National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Rimegepant for treating or preventing migraine [ID1539]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Abbvie	Yes, the wording of the remit reflects the issues of clinical and cost-effectiveness about the technology that NICE should consider.	Comment noted. No changes to the draft scope required.
	British Association for the Study of Headache (BASH)	[Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider?] Yes	Comment noted. No changes to the draft scope required.
	Biohaven (manufacturer)	We suggest that the wording of the remit should be revised to reflect 'The clinical and cost effectiveness issues pertaining to the comprehensive management of migraine across the continuum of migraine care with rimegepant'.	Comment noted. The current wording of the remit in the draft scope covers both acute and preventative migraine treatment. No changes

Section	Consultee/ Commentator	Comments [sic]	Action
			to the draft scope required.
	Novartis	We consider the proposed wording of the remit appropriate.	Comment noted. No changes to the draft scope required.
	Teva	The wording appears appropriate	Comment noted. No changes to the draft scope required.
	The Migraine Trust	[Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider?] Yes	Comment noted. No changes to the draft scope required.
	Association of British Neurologists	[Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider?] Yes	Comment noted. No changes to the draft scope required.
Timing Issues	Abbvie	Routine	Comment noted. No changes to the draft scope required.
	British Association for the Study of Headache (BASH)	Migraine affects 15% of the general population and 2-5% are affected on a daily basis with significant disability and absenteeism causing direct cost to the NHS and indirect cost to the economy in general. There are available treatments, although adverse effects and contraindications due to co-morbidities leave a significant number of patients with limited or no choice. Any new treatments to relieve this painful condition are always welcomed as soon as possible.	Comment noted. No changes to the draft scope required.

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	Biohaven (manufacturer)	The timing of the appraisal is completely appropriate given the significant unmet need with regard to the acute treatment of migraine, the decades-long lack of novel acute therapies for migraine treatment, and deficiencies related to both traditional and novel treatments for the prevention of migraine, described in response to the background section below.	Comment noted. No changes to the draft scope required.
	Novartis	No comments.	N/A
	Teva	A number of other anti-calcitonin gene-related peptide (CGRP) drugs have recently been made available in the NHS.	Comment noted. No changes to the draft scope required.
	The Migraine Trust	We would say there is an urgency to this appraisal (within 2021) as many people do not have appropriate acute treatment for migraine. This is due to lack of effects, side effects, potential medication overuse headache from current treatments or medical comorbidities that exclude current acute treatments.	Comment noted. No changes to the draft scope required.
	Association of British Neurologists	Migraine represents a huge burden to the UK population in terms of morbidity and days lost to employment	Comment noted. No changes to the draft scope required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Abbvie	Mostly accurate and complete.	Comment noted. The background section is intended to provide a brief overview of the

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		Prevalence data from 2003 could be possibly updated with more recent data, if available. "…preventive drug treatments have failed.." – needs clarity if these drugs could belong to same class/category.	disease and its management. No changes to the draft scope required.
	British Association for the Study of Headache (BASH)	The information provided is accurate and includes all the relevant facts of the impact of migraine.	Comment noted. No changes to the draft scope required.
	Biohaven (manufacturer)	The information does not address the significant unmet need in migraine patients that cannot tolerate, respond or are ineligible to receive the current standard of care.The most commonly used migraine specific medication class for acute treatment are triptans. For many patients triptan treatments are not adequate or lose efficacy over time, have intolerable side effects, or cardiovascular contraindications. Among the population with contraindications, patients have no approved options, and resort to the persistent use of medications, such as barbiturates and opioids that have the potential for misuse/abuse. There is recognition among both practitioners and patients/advocacy that frequent use of acute medications can lead to medication overuse headaches, a serious condition often requiring intensive medical management. With regard to prevention, novel available biologic therapies (CGRP antagonist -monoclonal antibodies) do ameliorate the severity of migraine by reducing migraine frequency which is beneficial relative to the traditional oral preventatives. However, these newer agents are associated with high rates of discontinuation, due to attenuation of effect, immunogenicity issues, and	Comments noted. The background section is intended to provide a brief overview of the disease and its management. No changes to the draft scope required.

