NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Rimegepant for treating or preventing migraine [ID1539]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Rimegepant for treating or preventing migraine [ID1539]

Contents:

The following documents are made available to consultees and commentators:

Access the **final scope** and **final stakeholder list** on the NICE website.

Pre-technical engagement documents

1. **Company submission** from Pfizer

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. Association of British Neurologists headache and pain advisory group
   b. British Association for the Study of Headache
   c. The Migraine Trust

4. **Evidence Review Group report** prepared by BMJ TAG

5. **Evidence Review Group report – factual accuracy check**

Post-technical engagement documents

6. **Technical engagement response from company**

7. **Technical engagement responses and statements from experts:**
   a. David Kernick, GP – clinical expert, nominated by Teva UK
   b. Andy Bloor – patient expert, nominated by The Migraine Trust
   c. Deborah Sloan – patient expert, nominated by The Migraine Trust

8. **Technical engagement responses from consultees and commentators:**
   a. Association of British Neurologists Advisory Group on Headache and Pain
   b. British Association for the Study of Headache
   c. The Migraine Trust
   d. Novartis
   e. Teva

9. **Evidence Review Group critique of company response to technical engagement** prepared by BMJ TAG

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Rimegepant for treating or preventing migraine [ID1539]

Document B

Company evidence submission

June 2022

File name	Version	Contains confidential information	Date
ID1539-Rimegepant-Migraine-DocumentB-[ACIC].docx	Final	**Yes**	**22 June 2022**

Contents

List of tables

List of figures

Abbreviations

Abbreviation	Definition
AAFP	American Academy of Family Physicians
AE	Adverse event
AHS	American Headache Society
AIC	Akaike Information Criterion
ALT	Alanine aminotransferase
AMPP	American Migraine Prevalence and Prevention
ARB	Angiotensin Receptor Blocker
AST	Aspartate aminotransferase
AUC	Area under the curve
BASH	British Association for the Study of Headache
BL	Baseline
BMI	Body Mass Index
BNF	British National Formulary
BSC	Best Supportive Care
CE	Conformitè Europëenne
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CEAF	Cost-effectiveness acceptability frontier
CFB	Change from baseline
CGI-C	Clinical Global Impression of Change
CGRP	Calcitonin gene-related peptide
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CM	Chronic migraine
CMH	Cochran-Mantel Haenszel
COPD	Chronic Obstructive Pulmonary Disorder
COVID-19	Coronavirus disease
CRD	Centre for Reviews and Dissemination
CRF	Case report form
CRO	Contract research organisation
CSR	Clinical study report
CT	Computerised tomography
CUA	Cost utility analysis
CV	Cardiovascular
CYP3A4	Cytochrome P450 3A4
DALYs	Disability adjusted life years
DB	Double blind
DBL	Database lock
DBT	Double blind treatment
DC	Discontinuation
DIC	Deviance Information Criterion
DSU	Decision Support Unit
EC	European Commission

ECG	Electrocardiogram
ED	Emergency department
eDiary	Electronic diary
EE	Economic evaluation
EF	Emotional function
EM	Episodic migraine
EMA	European Medicines Agency
EOD	Every other day
EOT	End of treatment
EQ-5D(3L)	Euro-Qol five dimension (three level)
ERE	Erenumab
ERG	Evidence Review Group
FDA	Food and Drug Administration
FE	Fixed effects
FRE	Fremanezumab
GAL	Galcanezumab
GBD	Global burden of disease
GI	Gastrointestinal
GLM	Generalised linear model
GLMEM	Generalised linear mixed effects model
GP	General practitioner
GPwSI	General practitioner with a special interest
HALT-90	Headache-Attributed Lost Time over 90 days
HALT-30	Headache-Attributed Lost Time over 30 days
HCP	Healthcare providers
HCRU	Healthcare resource use
HIV	Human immunodeficiency virus
HRG	Healthcare resource group
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ICF	Informed consent form
ICHD-III	International Classification of Headache Disorders, third edition
ID	Identification
HIS	International Headache Society
IQR	Interquartile range
ITT	Intention to treat
IV	Intravenous
IWRS	Interactive web response system
JAGS	Just Another Gibbs Sampler
KM	Kaplan-Meier
LSM	Least squares mean
LTT	Long-term treatment period
mAb	Monoclonal antibody
MBS	Most bothersome symptom
MD	Migraine day
MFIQ	Migraine Functional Impact Questionnaire

MHD	Monthly headache day(s)
MHRA	Medicines and Healthcare products Regulatory Authority
MIDAS	Migraine Disability Assessment Test
MIMS	Monthly Index of Medical Specialties
mITT	Modified intent to treat
MMD	Monthly migraine day(s)
MOH	Medication overuse headache
MQoLQ	Migraine Quality of Life Questionnaire
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
MRV	Magnetic resonance venography
MSQv2	Migraine Specific Questionnaire Version 2
MSQoL	Migraine Specific Quality of Life Questionnaire
MWPLQ	Migraine Work and Productivity Loss Questionnaire
NA	Not applicable
NB	Negative binomial
NBRM	Negative binomial regression model
NCT	National Clinical Trial
NHS	National Health Service
NHWS	National Health and Wellbeing Survey
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMB	Net monetary benefit
NR	Not reported
NS	Not significant
NSAID	Non-steroidal anti-inflammatory drug(s)
ODT	Orally dispersible tablet
OLE	Open-label extension
ONS	Office for National Statistics
OP	Observation period
OR	Odds ratio
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PBO	Placebo
PICOS	population, intervention, comparator, outcomes, study design
PoM	Preference of Medication
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PRN	*Pro re nata* (as needed)
PRO	Patient reported outcomes
PROMIS	Patient-Reported Outcomes Measurement Information System
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services
PSSRU	Personal Social Services Research Unit
PT	Preferred Term

QALH(s)	Quality Adjusted Life Hour(s)
QALY(s)	Quality Adjusted Life Year(s)
RCT	Randomised Controlled trial
RE	Random effects
RFP	Role function preventive
RFR	Role function restrictive
RIM	Rimegepant
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SM	Satisfaction with Medication
SoC	Standard of care
SOC	System organ class
SOP	Standard operating procedure
TA	Technology appraisal
TEAE	Treatment emergent adverse event
TIA	Transient ischemic attack
UK	United Kingdom
ULN	Upper limit of normal
US	United States
USA	United States of America
USD	United States Dollars
UTI	Urinary tract infection
VAS	Visual analogue scale
WPAI	Work Productivity and Activity Impairment
WTP	Willingness to pay
YLDs	Years of life lived with disability
ZINB	Zero-inflated negative binomial

B.1. Decision problem, description of the technology and clinical care pathway

B.1.1. Decision problem

The submission focuses on specific patient populations within the technology's marketing authorisation, which will be referred to briefly as "acute migraine" and "migraine prevention" throughout. The proposed target populations are narrower than the marketing authorisation because of their relevance to NHS clinical practice. Based on expert clinical opinion obtained at UK advisory boards in 2022,[1] the proposed populations of acute migraine and migraine prevention are aligned with potential use in the current treatment pathway:

- **Acute migraine:** As an option for patients who have had inadequate symptom relief after trials of at least two triptans or in whom triptans are contraindicated or not tolerated; and have inadequate pain relief with NSAIDs and paracetamol. In the acute setting, rimegepant would not be used in patients in whom triptans are a suitable option; the unmet need is greater for patients in whom triptans are ineffective or are not appropriate due to safety and tolerability considerations.
- **Migraine prevention:** As an option for patients with episodic migraine who have at least four migraine days per month, but fewer than 15 headache days per month and have failed three or more preventive oral drug treatments. In the preventive setting, rimegepant would not be used in patients in whom traditional oral therapies are efficacious, nor would it be used until they have failed three preventive treatments, consistent with prior appraisals of the anti-CGRP mAbs.

