in acute migraine treatment used a single attack design. The economic model therefore assumes that patients who do not respond to the first treatment would not respond to a subsequent treatment.* *Would you agree in the*	Acute therapy response ideally in clinical practice needs both clinically useful onset of benefit within a useful timeframe as well as reliability of response when acute treatment is repeated either for the same attacks or for multiple attacks in the month. Reliability over at least different 3 attacks treated is considered the standard for triptan usage based on prior clinical reliability of response studies. Patients want repeated reliability of beneficial response effect as well rapidity of the attack treatment benefit I am not aware of any Reliability of repeated attack therapy data or trials that has been published so far with this technology. There is data on triptans

treatment of acute migraine, it is generally recommended to try a particular treatment on two or three episodes before ending it? *Are you aware of any data on the effectiveness of rimegepant in subsequent migraine attacks after an initial failure that could from an alternative approach?*	
Baseline distribution of monthly migraine days (MMDs) *The company reported that baseline MMD was a key model driver in their one-way sensitivity analysis for rimegepant vs best supportive care (BSC).* *The ERG disagreed that study BHV3000-201, was the most appropriate source to inform the baseline distribution of MMDs. The ERG preferred baseline MMDs to be informed by the acute pooled RCTs to ensure consistency between sources used for pain relief, pain trajectories and baseline MMDs.*	The distribution of MMD in clinical practice varies from Daily migraine to 4 MMD or less. Acute abortive therapies are used at all frequencies of migraine if there is migraine attack related impairment of function and headache is major component

Is it appropriate to use study BHV3000-201 to inform the baseline distribution of MMDs? *What is the distribution of MMDs that would be seen in clinical practice?*	
Assuming rimegepant PRN can result in reductions in MMDs *Long-term reductions in MMD with PRN rimegepant were based on a post-hoc analysis of the long-term safety study in the company base case analysis.* *The ERG considered it more appropriate to remove reductions in MMD by PRN rimegepant from the base case analysis and include them in scenario analysis in the absence of long-term comparative evidence.* *Is it appropriate to assume rimegepant PRN can result in reductions in MMDs?*	It would be preferable to have more robust prospective comparative data on MMD reductions rather than post hoc analysis if Rimegepant is being proposed as a oral Migraine prevenative. It is unclear to me why a short half-life drug like Rimegepant given every 48 hours would definitely effect and reduce MMD frequency. It would be better to use this an interesting observation and do the Placebo controlled study in a specific preventive trial for both Episodic and defiantly Chronic migraine (given the patient population involved in the trial) to more accurately answer this question with certainty
Migraine prevention	

Discrepancy between the population described in the marketing authorisation and the decision problem described by the company (at least four migraine attacks per month vs at least four MMDs)	I note the ERG uncertainty. There should be consistency in definition
Generalisability of the rimegepant trial to the group with at least three prior preventive drug treatment failures (as specified by the company in the decision problem) *The decision problem described by the company focused on a subset of EM patients that had failed three prior preventive drug treatments. Those with non-response to more than two classes of preventive medications were excluded from the BHV3000-305 (rimegepant) trial. The company considers that results from the BHV3000-305 trial for rimegepant may provide a conservative estimate of treatment effect for a refractory*	I agree with the ERG. There is no robust data for preventive efficacy response failure of at least 3 prior preventative drugs for Rimegepant and even less robust data in a chronic migraine population. There is a need for s specific trail in this group of patients similar to the Anti CGRP Mabs for comparative or robust estimates of efficacy in more refractory populations (similar to Mabs FOCUS, CONQUER, LIBER|TY & DELIVER studies as there are currently no prior similar data on small molecule CGRP receptor antagonists available to model whether efficacy is adequate or worse according to baseline Migraine frequency and no of prior therapies.

population. The ERG disagreed. *Is the rimegepant trial generalisable to the group with at least three prior preventative drug treatment failures?* *Would you expect people with higher numbers of prior treatment failures to indicate refractory migraines?* *In your opinion, are refractory migraines more difficult to treat with new drug classes?*	
Uncertainty concerning the efficacy of rimegepant vs mAbs due to a lack of direct evidence and limitations of the network meta-analysis (NMA)	I agree generally with the ERG conclusion
Gradual vs immediate reversion to baseline MMD during the assessment period and after the assessment period	I do not know the answer to this. The Mabs suggests that CGRP blockade is a symptomatic therapy rather than disease modifying so I would theoretically expect a more abrupt or near immediate revision to baseline MMD within a week or two compared to 1-2 months with longer half life Anti CGRP MAbs
Response probability for rimegepant	
Applying the NMA results from Cycle 1 vs Cycle 3	

Comparator treatment acquisition costs *The company applied different acquisition costs in the initial 28-day cycle and subsequent 28-day cycles for the mAbs. For rimegepant, the acquisition cost in the initial 28-day cycle was the same as subsequent 28-day cycles.* *The ERG considers that initial 28-day treatment acquisition cost should equal the ongoing 28-day treatment acquisition cost for all treatments.* *What is the most appropriate approach for the acquisition costs assumed for the comparators (mABs)?*	I am not sure I understand this question fully.
Are there any important issues that have been missed in ERG report?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Rimegepant is new migraine mechanism based abortive therapy for migraine will allow previously uncatered for sufferer population to access a potentially effective therapy
The use of an oral, effective CGRP based therapy will allow easier logistical migraine mechanism focused management compared to delivery of injectable based therapies
The acute abortive efficacy over placebo appears satisfactory there are still some questions about the reliability of repeat dosing
The evidence and assumptions about its preventative action are not based on sufficiently robust methodology
The efficacy in chronic migraine populations and more refractory to 3 or more preventative therapies needs better clarification

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Rimegepant for treating or preventing migraine [ID1539]

NICE technical team questions for clinical experts following ACM1

Name: David Kernick

1. **Based on your experience and/or clinical judgement, for how many years do you think patients suffer from acute migraine attacks over their lifetime?**

Very much a guestimate based on max age of incidence – 15+ yrs and most stop post menopause say 50 yrs. There will be a very wide distribution. So 30 years is a reasonable first approximation.