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		concerns for women of childbearing potential given biologic ½ lives of 5 weeks. In contrast with the injectable CGRP biologics, rimegepant 75 mg ODT offers a novel convenient oral medication for the comprehensive management of migraine, requiring no injection, and with a relatively short half-life (approximately 11 hours) that allows immediate cessation of therapy in the event of pregnancy, hypersensitivity reaction, or serious adverse event (SAE). The rapid onset of effect with rimegepant differentiates it from injectable biologics and older therapies. An oral agent such as rimegepant with comparable efficacy to the biologics in terms of migraine frequency reduction offers a better alternative to patients for whom biologic preventatives are indicated.	
	Novartis	The wording of the ICHD-3 definition of chronic migraine is "Headache occurring on 15 or more days/month *for more than 3 months*, which, on at least 8 days/month, has the features of migraine headache" [italicised emphasis added]. The draft scope description omits this italicised wording. As this wording relating to "more than 3 months" is also included in the NICE recommendation wording for fremanezumab as an option for preventing chronic migraine [TA631], it is important to ensure the full ICHD-3 definition of chronic migraine is accurately reported. The NICE recommendation for both erenumab [TA682] and galcanezumab [TA659] is described as relating to "adults who experience 4 or more migraines per month". This is inaccurate, as the recommendation refers to adults who experience 4 or more migraine ***days*** per month.	Comments noted. The draft scope background and comparator sections has been updated to state migraine days to reflect NICE recommendations for erenumab and galcanezumab.
	Teva	No comment	N/A
	The Migraine Trust	The background information is accurate and complete.	Comment noted. No changes to the draft scope required.

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	Association of British Neurologists	Yes: although there are existing acute and preventative treatments for migraine many patients have inadequate response to these, treatments may be contraindicated because of co-morbidities and patients may not tolerate side effects	Comment noted. No changes to the draft scope required.
The technology/ intervention	Abbvie	Yes, the description of the technology is accurate, however, the addition of following will make it more informative. "Rimegepant is administered orally…." – the information will be more complete with the frequency of administration. ".. adults who have 4 to 18 migraine attacks of moderate to severe intensity per month" – the trial population appears to cover a broader spectrum of patients. At the appraisal stage, an important consideration will be how and/or what proportion of trial patients meet the definitions used for the approved listed comparators, including more specifically, the chronic migraine definition per ICHD-3 (≥15 Migraine Headache Days); consistently used for the NICE approved MAbs and botulinum toxin.	Comment noted. The technology/intervention section of the scope is intended to give a brief description of the technology and the trial populations it has been studied in. No changes to the draft scope required.
	British Association for the Study of Headache (BASH)	Yes. Rimegepant has been studied both as acute and preventive therapy for episodic (EM) and chronic migraine (CM). The preventive study (Croop et al, Lancet 2021) only studied patients with 4-18 days of headaches per month, although a large number of CM sufferers have > 20 days of headaches per month and represent significant proportion of CM sufferers who were excluded from the trial. Existing preventive treatment was allowed to continue (excluding CGRP monoclonal antibodies), although those who had failed to respond to >2	Comments noted. The committee will consider the evidence submitted. No changes to the draft scope required.

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		preventives were excluded, suggesting the trial did not include a truly refractory population.	
	Biohaven (manufacturer)	We believe the description provided does not acknowledge that the novel function of rimegepant to serve as both an acute and preventive migraine treatment transcends the exclusive categories or classes of existing migraine treatments that are defined as either acute OR preventive treatment. If approved, rimegepant will provide for the comprehensive management of migraine (i.e., both acute treatment and prevention of migraine regardless of baseline frequency of attacks) with a simple single dose that does not require patients to engage in polypharmacy for treatment of their migraines. The formulation (oral dispersible tablet), the single dose (75mg), and the flexible regimen, provide for effective treatment of acute migraine across 21 efficacy measures (seen in BHV3000-303), and confer additional benefits such as migraine frequency reduction, and HRQOL benefits seen in both the open label long term safety study (BHV3000-201) and the placebo controlled prevention study (BHV3000-305).	Comment noted. The technology/intervention section of the scope is intended to give a brief description of the technology and the trial populations it has been studied in. No changes to the draft scope required.
	Novartis	No comments	N/A
	Teva	No comments	N/A
	The Migraine Trust	[Is the description of the technology or technologies accurate?] Yes	Comment noted. No changes to the draft scope required.
	Association of British Neurologists	Rimegepant inhibits the action of calcitonin gene related peptide: CGRP is known to be involved in the neural pathways that generate migraine attacks, but not otherwise thought to be involved in transmission of signals that can cause severe pain.	Comments noted. The committee will consider the evidence submitted.