The decision problem addresses the evidence separately for rimegepant used for acute migraine treatment or in the prevention setting. A summary of the decision problem addressed within this submission is presented in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with migraine	**Acute migraine**	
		• For patients who have had inadequate symptom relief after taking at least 2 triptans or in whom triptans are contraindicated or not tolerated.	Rimegepant would not be used in patients in whom triptans are a suitable option. The unmet need for a new therapy is greatest in patients with inadequate response to or safety or tolerability issues with triptans. Experts acknowledge there is no clear evidence that using the third triptan after two triptan treatment failures was beneficial[1] and remains uncommon in clinical practice.[2] No RCTs have investigated how many patients would benefit from a third triptan after failure to respond to an initial two triptans.[3]
		Migraine prevention	
		• Migraine prevention: For patients with episodic migraine who have at least 4 migraine days a month, but fewer than 15 headache days a month and have failed 3 or more preventive therapies	In the preventive setting, rimegepant is expected to be used in patients who have failed 3 oral preventive therapies, i.e., alongside currently used injectable preventive monoclonal antibodies (mAb).
Intervention	Rimegepant	Rimegepant oral dispersible tablet (ODT) • **Acute** migraine: 75 mg as needed (PRN) • Migraine **prevention**: 75 mg every other day (EOD)	In line with final scope
Comparator(s)	**Acute migraine**		
	• Paracetamol, with or without an anti-emetic • An NSAID (such as aspirin, ibuprofen, diclofenac or naproxen), with or without an anti-emetic • An oral or non-oral triptan (such as sumatriptan, zolmitriptan, rizatriptan, almotriptan or eletriptan), with or without an anti-emetic	• BSC (placebo)	As noted above, the target population for rimegepant is in those who have exhausted all available acute treatment options (triptans, NSAIDs, paracetamol, and combinations thereof), thus leaving best supportive care (BSC) as the only relevant comparator. Placebo in Study BHV3000-303 is considered to approximate BSC. While RWE indicated a small proportion of these

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Paracetamol with an oral or non-oral triptan, with or without an anti-emetic • An NSAID with a triptan, with or without an anti-emetic • Best Supportive Care (BSC)		patients may try a third triptan or a mix of suboptimal treatment, there is no clear evidence that using those suboptimal treatments is of benefit
	Migraine prevention		
	• Oral preventive treatments (such as topiramate, propranolol, amitriptyline) • Erenumab (≥4 migraine days per month and after ≥3 preventive drug treatments have failed) • Galcanezumab (≥4 migraine days per month and after ≥3 preventive drug treatments have failed) • Fremanezumab (in chronic migraine and after ≥3 preventive drug treatments have failed) • Botulinum toxin type A (in chronic migraine that has not responded to ≥3 prior pharmacological prophylaxis therapies) • BSC	• Erenumab (≥4 migraine days per month and after ≥3 preventive drug treatments have failed) • Galcanezumab (≥4 migraine days per month and after ≥3 preventive drug treatments have failed) • Fremanezumab (≥4 migraine days per month and after ≥3 preventive drug treatments have failed)	As noted above, rimegepant would be used in patients in whom conventional oral therapies have failed. The mAb comparators included in this submission are used in a similar population to that expected for rimegepant: patients with ≥4 Monthly Migraine Days (MMD) and for whom ≥3 preventive treatments have failed. It is noted that the fremanezumab NICE recommendation was updated subsequent to the issuance of the final scope for this appraisal. In a rapid review of fremanezumab (TA764 [published February 2022]), the recommendation for fremanezumab was aligned with the recommendation for erenumab and galcanezumab (i.e. ≥4 MMD and after ≥3 preventive drug treatments have failed).[4] Botulinum toxin type A is excluded as a comparator, as the NICE recommendation is limited to chronic migraine (TA260)[5]. BSC is not deemed an appropriate comparator as the target population would be eligible to receive one of the injectable mAbs recommended by NICE for more than a year ago.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes	**Acute migraine**		
	• Reduction in headache pain (including freedom from pain)	• Pain freedom at 2 h and 8h	In line with final scope
	• Speed of onset	• Sustained pain freedom from 2 to 24 h and 2 to 48 h	
		• Pain relief at 2 h, at 8h	
		• Sustained pain relief from 2 to 24 h, from 2 to 48 h	
		• Assessment of migraine pain and symptoms and severity	
	• Freedom from most bothersome symptom (MBS)	• Freedom from most bothersome symptom (MBS) at 2 h	
	• Reduction in nausea and vomiting	• Freedom from nausea at 2 h	
	• Reduction in hypersensitivity (e.g. light, sound, smell)	• Freedom from photophobia at 2 h	
		• Freedom from phonophobia at 2 h	
	• Regain of normal functioning	• Functional disability at 2h	
	• Prevention of recurrence	• Prevention of recurrence	
	• Use of rescue medication	• Rescue medication within 24 h	
	• Adverse effects of treatment	• Adverse events	
	• Health-related quality of life	• Health-related quality of life	
	Migraine prevention		
	• Frequency of headache days per month	• Change from baseline in MMD at 12-weeks	In line with final scope
	• Frequency of migraine days per month	• % patients with ≥50% reduction in MMD from baseline at 12-weeks	
	• Severity of headaches and migraines		
	• Number of cumulative hours of headache or migraine on headache or migraine days		

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Reduction in acute pharmacological medication	• Number of triptan or ergotamine days per month	
	• Health-related quality of life	• Change from baseline in MIDAS at 12-weeks	
		• Change from baseline in MSQv2 at 12-weeks	
	• Adverse effects of treatment	• Adverse events	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	As per the NICE reference case the cost-effectiveness of rimegepant is expressed in terms of incremental costs per QALY, and costs have been considered from the perspective of the NHS and PSS.	In line with final scope. Two separate cost-utility models to address the acute migraine and migraine prevention context.
Subgroups to be considered	**Acute migraine**		
	If the evidence allows, the following subgroups will be considered:		
	• Subgroups defined by migraine severity		Subgroup analyses by migraine severity was not pre-specified in the trials.
	• People currently having treatment for the prevention of migraine	• People currently having treatment for the prevention of migraine	
	• People with or at risk of developing medication overuse headache	• Subgroup analysis by number of previous triptan failures.	Data on participants at risk of developing medication overuse headache was not collected in the trials.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• People for whom triptans are contraindicated or not tolerated	• People for whom triptans are contraindicated due to CV risk	
	• Subgroups defined by number of headache days per month	• Number of headaches days per months (<4 vs >4)	
		• Other pre-specified subgroup analyses: by age, race, sex, and migraine aura	
	Migraine prevention		
	If the evidence allows, the following subgroups will be considered: • People with chronic or episodic migraine • Subgroups defined by the number of previous preventive treatments • Subgroups defined by the frequency of episodic migraine	• Prophylactic migraine medication use at randomisation • Headaches per month (<6, ≥6; <8, ≥8; <12, ≥12; <15, ≥15) • Other pre-specified subgroup analyses: by age, race, sex, ethnicity, body mass index (BMI), aura, historical chronic migraine, MMD in observation period, cardiovascular (CV) risk contraindicating triptans	The licence for rimegepant is for episodic migraine[6] and, as such, no data are presented for chronic migraine in the submission, It was not possible to analyse according to the number of previous preventive treatments as these data were not collected in the trial. Real-world data available from the US, where rimegepant was approved by the FDA for the prevention of migraine in May 2021, show that over [redacted]% of prescriptions are in patients who have previously been on at least one alternative prevention agent.
Special considerations including issues related to equity or equality		• Frequent and severe migraine is classified as a disability under the 2010 Equality Act. • Migraine is about three times more common among women than men, which raises potential equity issues Please refer to Section B.1.4 for a discussion of equality considerations.	