2. **Based on the discussions at the first committee meeting, when long-term MMD reductions are not assumed what is the most appropriate time horizon to use for rimegepant as an acute migraine treatment?**

20 years is OK but one would anticipate that the prevention action will minimise need for acute.

3. The company's revised base case is from a primary care perspective (see company response form, section 7). Please explain how rimegepant could be offered in the primary care setting and identify if all the appropriate costs/resources have been considered in the company's revised base case.

No reason why neurol should only see patient once and GP follow up. At 6 mth and then yearly. No reason why GP should not initiate.

EAG's cost-effectiveness results

1.1 Acute migraine treatment

Table 1. EAG's base case acute model rerun with new rimegepant list price

Results per patient	Rimegepant	BSC	Incremental value
Revised base case			
Total costs	£1,351	£225	£1,126
QALYs	1.27	1.22	0.04
ICER (£/QALY)	-	-	£27,621

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

Table 2. Company's base case acute model rerun with new rimegepant list price

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

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

Table 3. EAG's base case acute model rerun with new rimegepant list price, placebo effect not removed at 1 year

Results per patient	Rimegepant	BSC	Incremental value
Revised base case			
Total costs	£1,351	£169	£1,182
QALYs	1.27	1.25	0.02
ICER (£/QALY)	-	-	£58,486

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

1.2 Migraine prevention (list prices)

1.2.1 Deterministic results

Table 4. EAG's preferred base case prevention model rerun with new rimegepant list price (deterministic pairwise results)

Results per patient	Ere (4)	Gal (3)	Fre (2)	Rim (1)	Incremental value		
					(1-4)	(1-3)	(1-2)
Total costs	£22,237	£24,042	£23,502	£16,665	-£5,572	-£7,377	-£6,837
QALYs	9.036	9.053	9.052	8.997	-0.038	-0.056	-0.054
ICER (£/QALY)	-				£146,031	£132,184	£125,740
NHB £20,000/QALY					0.240	0.313	0.287
NHB £30,000/QALY					0.148	0.190	0.174

Abbreviations: EAG, External Assessment Group; Ere, erenumab; Fre, fremanezumab; Gal, galcanezumab; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

Table 5. Company's preferred base case prevention model rerun with new rimegepant list price (deterministic pairwise results)

Results per patient	Ere (4)	Gal (3)	Fre (2)	Rim (1)	Incremental value		
					(1-4)	(1-3)	(1-2)
Total costs	£22,660	£24,466	£23,926	£16,743	-£5,917	-£7,723	-£7,182
QALYs	9.036	9.053	9.052	8.997	-0.038	-0.056	-0.054
ICER (£/QALY)	-				£155,079	£138,370	£132,089
NHB £20,000/QALY					0.258	0.330	0.305
NHB £30,000/QALY					0.159	0.202	0.185

Abbreviations: EAG, External Assessment Group; Ere, erenumab; Fre, fremanezumab; Gal, galcanezumab; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

Table 6. Company's scenario 1 model rerun with new rimegepant list price (deterministic pairwise results)

Results per patient	Ere (4)	Gal (3)	Fre (2)	Rim (1)	Incremental value		
					(1-4)	(1-3)	(1-2)
Total costs	£22,660	£24,466	£23,926	£16,706	-£5,954	-£7,760	-£7,220
QALYs	9.036	9.053	9.052	8.997	-0.038	-0.056	-0.054
ICER (£/QALY)	-				£156,055	£139,037	£132,773
NHB £20,000/QALY					0.260	0.332	0.307
NHB £30,000/QALY					0.160	0.203	0.186

Abbreviations: EAG, External Assessment Group; Ere, erenumab; Fre, fremanezumab; Gal, galcanezumab; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

1.2.2 *Probabilistic results*

Table 7. EAG's preferred base case prevention model rerun with new rimegepant list price (probabilistic pairwise results)

Results per patient	Ere (4)	Gal (3)	Fre (2)	Rim (1)	Incremental value		
					(1-4)	(1-3)	(1-2)
Total costs	£22,105	£24,009	£23,215	£16,574	-£5,531	-£7,435	-£6,641
QALYs	9.020	9.039	9.031	8.986	-0.034	-0.053	-0.045
ICER (£/QALY)	-				£162,831	£140,386	£146,370
NHB £20,000/QALY					0.243	0.319	0.287
NHB £30,000/QALY					0.150	0.195	0.176

Abbreviations: EAG, External Assessment Group; Ere, erenumab; Fre, fremanezumab; Gal, galcanezumab; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

Table 8. Company's preferred probabilistic base case prevention model rerun with new rimegepant list price (probabilistic pairwise results)

Results per patient	Ere (4)	Gal (3)	Fre (2)	Rim (1)	Incremental value		
					(1-4)	(1-3)	(1-2)
Total costs	£22,338	£24,251	£23,458	£16,768	-£5,570	-£7,483	-£6,690
QALYs	9.022	9.042	9.034	8.988	-0.034	-0.054	-0.046
ICER (£/QALY)	-				£161,493	£139,414	£145,193
NHB £20,000/QALY					0.244	0.320	0.288
NHB £30,000/QALY					0.151	0.196	0.177

Abbreviations: EAG, External Assessment Group; Ere, erenumab; Fre, fremanezumab; Gal, galcanezumab; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.