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		The phase 2/3 placebo controlled study looking at Rimegepant for prevention of migraine (Croop at el Lancet 2021) excluded those with more than 18 headache days per month and those with non-response to more than 2 preventative drug categories	No changes to the draft scope required.
Population	Abbvie	Yes, appropriately defined. No, separate subgroups are not needed since it is noted that various subgroups as listed in “other considerations” will be explored, evidence permitting.	Comment noted. No changes to the draft scope required.
	British Association for the Study of Headache (BASH)	The disease burden of migraine is related to the number of days of headache per month, and its severity. Those with EM have <15 days of headache per month, although patients with 8-14 days (often referred as high frequency EM) have disease burden similar to CM, in comparison to those with <8 days/month. Similarly, the morbidity is high in those CM sufferers with >20 days of headache/month, particularly those that had failed >2 preventive treatments.	Comment noted. No changes to the draft scope required.
	Biohaven (manufacturer)	We feel it important to describe the eligible population in more detail. Suggest: patients requiring acute or preventive treatment. A relevant sub-group for acute treatment would be patients who are refractory/intolerant to triptans or who have a CV contraindication, for whom no approved migraine treatments are available. In the recent ICER review of novel acute agents, rimegepant was deemed to be cost effective (at $40,000/QALY gained) compared to the US equivalent of best alternative care.	Comment noted. The population defined in the scope is kept broad. If evidence allows, considerations of acute and preventative migraine separately should be provided. Relevant subgroups are highlighted in the “other

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			considerations" section of the draft scope, if evidence allows. No changes to the draft scope required.
	Novartis	Yes, the population is appropriate. However, given the differences in comparators and relevant outcomes between acute migraine and migraine prevention contexts (see below), it is appropriate to consider these two contexts within the adult migraine population as separate decision problems.	Comment noted. The comparator section of the draft scope highlights the different treatment options between acute migraine and migraine prevention. The "other considerations" section of the draft scope highlights relevant subgroups, if evidence allows. No changes to the draft scope required.
	Teva	No comments.	N/A
	The Migraine Trust	Yes, the population is appropriate defined	Comment noted. No changes to the draft scope required.
	Association of British Neurologists	For preventative treatment it is usual to consider episodic and chronic migraine separately as they represent different disease burdens	Comment noted. The comparator section of the draft scope highlights the different treatment options

Section	Consultee/ Commentator	Comments [sic]	Action
			between acute migraine and migraine prevention. The "other considerations" section of the draft scope highlights relevant subgroups, if evidence allows. No changes to the draft scope required.
Comparators	Abbvie	Yes, these are the standard approved treatments with which the technology should be compared. However, it will be important to ascertain how the eligibility criteria of the rimegepant trial compares to those of the comparators, at the appraisal stage. The reimbursed indication should be clearly indicated for each of the comparators as "episodic and chronic" or "chronic", as applicable. The definition of both episodic and chronic should be stated upfront. For erenumab and galcanezumab, "four or more migraines per month" should be corrected with "four or more migraine headache days per month". For fremanezumab, chronic migraine should be defined. For acute treatment, recommendations per the BASH guidelines (2019)[2] including simple analgesics, anti-emetics and triptans can be described as best alternative care.	Comment noted. The comparator section of the draft scope highlights the different treatment options between acute migraine and migraine prevention. The "other considerations" section of the draft scope highlights relevant subgroups, if evidence allows. The committee will consider the evidence submitted. The draft scope background and comparator sections has been updated to

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			state migraine days to reflect NICE recommendations for erenumab and galcanezumab.
	British Association for the Study of Headache (BASH)	The inclusion of CGRP monoclonal antibodies and OnabotulinumtoxinA as comparators for preventive treatment is inappropriate as they are indicated only following failure of three preventive treatments, and Rimegepant trials excluded those with failure of >2 preventives. Appropriate preventives to use as comparators would include amitriptyline, propranolol, topiramate (recommended in the NICE guidelines), and candesartan (recommended in BASH and SIGN guidelines).	Comment noted. The comparator section of the draft scope highlights the populations for which these treatments are comparators. The committee will consider the evidence submitted. No changes to the draft scope required.
	Biohaven (manufacturer)	Yes we agree that a relevant comparator is 'best alternative care' but should be defined as 'patients who are refractory/intolerant to triptans or who have a CV contraindication, for whom no approved migraine treatments are available.	Comment noted. No changes to the draft scope required.
	Novartis	We agree that the comparators are different for the acute migraine and migraine prevention contexts, and hence these two contexts will require different decision problems.	Comment noted. The draft scope background and comparator sections has been updated to state