B.1.2. Description of the technology being appraised

The summary of product characteristics (SmPC) has been included in Appendix C.

The technology being appraised (rimegepant) is described in Table 2.

Table 2: Technology being appraised

UK approved name and brand name	VYDURA (rimegepant oral dispersible tablets [ODT])
Mechanism of action	The most prominent feature of migraine is recurrent neurovascular headache involving alterations in the subcortical aminergic sensory modulatory systems.[7] Migraine attacks initiate from primary neuronal processing dysfunction, which can include cortical spreading depression or activation of a brainstem migraine generator region.[8] The dysfunction initiates a sequence of intracranial and extracranial changes that lead to recurrent activations of the trigeminal nociceptive neurons, resulting in the activation of vascular CGRP receptors and the CGRP-dependent release of mediators at central and peripheral nerve endings.[9] When CGRP is released in the peripheral nerve endings, meningeal vasodilation occurs causing neurogenic inflammation. The release of CGRP within the brainstem is thought to facilitate pain transmission.[8] Once the trigeminocervical pain system is activated, central projections are sent to the trigeminothalamic tract, thalamus, and cortex.[10,11] Since its discovery in the 1980s, understanding of the pathophysiological involvement of CGRP in the trigeminovascular system has advanced considerably. [12] Contemporary studies have confirmed that release of CGRP in the trigeminovascular system is increased during migraine attacks. CGRP modulates signaling, vasodilation, and inflammation, all of which are central to the triggering and amplification of a migraine attack, thereby making it a prime target for achieving the desired clinical effects for treatment. Rimegepant is a next-generation, oral, selective, and potent small molecule CGRP receptor antagonist with a novel mechanism that targets the underlying pathophysiology of migraine. Rimegepant selectively binds with high affinity to the human CGRP receptor and antagonises CGRP receptor function, inhibiting CGRP-induced enhancement of pain signaling, blocking CGRP-induced vasodilation without active vasoconstriction, and halting CGRP-induced neurogenic inflammation. Unlike the anti-CGRP biologics, rimegepant 75 mg offers a novel convenient oral medication with dual benefits for both the acute and preventive treatment of migraine, requiring no injection, and a half-life of approximately 11 hours which is short compared to anti-CGRP biologics and allows immediate cessation of treatment in the event of pregnancy, hypersensitivity reaction, or severe AE. Furthermore, the favourable safety profile of rimegepant offers benefit over other preventive treatments with known poor tolerability profile (e.g., topiramate and propranolol), which is associated with poor adherence and suboptimal outcomes. Rimegepant is the first oral CGRP antagonist to be approved.[13]

Marketing authorisation/CE mark status	The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion on 24 February 2022.[6,13] The rimegepant GB marketing authorisation was received from the Medicines and Healthcare products Regulatory Agency (MHRA) on 10 June 2022 and the approved indication is identical to that approved by EMA.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Rimegepant is indicated for the: • Acute treatment of migraine with or without aura in adults. • Preventive treatment of episodic migraine in adults who have at least four migraine attacks per month.[6]
Method of administration and dosage	Rimegepant is supplied as oral dispersible tablets in a blister pack of eight oral dispersible tablet or as unit dose blisters of 2 oral dispersible tablets.[6] • **Dosage for acute treatment of migraine:** The recommended dose of rimegepant is 75 mg taken orally as needed, not more than once daily.[6] The maximum dose per day is 75 mg.[6] • **Dosage for preventive treatment of episodic migraine:** The recommended dose of rimegepant is 75 mg taken orally every other day (EOD).[6] Rimegepant is self-administered by placing the oral dispersible tablet on or under the tongue.[6] The tablet will rapidly disintegrate in the mouth and it can be taken without liquid. It can be taken with or without meals.[6]
Additional tests or investigations	None needed
List price and average cost of a course of treatment	Rimegepant (VYDURA®) 8 x 75 mg ODT: £160 Acute (per attack): £20 Prevention (per month): £300 (assuming 15 tablets)
Patient access scheme (if applicable)	Not applicable.

B.1.3. Health condition and position of the technology in the treatment pathway

B.1.3.1. Overview of disease or condition

Migraine is a common, often disabling neurologic disease characterised by recurrent attacks of head pain that are typically unilateral, throbbing, and associated with a range of symptoms that may include photophobia, phonophobia, nausea, and vomiting.[14-16] Clinically, migraine attacks comprise four phases: the premonitory/prodrome, aura, headache, and postdrome.[17] Migraine is a complex disorder, susceptibility is affected by the interaction between multiple genetic and environmental factors.[9]

In addition to a higher prevalence in women, migraine attacks in women tend to be more frequent than those in men, and the attacks are more severe, have a longer duration, and are more challenging to treat.[18] Migraine prevalence appears to increase until 40 years of

age and then decline in older adulthood, particularly after menopause in female patients.[18,19] There are two major types of migraine: migraine with aura and migraine without aura.[14] Migraine with aura occurs in approximately a third of patients,[16] and includes migraine with typical aura or with brainstem aura, hemiplegic migraine, and retinal migraine.[14] Migraine can be also classified, based on the frequency of migraines or headaches, as episodic migraine (EM) or chronic migraine (CM) (see below).[14]

B.1.3.1.1. Migraine diagnosis and classification

Diagnosis

Migraine diagnosis is a clinical diagnosis and there are no confirmatory diagnostic tests available.[20] Migraine diagnosis is made in accordance with the criteria listed in Table 3,[14] and is based on a patient's medical history and findings of a physical examination.[9] It is important to differentiate migraine from other types of primary headaches such as cluster and tension headaches, generally not dangerous, and can be diagnosed with the help of headache diaries and trigger trackers; and secondary headaches, which are caused by more serious underlying conditions and can be diagnosed with the help of invasive or advanced diagnostics such as lumbar puncture, computerised tomography (CT), and magnetic resonance imaging (MRI).[21,22] Diagnosis should also include the differentiation of migraine from trigeminal neuralgia, a much less prevalent but distinct disorder of severe facial pain.[22] The diagnosis of migraine consists of two steps: the first step is to rule out a secondary headache disorder, and the second step is to use the frequency and duration of migraines to confirm a specific primary headache syndrome.[23]

Table 3: ICHD Diagnostic Criteria for Migraine

Migraine without Aura	Migraine with Aura	Chronic Migraine (CM)
A. At least five attacks fulfilling criteria B to D **B.** Headache attacks lasting 4 to 72 h (untreated or unsuccessfully treated) **C.** Headache has at least two of the following four characteristics: 1. Unilateral location 2. Pulsating quality 3. Moderate or severe pain intensity 4. Aggravation by or causing avoidance of routine physical activity (e.g.,	**A.** At least two attacks fulfilling criteria B and C **B.** One or more of the following fully reversible aura symptoms: 1. visual 2. sensory 3. speech and/or language 4. motor 5. brainstem 6. retinal **C.** At least three of the following six characteristics: 1. at least one aura symptom spreads gradually over ≥5 minutes	**A.** Headache on ≥15 days per month for at least three months **B.** Occurring in a patient who has had at least five attacks fulfilling criteria for migraine without aura and/or migraine with aura **C.** On ≥8 days per month for at least three months one or more of the following criteria were fulfilled: 1. **Criteria C and D** for migraine without aura (see left table column)