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		We agree with the comparators included in the draft scope for these two contexts. All treatments listed as comparators in the 'Comparators' section of the draft scope are recommended as acute treatments or preventive treatments, accordingly, in the British Association for the Study of Headache (BASH) national headache management guidelines.[1] The wording specifying the populations in which erenumab and galcanezumab are comparators should say "4 or more migraine ***days*** per month" [days is currently missing]. [1]British Association for the Study of Headache (BASH). National Headache Management System for Adults 2019.	migraine days to reflect NICE recommendations for erenumab and galcanezumab.
	Teva	No comment	N/A
	The Migraine Trust	Yes, the listed comparators are the standard treatments currently used in the NHS	Comment noted. No changes to the draft scope required.
	Association of British Neurologists	For acute treatment 'best alternative care' could reasonably be described as the combination of a non-oral triptan and NSAID. For preventative treatment 'best alternative care' could reasonably be described oral preventive treatments (such as topiramate, propranolol, amitriptyline). Whist botulinum toxin and CGRP monoclonal antibodies are available as preventive treatment options, NICE guidelines suggest that these should only be used for patients who have failed at least 3 other classes of preventative treatment: the Croop et al 2021 study of preventive treatment with Rimegepant excluded those with non-response to more than 2 drug	Comments noted. The comparator section of the draft scope highlights the populations for which these treatments are comparators. The committee will consider the evidence submitted. No changes to the draft scope required.

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		categories and therefore a comparison with botulinum toxin an CGRP mabs is not reasonable in this context.	
Outcomes	Abbvie	Yes. It is understood that only the top-line outcome measures are listed in the scoping doc. and that the details (sub-groups) will be added in the full scope. For e.g. frequency of migraine headache days per month is listed as an outcome measure in the scoping doc but further details such as 50% responder rate for episodic and 30% for chronic migraine are missing. It is recommended that the outcome measures closely align to identified/listed comparator to facilitate robust comparison. Example and recommendations of additional outcome measures are listed below: • percentage of patients with episodic migraine with ≥50% reduction from baseline in mean monthly MHDs • percentage of patients with chronic migraine with ≥30% reduction from baseline in mean • change from baseline in the mean number of migraine days per month over the entire double-blind treatment phase (Weeks 1 to 12) change from baseline in the mean number of migraine days per month in the first 4 weeks (Weeks 1 to 4) of the double-blind treatment phase.	Comments noted. The committee will consider the relevant outcome measures. No changes to the draft scope required.
	British Association for the Study of Headache (BASH)	We agree the outcome measures suggested by NICE, although not all of them were used as outcomes in the Rimegepant studies. The acute Rimegepant study (Croop et al, Lancet 2019), used a 2 hour response for pain and the most bothersome symptom.	Comment noted. No changes to the draft scope required.

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		The preventive treatment trial (Croop et al, Lancet 2021) measured headache and migraine days, use of rescue medication, MSQ and MIDAS (health related quality of life measures).	
	Biohaven (manufacturer)	We agree with the list of outcomes measures but these should be described as one single listing pertaining to the comprehensive treatment of migraine. Further, given the corroboration of migraine frequency reduction seen in BHV3000-201 by an observed similar result in BHV3000-305, we maintain that this outcome pertains to the total treatment eligible population. We further recommend, that given the debilitating nature of migraine across its continuum, consideration should be given to indirect burden, such as measures of absenteeism/presenteeism, in work, school or leisure activities of daily living. We recently reported that 22% of migraine patients experience 30 days of absenteeism/presenteeism over 3 months.	Comments noted. The draft scope highlights that outcomes and comparator treatments vary between acute migraine and migraine preventive treatments. The committee will consider the evidence presented. The NICE methods guide outlines the relevant considerations in an appraisal. In section 5.1.10, it states that "*Productivity costs are not included in either the reference-case or non-reference-case analyses".* No changes to the draft scope required.
	Novartis	We agree with the draft scope that the relevant outcomes differ for the acute migraine and migraine prevention contexts.	Comments noted. The committee will consider

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		For migraine prevention, the outcome of response rate should be included, as defined by a ≥30% reduction in monthly migraine days (MMDs) and a ≥50% reduction in MMDs for chronic migraine and episodic migraine populations, respectively. As part of the erenumab appraisal [TA682] it was concluded that a 30% reduction in migraine frequency is considered a clinically meaningful response to treatment in chronic migraine, and a 50% reduction is considered a clinically meaningful response in episodic migraine. This same conclusion was reached by the appraisal committees for the fremanezumab [TA631] and galcanezumab [TA659] appraisals. As a clinically meaningful outcome, this should be included for the assessment of migraine prevention.	the relevant outcome measures. No changes to the draft scope required.
	Teva	No comment	N/A
	The Migraine Trust	Yes, the outcomes are appropriate and relevant for the technology appraisal.	Comment noted. No changes to the draft scope required.
	Association of British Neurologists	Yes: a combination of overall health related quality of life and a measure of reduction in migraine symptoms (e.g. 2 and 24 hrs pain freedom post-dose) should be used.	Comment noted. No changes to the draft scope required.
Economic analysis	Abbvie	Since migraine is a long-term condition, a time horizon of 25 years should be sufficiently long to capture costs and outcomes associated with the disease.	Comment noted. The committee will consider the relevant time horizons in the appraisal. No changes to the draft scope required.

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	British Association for the Study of Headache (BASH)	There should be a separate time horizon for cost effectiveness related to acute and preventive treatment. A longer time horizon is used for preventive therapy considering natural history of the disease.	Comment noted. The committee will consider the relevant time horizons in the appraisal. No changes to the draft scope required.
	Biohaven (manufacturer)	We maintain that the time horizon for the economic analysis should be sufficiently long to capture the total value of rimegepant treatment (i.e., including migraine frequency, reduction associated with repeated effective acute treatment, and the anticipated amelioration of medication overuse headache). The recent ICER Evidence Review concluded that "For adults with moderate-severe migraine attacks patients for whom triptans are not effective, not tolerated, or are contraindicated, rimegepant cost effectiveness ratios fell below commonly cited thresholds for cost-effectiveness (i.e., $50,000-$150,000/QALY gained) at an estimated net price that conferred a Cost Effectiveness ratio of $39,800/QALY gained". These cost effectiveness ratios thus anticipate a favorable finding for rimegepant in this base-case given consistent model designs (i.e., between ICER and NICE). We further recommend consideration of an integrated cost-effectiveness model that captures the continuum of care (i.e., acute treatment benefits, long-term benefits of repeated effective acute treatment (e.g., migraine frequency reduction, HRQOL improvements and associated health state utility increments), and the cumulative benefit of same on the progressive severity of migraine in the prevention population.	Comments noted. No changes to the draft scope required.
	Novartis	No comments	N/A

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	Teva	A lifetime time horizon was preferred in recent appraisals of migraine drugs (TAs: 631, 659 and 682), although how this was defined differed. Careful consideration should be given to the definition of 'lifetime'.	Comment noted. The committee will consider the relevant time horizons in the appraisal. No changes to the draft scope required.
	Association of British Neurologists	The time horizon for the economic analysis of migraine treatments is difficult to estimate as migraine incidence may fluctuate widely during an individual's lifetime, but a 5-10 year time horizon may be appropriate for preventative treatment, There should be a separate time horizon for cost effectiveness related to acute and preventive treatment.	Comment noted. The committee will consider the relevant time horizons in the appraisal. No changes to the draft scope required.
Equality and Diversity	Abbvie	The proposed scope and remit do not exclude any people protected by the equality legislation, lead to a recommendation that has a different impact on people protected by equality legislation than on the wider population or lead to recommendations that have an adverse impact on people with a particular disability or disabilities.	Comment noted. No changes to the draft scope required.
	British Association for the Study of Headache (BASH)	The disease affects women nearly three times more than men. Migraine is more common in age group 18-45.	Comments noted. The committee will consider the relevant equalities issues in this appraisal. No changes to the draft scope required.

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	Biohaven (manufacturer)	We feel that the intended indication for rimegepant, i.e., for the comprehensive management of migraine in adults, including prophylaxis of migraine and acute treatment of migraine with or without aura), does assure equality among the treatment eligible population. Migraine is an exceedingly disabling condition, particularly among people in the general population, and while in their most productive years. Impact to quality of life, and work-loss productivity are seen even in the early stages of the disease, leading to loss of employment and health care resource utilization (ER and office visits, medication overuse headache, and opioid dependence. Lastly, we feel that our recommendations with regard to the proposed remit and scope, coupled with our intended comprehensive indication, do assure equality of treatment for all patients	Comment noted. No changes to the draft scope required.
	Novartis	No comments.	N/A
	Teva	No comment	N/A
	Association of British Neurologists	No concerns	Comment noted. No changes to the draft scope required.
Other considerations	Abbvie	None.	N/A
	British Association for the Study of Headache (BASH)	Medication overuse is seen in up to two-thirds of patients with CM. It is unclear from the Rimegepant preventive study if those with medication overuse were excluded from the study.	Comment noted. The appraisal committee will consider the available evidence. No changes to the draft scope required.