Migraine without Aura	Migraine with Aura	Chronic Migraine (CM)
walking or climbing stairs) **D.** During headache at least one of the following: 1. Nausea and/or vomiting 2. Photophobia and phonophobia **E.** Not better accounted for by another diagnosis	2. two or more aura symptoms occur in succession 3. each individual aura symptom lasts 5-60 minutes 4. at least one aura symptom is unilateral 5. at least one aura symptom is positive 6. the aura is accompanied, or followed within 60 minutes, by headache D. Not better accounted for by another diagnosis	2. **Criteria B and C** for migraine with aura (see middle column) 3. Headache considered by patient to be onset migraine and relieved by a triptan or an ergotamine derivative **D.** Not better accounted for by another diagnosis

The diagnostic criteria for CM have evolved over time and result in variability in estimated prevalence globally.
Abbreviations: CM, chronic migraine; ICHD, International Classification of Headache Disorders
Reference: International Classification of Headache Disorders 3rd Edition, 2018[14]

Classification

Migraine is classified according to whether or not patients experience aura, or a preceding sensation such as flashing lights, blurred vision, weakness, numbness, or ringing in the ears.[14]

Migraine can be also classified, based on the frequency of migraines or headaches, as episodic migraine (EM) or chronic migraine (CM), and the focus of this submission is EM based on the rimegepant indication. The generally accepted definition of CM is ≥15 monthly headache days (MHDs), with ≥8 days showing typical migraine features, while patients with EM have headache occurring on less than 15 days a month over the last three months, which on some days is migraine.[24] Currently, CM is classified as a separate subtype, as the frequency of the headaches may make it difficult to distinguish between individual attacks or episodes.[9,14,25,26] Variability of MHDs within individuals over time makes a fixed cut-off point challenging for CM versus EM. Migraine frequency can vary over time in both directions, and the within-person variation in migraine frequency is substantial.[27-29]

B.1.3.1.2. Clinical presentation of migraine

Patients with migraine experience debilitating symptoms during migraine attacks, and they also experience the cumulative burden of repeated attacks.

Typically, migraine attacks occur in 4 phases — the prodrome, aura, headache, and postdrome — although there may be considerable overlap in the phases as an attack develops.[17]

- The prodrome phase may last 24 to 48 hours, and patients may experience symptoms of yawning, irritability, reduced concentration, depression, neck stiffness, cravings for certain foods, and constipation.[9,17]

- The aura phase typically lasts approximately 1 hour and can include positive (e.g. jerking, paraesthesia, seeing bright shapes or objects) or negative (e.g. loss of feeling, hearing, vision) symptoms affecting the motor-, somatosensory-, auditory- and visual systems.[9] Typically, aura develops gradually, however it can be confused with a stroke or transient ischaemic attack (TIA).[9]

- During the headache phase, patients often experience unilateral, throbbing pain that lasts from four to 72 hours and is accompanied by photophobia, phonophobia, nausea, and occasionally vomiting.[9,17]

- The postdrome phase, also known as the hangover phase, occurs in about 80% of patients and can last for another 24 to 48 hours.[30,31] The symptoms are similar to those of the prodrome phase and can include fatigue, exhaustion, difficulty concentrating, or euphoria.[9,17]

B.1.3.2. Disease burden

B.1.3.2.1. Epidemiology

Migraine is one of the most frequent neurological diseases. It is thought that, mainly because of the transient nature of primary headache, the burden is generally underestimated. [32]

The National Institute for Health and Care Excellence (NICE) estimated that there are 190,000 migraine attacks experienced every day in England and six million people suffer from migraine in the UK.[5] Based on the 2003 survey conducted among the population aged 16-65 years in mainland England, the one-year prevalence of migraine with or without aura was 14.3% among the adult population.[33] One in seven adults (5.85 million) are affected and 100,000 people miss school or work as a result of this condition each day.[34]

B.1.3.2.2. Clinical burden

Migraine is a major public health issue throughout the world with a significant clinical burden that has increased over the past three decades.[35]

Migraine chronification:

In some patients with EM, the headache frequency may increase over time until it crosses the threshold for CM which is defined as 15 monthly headache days (MHDs) per month, with ≥8 showing typical migraine features for at least three consecutive months. This process is termed migraine chronification. Every year, 2.5% to 7.6% of people with EM will develop CM.[27,29,36] Risk factors for developing CM include age and race, socioeconomic status, migraine medication overuse, ineffective acute treatments, most migraine comorbidities, stress, hormonal changes, high frequency of episodic migraine (≥10 headache days per month), and long duration of illness.[23,37-40]

Suboptimal acute treatment may increase the risk of progressing from EM to CM. Patients with very poor acute treatment efficacy have more than a three-fold increased risk of progressing from EM to CM.[41] Frequent and extended activation in nociceptive pathways (involved in pain processing) may facilitate pathophysiological changes indicative of CM.[42] This suggests that effective migraine management not only provides immediate relief to the patient, but prevents further progression of disease. In fact, relapsing pain and more frequent use of acute medications (NSAIDs or triptans) have been shown to be associated with increased risk of CM.[43,44] Inadequate management of migraines with triptans, illustrated by the high rates of discontinuation and frequent medication overuse headache (MOH), further increases the risk of chronicity. This highlights the need for novel therapies for preventing disease progression and alleviating the clinical and economic burden associated with increased monthly frequency of migraine.

Medication overuse:

Medication overuse headache (MOH) is believed to affect up to 2% of the general population, with much higher prevalence reported in chronic daily headache patients, and with 65% of cases having migraine as the underlying primary headache disorder.[45]

MOH occurs when patients with a pre-existing primary headache develop a new type of headache or a significant worsening of their pre-existing headache, in association with medication overuse.[14] As shown in Table 4, MOH is defined by the ICHD as headache occurring on 15 or more days per month developing as a consequence of regular overuse of acute or symptomatic headache medication (on 10 or more, or 15 or more days per month, depending on the medication) for more than three months.[14] The use of opioids, combination analgesics, ergots, or triptans on ≥10 days per month; and paracetamol or NSAIDs on ≥15 days per month can cause MOH.[46] The treatment of choice for MOH is to stop using the

medication that is being overused; however, this can be challenging due to the withdrawal or detoxification process, which can take up to 10 days and require inpatient hospital withdrawal in the case of certain medications such as opioids.[47,48]

Table 4: MOH Diagnosis Criteria

ICHD-III MOH
A. Headache occurring on ≥15 days/month in a patient with a pre-existing headache disorder
B. Regular overuse for more than three months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache
C. Not better accounted for by another ICHD-III diagnosis

Abbreviations: ICHD-III = The International Classification of Headache Disorders 3rd Edition; MOH = medication overuse headache
References: IHS 2019[14]

Certain analgesics and front-line abortive medicines, like triptans, are associated with greater risk of MOH.[49] Overuse of triptans has been found to lead to MOH faster (1.7 years) and with lower dosages (18 single doses per month) compared with other acute medication such and analgesics (4.8 years; 114 single doses per month).[50] In the 'Migraine in America Symptoms and Treatment (MAST) study', patients with acute medication overuse reported significantly more MHDs (12.9±8.6 vs. 4.3±4.3, p<0.001) compared to patients without acute medication overuse.[51] In most cases, MOH resolves when overuse is discontinued.[14] MOH as a result of overuse of certain medications can increase the risk of developing CM.[52]

B.1.3.2.3. Humanistic burden

Migraine is the second highest cause of disability worldwide[53] and the most disabling of all health conditions in those younger than 50,[54] with considerable negative effects on patients' quality of life. Migraine is an episodic but recurrent pain syndrome characterised by neurological and gastrointestinal symptoms, and is associated with impaired functioning, quality of life and psychological impairment.[55]

Among patients with migraine, those with a higher frequency in headache days and more severe depression and anxiety have increased disability when measured with the migraine disability assessment MIDAS.[56,57] In addition, patients with migraine experiencing three or more headache days per month reported severe disability which worsened to very severe levels after ten or more headache days.[58] An increased MIDAS score in patients with migraine has also been correlated with having several sensory hypersensitivities, younger age, increased MMD, and a higher Kessler Psychological Distress (K6) score.[59]

A survey conducted in a random sample of adults in England revealed that 25% of respondents with migraine (N=574) reported high levels of pain (rated 9-10 on a 10-point

scale).[33] A mean pain rating of 7.5 on a 10-point scale (where 10=most intense pain) was observed in both males (n=113) and females (n=461).[33] Pain and discomfort during attacks often results in poor quality of sleep, which in turn is associated with poor health, significant functional and cognitive impairment, and psychiatric comorbidity.[60,61]

The intense pain and other symptoms associated with migraine can have a substantial negative impact on daily life in those experiencing attacks.[62] Many patients suffering from severe migraine attacks are unable to perform daily activities and can be confined to bed during an attack. Some studies have found that approximately 80% of individuals with migraine are unable to work or function normally during attacks, 69% need help with daily activities on a median of nine to 10 days over a three-month period, and most (53%) report severe impairment and/or requiring bed rest.[63,64] Patients with migraine often seek clinical care for relief, leading to frequent visits to healthcare professionals (HCPs) and EDs.[65]

Attacks can vary in duration, and can last for days if left untreated.[66] Migraine not only adversely affects patients during an attack, but also has an impact between attacks.[67] This is referred to as interictal burden; it presents as worry and concern about when the next painful attack will be, and what its impact will be on plans and activities.[67] According to a 2022 qualitative analysis from the US, Canada, and the UK, patients with migraine (n=35) relayed feelings of unreliability and inability to make plans during the interictal period and reported feeling anxious about a forthcoming migraine, requiring changes to their lifestyle, needing to decrease or stop working, and avoiding social or family activities.[68]

Evidence suggests that migraine-related disability is similar to that of other serious diseases, such as acute myocardial infarction, dementia, and moderate multiple sclerosis.[69] The burden of migraine increases with an increase in MMD. Compared to people with fewer MMD, people with more MMD experience a higher burden on health, relationships, career, and finances; increased disability, comorbidities, and health care resource utilisation; and decreased quality of life and productivity.[70-75]

In addition to the impacts of migraine itself, many patients respond insufficiently to treatments or experience intolerable adverse effects.[76-78] Almost half of patients who have concerns about the efficacy or tolerability of their treatment are moderately or severely disabled, and only 20% of those who discontinue their treatment are able to function normally and work while having headaches.[78]

Several quality of life and patient-reported outcome (PRO) measures have been utilised in the literature to evaluate the impact of disability and reduction in quality of life.[79,80] Migraine-

specific HRQoL measures include the Migraine Disability Assessment (MIDAS) questionnaire,[77] the Migraine-Specific Quality of Life Survey (MSQ),[79] and the Migraine Functional Impact Questionnaire (MFIQ).[81] Other measures that can be used to assess migraine burden and changes due to treatment include the Headache-Attributed Lost Time (HALT) over 90 days (HALT-90) or 30 days (HALT-30).[82] These indexes were derived from MIDAS.[82]

B.1.3.2.4. Economic and societal burden

Migraine has a substantial impact on the healthcare system. In the UK, around 2.5 million primary care appointments are linked to headaches and migraines, around 100,000 of which are referred to hospital for further assessment (2018/2019).[83] The number of admissions to hospitals in England for headaches and migraines has increased by 14% over a five-year period, NHS Digital data shows an increase emergency admissions from 95,548 in 2014/15 to 108,711 emergency admissions in 2018/19.[83] In total, it is estimated that the NHS spends around £150 million per year on treating migraines and £250 million on care for headache sufferers.[83] In patients with migraine, as the number of headache days increase so does the burden of disease including healthcare utilisation.[84] Further, the NHS has reported (NHS RightCare, 2019)[85] an addressable issue of inappropriate referral to secondary care for migraine patients. Avoidable specialist neurology appointments delay access for patients with potentially serious secondary headache disorders or other neurological conditions that require investigation urgently. Introduction of new treatment options into the primary care setting can help to reduce such inappropriate referrals to secondary care, bringing benefit to patients, reducing waiting times and reducing NHS costs associated with unnecessary attendances in secondary care.

Migraine is also associated with substantial impacts on work productivity and social interactions and is a considerable burden on employers, families, patients, and society.[16,73,86-90] There are a number of instruments that assess the impact of disease on work productivity, including the generic Work Productivity and Activity Impairment (WPAI) questionnaire and the migraine-specific Migraine Work and Productivity Loss Questionnaire (MWPLQ).[91] There is a particular impact on women, as migraine is about three times more common among women than men[92] making improving migraine treatment a need well aligned with the new Women's Health Strategy for England.[93]

As migraine prevalence is greatest among individuals aged 35-49 years, migraine-related disability has an enormous impact on what are typically the most productive years of life.[66,94,95] The Office for National Statistics (ONS) data indicate that headaches and

migraines account for 4.9% of sickness absence (2020) in the UK.[96] Migraine-related absenteeism (sick days off work) and presenteeism (reduced effectiveness at work) combined is estimated to be responsible for 55–86 million equivalent workdays lost per annum at a cost of between £5.6 and £8.8 billion in lost productivity (using prevalence estimates of 15% and 23.3%).[97] NHS data indicate around £4.4 billion a year lost to three million migraine-related sick days.[83] The impact of migraine is also felt among NHS's own staff, for example in a single month of November 2021, 2.3% of total NHS staff absences were due to migraine or headache, the migraine absence accounted for 51,179 FTE days lost.[98]

Other source of data corroborate these findings, using data from the Eurolight project (outpatient care, investigations, acute medications, hospitalisations, and prophylactics) direct costs are estimated to be between £600 million and £1 billion per annum (data applied to 15% UK prevalence and GBD 2016 UK adult migraine prevalence, respectively).[97] Direct costs are responsible for approximately 10% of the total cost burden.[97] When combined, indirect and direct costs attributed to migraine in the UK are estimated to be in the region of £6.2 to £9.7 billion per year.[97]

B.1.3.3. Clinical pathway of care

Migraine can be managed by avoiding or managing triggers (when identified), using non-pharmacological and complementary therapies such as acupuncture and cognitive behavioural therapy, or using acute or preventive pharmacological treatments.[22,99,100] Acute treatments are taken for symptomatic relief during attacks, and preventive treatments are taken regularly to prevent attacks and/or reduce the frequency and severity of attacks.[39,101] The main classes of acute treatments include analgesics and triptans.[39,102] Classes of preventive treatments include antiepileptics/anticonvulsants, antidepressants, beta-blockers, calcium channel antagonists, serotonin reuptake inhibitors, botulinum neurotoxins, and calcitonin gene-related peptide (CGRP) antagonists.[39,103] Many patients will require both acute and preventive treatments if they have frequent and severe headaches.[103]

Currently, there is no single medication recommended by NICE for both the acute and preventive treatment of migraine. Existing medications are often underutilised and/or discontinued due to lack of efficacy and tolerability as well as concerns of increased risk of MOH.[16,77,104,105] In addition, linked to these concerns, patients tend to treat too late, or at a lower dose.[16,77,104,105] Patients can become resistant or refractory to treatment, and inadequate response to treatment can result in increased disease burden, disability, and despair.[106]