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	Biohaven (manufacturer)	We agree with the subpopulations so defined in this section, and would recommend that these not be considered as additional issues, but relegated to the base-case consideration for assessment of the cost-effectiveness of Rimegepant.	Comment noted. If evidence allows, considerations of acute and preventative migraine separately should be provided. The subgroups identified in the "other considerations" section have been highlighted as relevant and can be considered if evidence allows. No changes to the draft scope required.
	Novartis	We agree with the relevance of the subgroups proposed for migraine prevention. Two of the relevant comparators for migraine prevention (fremanezumab [TA631]; botulinum toxin [TA260]) are only recommended by NICE for use in chronic migraine (i.e. excluding episodic migraine) and several of the treatments listed in the 'Comparators' section for migraine prevention are recommended only after at least 3 preventive drug treatments have failed. Therefore, subgroup analyses by chronic/episodic migraine and by number of previous preventive treatment failures are appropriate.	Comment noted. No changes to the draft scope required.
	Teva	No comment	N/A
	The Migraine Trust	It would be helpful to identify any potential drug interactions or medications to avoid when using this treatment. For example, can it be used with other acute treatments, how many attacks do you need to treat before efficacy is assessed.	Comments noted. This information should be included in the summary of product

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			characteristics for this technology when available. No changes to the draft scope required.
	Association of British Neurologists	Medication overuse is seen in up to two third of patients with chronic migraine. It is unclear from the Rimegepant preventive study if those with medication overuse were excluded from the study.	Comment noted. The appraisal committee will consider the available evidence. No changes to the draft scope required.
Innovation	Abbvie	Although various oral preventive treatments are available including medications from classes such as β-blockers, tricyclic antidepressants, antiepileptics, and angiotensin receptor antagonists, none are developed specifically for the treatment of migraine. Low efficacy and poor tolerability are commonly cited as reasons for failure and discontinuation of migraine preventive treatments.[3] The recently approved CGRP MAbs require subcutaneous administration every month or every 3 months, which is likely to have compliance disadvantages. Another important limitation of the MAbs is the need for low temperature storage conditions. Therefore, the development of oral alternatives can provide a clinically important treatment option within the CGRP class. The frequency of administration for rimegepant, however, could be an important compliance associated limiting factor. Considering the above, it is yet to be seen how Rimegepant's efficacy compares to other approved treatments for this indication.	Thank you for your comment. The extent to which the technology may be innovative will be considered in any appraisal of the technology. No changes to the draft scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		[Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?] No	
	British Association for the Study of Headache (BASH)	Rimegepant is the first ever treatment that is efficacious both as acute and preventive treatment. Existing specific acute and preventive migraine treatments targeted at CGRP (triptans, and CGRP monoclonal antibodies, respectively) are relatively contraindicated in patients with cardiovascular morbidity, This is not the case for Rimegepant. Adverse events with Rimegepant are few and mild, and the discontinuation rate was only 2%, suggesting excellent tolerability.	Thank you for your comment. The extent to which the technology may be innovative will be considered in any appraisal of the technology. No changes to the draft scope required.
	Biohaven (manufacturer)	Rimegepant is the first and only migraine treatment that functions as **both** an acute and preventive migraine treatment and able to be utilized aross the spectrum of disease (regardless of frequency of migraines) and the continuum of care (acute and preventive treatment). For the reasons cited above, we do maintain that rimegepant does constitute a ‘step change’ in the treatment of migraine. The long-term benefit of repeated effective acute treatment with rimegepant confers benefits such as migraine frequency reduction, HRQOL and work-loss productivity benefits, that are likely to alter the course of migraine disease progression (i.e., reduced risk for MOH, and transition to chronicity). With regard to patients who require preventative treatments, rimegepant provides an equally effective alternative to the biologics, without several of the liabilities of biologic	Thank you for your comment. The extent to which the technology may be innovative will be considered in any appraisal of the technology. No changes to the draft scope required.

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		treatment (attenuation of effect, immunogenicity, WOCBP issues such as 5 week ½ life.). We maintain that the totality of data to be provided to the Appraisal Committee will illustrate the unique value of rimegepant. In addition to the registrational trials, data will be provided that illustrates migraine frequency reduction, HRQOL and work-loss productivity, (all mapped to improvements in health state utilities, reduced pill burden, and direct health care resource costs). Further, a series of indirect comparisons (both network meta-analyses, and matched adjusted indirect comparisons) will illustrate improved efficacy and tolerability versus triptans, and comparable efficacy with better tolerability versus the biologic preventative agents.	
	Novartis	For migraine prevention NICE has already recommended three CGRP inhibitors. For acute migraine treatment, if recommended, rimegepant would be the first CGRP inhibitor recommended for use in this context.	Thank you for your comment. The extent to which the technology may be innovative will be considered in any appraisal of the technology. No changes to the draft scope required.
	Teva	In terms of mechanism of action, the technology is of limited innovation, as it acts in the same manner (CGRP receptor antagonist) as some established migraine therapies (*e.g.* fremanezumab) The oral form, and implications there of, differentiates this intervention from existing subcutaneous anti-CGRP drugs in the prevention of migraine In the acute treatment of migraine, the technology could represent an alternative for people for whom triptans are contraindicated or not tolerated	Thank you for your comment. The extent to which the technology may be innovative will be considered in any appraisal of the technology. No changes