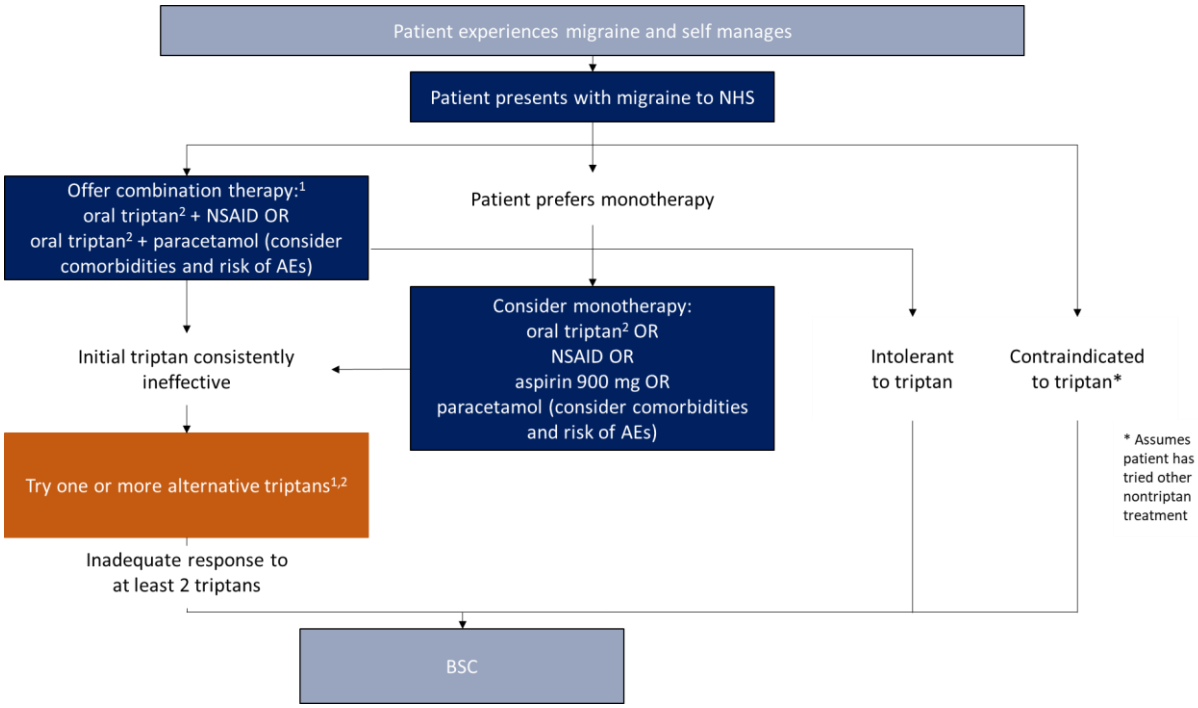
Current recommendations for migraine management include using acute or preventive pharmacologic treatments along with supportive measures including avoiding or managing triggers and using non-pharmacologic and complementary therapies such as acupuncture and cognitive behavioural therapy.[99]

B.1.3.3.1. Acute migraine in clinical practice

Acute migraine: Current treatments and pathway

The current treatment pathway for therapies in people with acute migraine based on NICE guidance is summarised in Figure 3. The pathway is based mainly on CG150, which includes, unless contraindicated, simple analgesics (i.e. ibuprofen, aspirin or paracetamol) or a triptan with or without paracetamol or an NSAID. Oral triptans are recommended unless vomiting restricts treatment. Anti-emetics (e.g. metoclopramide or prochlorperazine) should be considered even in the absence of vomiting.

Figure 1: Clinical pathway of care: treatment of acute migraine



Abbreviations: AEs, adverse events; BSC, best supportive care; NSAIDs, non-steroidal anti-inflammatory drugs
Notes:
[1]Consider an anti-emetic in addition to other acute treatment for migraine even in the absence of nausea and vomiting
[2]When prescribing a triptan, start with the one with the lowest acquisition cost
References: NICE CG150[107]

Acute migraine: Unmet need

Limitations of current available therapies

The unmet need in acute migraine—an indication in which there have been no new therapies approved in Europe or the UK in over 20 years—includes issues relating to efficacy, safety and tolerability, as well as medication overuse headache (MOH).

The main classes of acute treatments include paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), and triptans, which may be used alone or in combination (eg, NSAID + triptan or paracetamol + triptan).[107] While triptans are commonly used for the acute treatment of migraine attacks, some patients may not have adequate symptom control due to lack of efficacy, intolerable side effects, and safety concerns for those with a history of vascular disease, multiple risk factors for vascular diseases, and during pregnancy.[108] The British Association for the Study of Headache (BASH) guidelines, recommend that after two treatment failures with an initial triptan, an alternative triptan is offered, as the first one is unlikely to be effective in subsequent attacks.[109] Limited studies have investigated whether a patient not responding to a first triptan may benefit from a second one.[110,111] Five studies[112-116] provide some evidence that switching from a triptan that is ineffective to a second one can result in varying levels of success. It is not clear whether there are factors that mean some patients respond poorly to all triptans.[110,111] In addition, a systematic literature review published in 2020, suggested some patients may benefit from trying a second triptan after failure of one, but there are no prospecti/ve clinical trials or observational studies supporting the use of a third triptan after two have failed.[3]

The needs of many patients with migraine are therefore not met with traditional acute treatments.[78,117] It has been estimated that 15% to 25% of patients currently using migraine-specific acute therapies may have inadequate symptom control and would benefit from access to novel treatments.[108] A two-year retrospective cohort study of newly prescribed triptan users in the UK (n=3,618), France (n=2,051), and Germany (n=954) highlights the unmet need for acute migraine treatment.[118] The study found that >55% of patients did not obtain a refill prescription for the first triptan that they were prescribed.[118] In the UK, 56% of patients did not refill their index triptan, with 5% switching to a different triptan, 2% switching to a different class of prescription medication, and 49% receiving no further migraine prescription after the index triptan, underscoring the lack of suitable options for patients who do not benefit from triptans. Side-effects are a basis for patients limiting triptan use, i.e. they may refill the prescription but not treat every attack (thus losing benefit) because of concerns about side effects. Sometimes patients will try to endure a migraine because triptan side-

effects are disabling (brain fog). Among patients who did refill the index triptan, 15% only obtained one refill. By the end of the two-year study period, 84% of UK patients were receiving no migraine prescriptions.[118] However, 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.[2]

This unmet need has been consistently demonstrated in clinical practice and trial data showing that new users of triptans have relatively low persistence and retention rates.[118-121] Also, common alternatives to triptans, such as NSAIDs, are associated with an increased risk of serious gastrointestinal safety and renal toxicity events[122-124]

Between 55.2% and 81.5% of patients who use triptans report discontinuation of treatment.[125] Common reasons for discontinuing triptans include inadequate efficacy, adverse effects, and contraindications.[104,126,127] For the more than 20 years that triptans have been recommended as first-line therapy,[128,129] there has been a largely unmet need for additional treatment options for patients with migraine who are not eligible to use triptans due to AEs, lack of response, or cardiovascular contraindications.[117,130-132]

Progressing to chronic migraine

Suboptimal acute treatment may increase the risk of progressing from episodic to CM. Patients with very poor acute treatment efficacy have more than a three-fold increased risk of progressing from episodic to CM.[41] This suggests that effective management of the acute attack not only provides immediate relief to the patient and an early return to normal activities but prevents recurrent attacks. In fact, relapsing pain and an increase in days per month of acute medication utilisation (e.g., NSAIDs or triptans) has shown to be associated with increased risk of CM.[43,44] and the risk of developing medication overuse headache. A more targeted and efficacious approach to treating the acute attack, involving selective CGRP inhibition, may have potential to prevent escalation to episodic or chronic migraine, with their associated clinical and economic burden.

Emergency migraine care

Another critical component of unmet need in acute migraine is that some patients must seek emergency care due to unresolved pain and overlap of migraine symptoms with potentially life-threatening conditions (e.g., sub-arachnoid haemorrhage or stroke), and due to inadequacies or perceived inadequacies of treatment options in primary care. An analysis from the Neurology Alliance, showed a marked increase (17%) in migraine-related hospital

admissions compared to 2012/13. In the same period population growth was just 3%.[133] The analysis reported that emergency admissions now account for 97% of all hospital inpatient admissions with an ICD-10 code indicating a primary diagnosis on admission episode of headache or migraine.[133] These data could indicate that people with migraine are increasingly relying on emergency services for medical care, rather than going through primary care, likely adding significant, avoidable costs to the NHS.

In a 2017 EU5 study, over six months, migraine patients had an increasing ED visits with increasing MHDs, (a mean of 0.28 ED visits for those with one to three MHDs, 0.38 for those with four to seven MHDs, and 0.42 for those with eight to 14 MHDs).[134] Effective and tolerable oral acute migraine treatments have potential to significantly reduce the need for emergency migraine care, which may entail measures such as subcutaneous sumatriptan or parenteral NSAIDs, with or without antiemetics.[109] An audit was conducted of all adult presentations to the emergency department of Guy's and St Thomas' Hospitals which were coded as "headache" over the first six months of 2018.[135] Of 78,273 attendances to the emergency department, there were 976 presentations to the emergency department with "headache" as the primary complaint.[135] "Migraine" was the most frequent of all diagnoses, accounting for 30% of all headache presentations and 25% of headache admissions.[135] With regard to investigations, 21% of patients with migraine had CT scans, while 4.4% had MRI or MRA scans, and 5% had lumbar punctures. The cost of admitting and investigating migraine was estimated as £131,250 over the six-month period.[135]

Medication overuse headache

As discussed in Section B.1.3.2.2, certain analgesics and front-line abortive medicines, like triptans, are associated with an increase in the risk of MOH.[49] Overuse of triptans has been found to precipitate MOH more rapidly and with lower dosages than other acute medications, such as analgesics.[50]

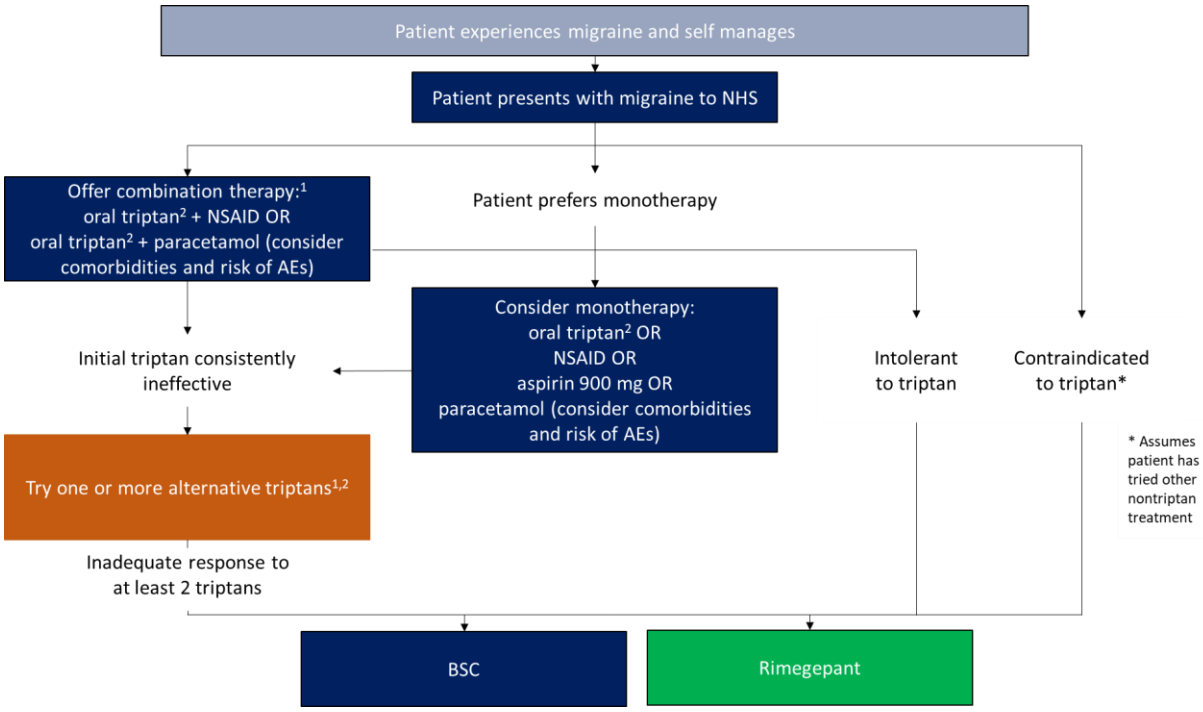
The recognised unmet need for adequate and safe treatment of migraine has resulted in the development of new drugs e.g. 5-hydroxytryptamine (5-HT_{1F}) receptor agonists (e.g. lasmiditan), and small molecule CGRP receptor antagonists (gepants, e.g. rimegepant).[136]

Proposed positioning of rimegepant for the treatment of acute migraine

The clinical pathway of care, based on NICE advice for acute migraine, with the proposed place in therapy of rimegepant is shown in Figure 2. Rimegepant would be an option for patients with migraine (with or without aura) who have had inadequate symptom relief after taking at least two triptans or in whom triptans are contraindicated or not tolerated.

Rimegepant targets the molecular causes of migraine by selectively binding with high affinity to the CGRP receptor, which is thought to relieve migraine by: 1) blocking neurogenic inflammation; 2) decreasing artery dilation; and 3) inhibiting pain transmission.[137] As discussed in Section B.2, rimegepant acts rapidly on acute migraine attacks with a well-tolerated safety profile. A potential ancillary benefit of rimegepant use in the acute setting is the potential to also reduce migraine frequency over time.[138-141] Rimegepant therefore provides an additional treatment option, giving patients who have tried and failed (or are contraindicated for) the existing treatments the ability to achieve symptom relief, with potential for reduced disability, improved productivity, and enhanced quality of life.