Section	Consultee/ Commentator	Comments [sic]	Action
			to the draft scope required.
	The Migraine Trust	It has the potential to have a substantial positive impact especially to those currently unable to use triptans or NSAIDs or have no or inadequate benefit from these.	Thank you for your comment. The extent to which the technology may be innovative will be considered in any appraisal of the technology. No changes to the draft scope required.
	Association of British Neurologists	Yes: Rimegepant is the first ever treatment to be shown to be effective as both an acute and preventive treatment. It is particularly relevant to those with cardiovascular co-morbidities in whom standard migraine treatment with triptans is relatively contraindicated. For those without cardiovascular co-morbidities, it represents an alternative to existing acute and preventative treatments which may be ineffective or not well tolerated: adverse events are few, mild and the discontinuation was only 2% suggesting good tolerability.	Thank you for your comment. The extent to which the technology may be innovative will be considered in any appraisal of the technology. No changes to the draft scope required.
Questions for consultation	Abbvie	***Which treatments are considered to be established clinical practice in the NHS for acute migraine or preventing migraine?*** For acute migraine, the treatments as listed in the BASH guidelines (2019)[2] inclusive of simple analgesics (aspirin, diclofenac, ibuprofen, ketoprofen, naproxen, paracetamol and tolfenamic acid) and anti-emetics (domperidone,	Comments noted. No changes to the draft scope required.

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		prochlorperazine and metoclopramide) and triptans (almotriptan, eletriptan, flovatriptan, naratriptan, sumatriptan and zolmitriptan). For prophylaxis, galcenezumab, fremanezumab and erenumab are relatively new NICE approved drugs, although yet to be ascertained if they are accepted clinical practice. Botulinum toxin (Botox) in chronic migraine is NICE approved since 2012 and is an established and widely-used treatment. ***How should best supportive care be defined? Should best supportive care be considered as a comparator?*** Best supportive care should be defined as care/treatment that is made available as the last resort after the failure of approved treatments and/or in the absence of approved treatment/s for the indication. In this case, BSC comprises of treatments used for acute management of migraine using simple analgesics (i.e. ibuprofen, aspirin or paracetamol), a triptan with or without paracetamol or non-steroidal anti-inflammatory drugs. Previous appraisals for CGRP MAbs have treated BSC as a comparator and this would continue to be relevant where rimegepant were being considered for patients who had failed on advanced lines of treatment such as other CGRPs or botulinum toxin. Where CGRPs or botulinum toxin are alternative treatment options (ie in the space where they have been approved by NICE) then these, rather than BSC, should be the relevant comparators. ***To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.*** Experience suggests that issues with NHS capacity stemming from factors such as the UK's relatively low number of neurologists and scarcity of	

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		headache specialists can act as an adoption barrier for advance lines of migraine treatment.	
	Biohaven (manufacturer)	All questions pertaining to the consultation have been addressed. We further concur and support NICE's decision to conduct a Single Technology Appraisal for rimegepant. We fully endorse the STA process and intend to cooperate with NICE with regard to addressing supportive data requirements as needed. We reiterate our last recommendation that an integrated cost effectiveness model be developed to fully capture the unique benefits of rimegepant across the continuum of migraine care.	Comment noted. No changes to the draft scope required.
	Novartis	*How should best supportive care be defined? Should best supportive care be considered as a comparator?* In the migraine prevention context, recent NICE technology appraisal guidance for recommended migraine prevention treatments (erenumab [TA682], fremanezumab [TA631] and galcanezumab [TA659]) has referred to best supportive care (BSC) as "treatment for migraine symptoms". The relevance of BSC as a comparator in the migraine prevention context depends on where the rimegepant manufacturer positions rimegepant relative to currently recommended treatment options. For example, if rimegepant is positioned for use after failure of all other recommended treatment options for migraine prevention that are detailed in the 'Comparators' section of the draft scope then BSC would be a relevant and appropriate comparator. *Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom rimegepant is expected to be more clinically effective and cost effective or other groups that should be examined separately?*	Comment noted. No changes to the draft scope required.

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		Please see our comment on subgroups in the 'Other considerations' section above. *Where do you consider Rimegepant will fit into the existing NICE pathway Headaches?* Pending the outcome of appraisal for the acute migraine context against the comparators outlined in the draft scope, we would envisage that rimegepant would fit within the "Acute treatment" section of the "Management of migraine (with or without aura)" part of the NICE Headaches pathway. Separately, pending the outcome of appraisal for the migraine prevention context against the comparators outlined in the draft scope, we would envisage that rimegepant would additionally fit within the "Prophylactic treatment" section of the "Management of migraine (with or without aura)" part of the NICE Headaches pathway. *NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process.* We consider an STA to be the appropriate NICE assessment route.	
	Teva	**Have all relevant comparators for rimegepant been included in the scope?** No comment **Which treatments are considered to be established clinical practice in the NHS for acute migraine or preventing migraine?**	Comment noted. No changes to the draft scope required.

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		All of the treatments described in the scope should be considered as established clinical practice. Guidance for fremanezumab (TA631) was published 03 June 2020, so this treatment can be considered established clinical practice in the NHS for preventing migraine for the purposes of this appraisal. **How should best supportive care be defined? Should best supportive care be considered as a comparator?** Best supportive care should be defined and considered as in the previous appraisals. **Are the outcomes listed appropriate?** No comment. **Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom rimegepant is expected to be more clinically effective and cost effective or other groups that should be examined separately?** • **Would rimegepant be used in combination with existing treatments for the prevention of migraine?** • **If used for the prevention of migraines, would additional treatment be used in event of acute migraine or would treatment continue with rimegepant?** • **Would rimegepant be used in combination with existing treatments for acute migraine attacks?** No comment.	

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		Where do you consider rimegepant will fit into the existing NICE pathway, Headaches? This will ultimately depend on its cost-effectiveness. As an acute treatment, it could be an alternative for people for whom triptans are contraindicated or not tolerated. As a preventive treatment, it could be an option for people who have failed several previous lines of treatment.	
	The Migraine Trust	• **How should best supportive care be defined? Should best supportive care be considered as a comparator?** Best supportive care usually refers to treatment for the migraine symptoms which is appropriate. It should be considered a comparator. • **Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom rimegepant is expected to be more clinically effective and cost effective or other groups that should be examined separately?** Yes, the subgroups suggested are appropriate. • **Would rimegepant be used in combination with existing treatments for the prevention of migraine?** This is generally explored in practice or at a later stage. Usually the preference is to take as few medications as needed, however, it's something that could potentially be useful for some people (if supported by evidence of effectiveness and safety). • **If used for the prevention of migraines, would additional treatment be used in event of acute migraine or would treatment continue with rimegepant?** This is something that may become clearer when it is used in practice or at a later stage. There may be factors that influence this likelihood that we are	Comment noted. The committee will consider the evidence submitted. No changes to the draft scope required.

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		currently unaware of. It may also be something that needs to be evaluated on an individual basis, for example, if triptans are safe and tolerable they may be a preferred acute option for quicker relief, alongside rimegepant as a preventive treatment (in a similar way to current treatment management). • **Would rimegepant be used in combination with existing treatments for acute migraine attacks?** This is generally explored in practice or at a later stage. Usually the preference is to take as few medications as needed, however, it's something that could potentially be useful for some people (if supported by evidence of effectiveness and safety). • **Where do you consider rimegepant will fit into the existing NICE pathway, Headaches?** It's likely to depend on cost, access and long-term safety. However, it could come after simple analgesics, especially for people who can't tolerate other treatment options. • **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** A barrier is likely to be point of access. If they are only available via a specialist that is likely to create issues with access, especially as an acute treatment option. It would be helpful for GPs (and not only specialists) to be allowed to prescribe as they are the usual first point of access for an acute migraine treatment and the long waiting times to see specialists.	
Additional comments	Novartis	The 'Related NICE recommendations and NICE Pathways' section of the draft scope refers to the 'Headaches (2020) NICE Pathway'. However, the most recent update of this pathway was in May 2021, so this should be reflected accordingly.	Comment noted. The draft scope has been updated to include this correction.

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	Teva	Any additional comments on the draft scope. In the section 'Related NICE recommendations and NICE Pathways', for consistency, fremanezumab, erenumab and botulinum toxin A should also have their review dates stated (or in the case of botulinum toxin A, that it will be reviewed only if significant new evidence available etc), otherwise delete for galcanezumab. The link to the botulinum toxin A guidance incorrectly links to the erenumab guidance.	Comment noted. The review dates have been added to other NICE technology appraisal guidance in the draft scope. The link to the botulinum toxin type A guidance has been corrected.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

- GlaxoSmithKline