Figure 2: Rimegepant in clinical pathway of care: treatment of acute migraine



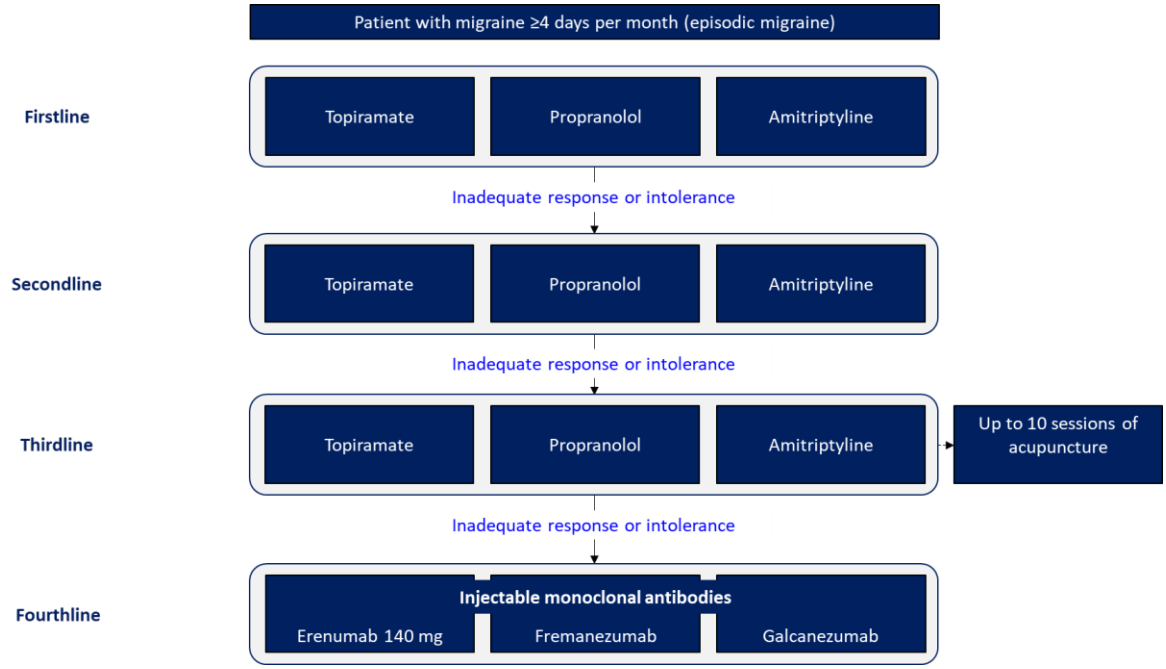
Abbreviations: AEs, adverse events; NSAIDs, non-steroidal anti-inflammatory drugs
Notes:
[1]Consider an anti-emetic in addition to other acute treatment for migraine even in the absence of nausea and vomiting
[2]When prescribing a triptan, start with the one with the lowest acquisition cost
References: NICE CG150[107]

B.1.3.3.2. Preventive treatment of migraine in clinical practice

Preventive treatment of migraine: current treatments and pathway

The goal of preventive therapy in migraine is to decrease the overall clinical characteristics of migraine including frequency, intensity and duration of attacks to improve responsiveness to acute therapy, and to reduce the migraine-related disability while avoiding occurrence of MOH. The current pathway based on NICE guidance is summarised in Figure 3.

Figure 3: Clinical pathway of care for the preventive treatment of episodic migraine



References: NICE CG150; NICE TA260; NICE TA659; NICE TA682; NICE TA764[4,5,107,142,143]

The current NICE guidelines recommend oral preventive treatments including the antiepileptic, topiramate, the beta-blocker, propranolol, and the antidepressant, amitriptyline, as first-, second-, and third-line preventive treatment options.[107] These may be sequenced in any order based on the patient's preference, comorbidities and risk of AEs.[107] The decision to move to the next line of treatment is based on lack of efficacy or poor tolerability.[107] Some patients find relief from a course of acupuncture.[107] Patients should be reviewed every six months to assess a need for continuation of prophylaxis.

The BASH guidelines[109] and recent NICE guidance recommend the following injectable monoclonal antibody (mAb) calcitonin gene-related peptide (CGRP) antagonists erenumab 140 mg, galcanezumab and fremanezumab as treatments for EM and CM if at least three preventive drug treatments have failed.[4,142,143]

The BASH guidelines[109] also recommend off-label candesartan (an angiotensin II receptor blocker [ARB); however, while candesartan has been shown to be beneficial in the preventive treatment of migraine it is not licensed for this indication.[144]

For patients with CM who have a history of three or more failed treatments, botulinum toxin A is also recommended as a fourth-line treatment.[5]

While preventive therapies for migraine aim to reduce MMD, it is rare that a patient will eliminate migraine headaches completely. The migraine attacks that occur while a patient is taking prophylactic treatments are referred to as “breakthrough” events, and patients are likely to treat these migraine attacks with acute therapies to provide symptom relief (e.g., triptans), and rescue medications in the case that those acute therapies fail (e.g., NSAIDs and opioids). While preventive migraine therapies aim to achieve a clinically meaningful reduction in MMD, the vast majority of patients will use acute medications to manage breakthrough events.[145-147]

Preventive treatment of migraine: Unmet need

Limitations of current available therapies

There are several challenges relating to the attributes of currently available preventive migraine treatments.

Traditional preventive treatments (e.g. topiramate, beta-blockers and antidepressants) have not been specifically designed for migraine, many are only moderately effective and have suboptimal outcomes with high rates of adverse effects, poor tolerability, and have interactions or contraindications.[16,148-152] These options are associated with patients frequently switching, discontinuing or delaying therapies due to a lack of efficacy or poorer tolerability and impact adherence. Some therapies may impact the effectiveness of hormonal contraceptives, e.g. topiramate.[107]

Discontinuation rates have been reported for propranolol (23%), amitriptyline (45%), and topiramate (43%). AEs were the most common reason cited for discontinuing therapy, including 17% for amitriptyline and 24% for topiramate.[148,153,154]

Adherence to migraine prophylactic therapies is low, with patients frequently switching, discontinuing or delaying taking prescription therapies due to a lack of efficacy or poor tolerability.[155] Less than half of patients on prophylactic treatments report being satisfied with their current treatment regimen, and many resort to over-the-counter medications (e.g. NSAIDs, or sumatriptan). Real-world data shows that adherence rates range from 17–20% after one year, and that persistence falls below the threshold of 80% after only six months.[119,154] Adverse events (AEs) such as taste perversion, weight loss and paraesthesia are common in oral prophylactic treatment options for migraine. A recent systematic review of 159 randomised controlled trials (RCTs) of treatments for episodic migraine reported that 2.1–16.6% of patients discontinued treatment due to adverse events after two to three months of follow-up.[156] Patients who cannot tolerate traditional oral therapies will receive no

benefit at all.[157] In clinical practice, clinicians consider not only the efficacy of the drug in question, but also the patient's comorbidities, contraindications, likely compliance, and the risk of AEs as part of their decision-making.

In accordance with current guidelines,[107,109] switching between preventive treatments is common, however persistence worsens as patients cycle through various treatments.[153] The proportion of patients who experienced ≥4 MMD increased with increasing switches between preventive treatments.[158] In an Italian study of 1,100 patients with migraine, only 12% had ≥50% reduction in migraine frequency with first-line preventive treatments and 550 dropped out due to adverse effects.[159] Current preventive treatments have significant limitations in relation to efficacy, tolerability, sustainability, and specificity, resulting in dissatisfaction, non-adherence, and increased burden.[160]

Anti-CGRP mAbs have been developed to address this unmet need for effective tolerable treatments for migraine prevention. A number of these treatments are approved for EM and CM, including erenumab, fremanezumab, galcanezumab, and eptinezumab.[161-168] These anti-CGRP mAb preventive treatments have advantages over traditional migraine therapies including no need to escalate the dose slowly, a relatively rapid onset of action and treatment benefit, and efficacy in patients refractory to other preventive treatments.[16,169] However, there are several challenges to consider with anti-CGRP mAbs. The injectable mAbs have long half-lives ranging from 27 to 30 days,[165,166,168] which can require waiting several months to eliminate the drug from the body if a change to treatment is desired. This can pose a challenge for women of childbearing age, who form a large portion of the migraine population, and who may need to make treatment changes to plan or manage pregnancy. The monthly administration schedule also leads to waning of effectiveness between doses, with patients more likely to experience breakthrough migraine attacks near the end of the treatment cycle.[170] The three mAbs currently recommended by NICE can be self-injected by patients after being trained, although patients generally prefer self-administered oral medication over injections.[165,166,168,171] Training patients on injections also adds to the burden on healthcare professionals, who have a substantial backlog and limited staffing due to the effects of the COVID-19 pandemic meaning that wait time for treatment can be lengthy.[172] However, some patients still need ongoing support for injections.[4]

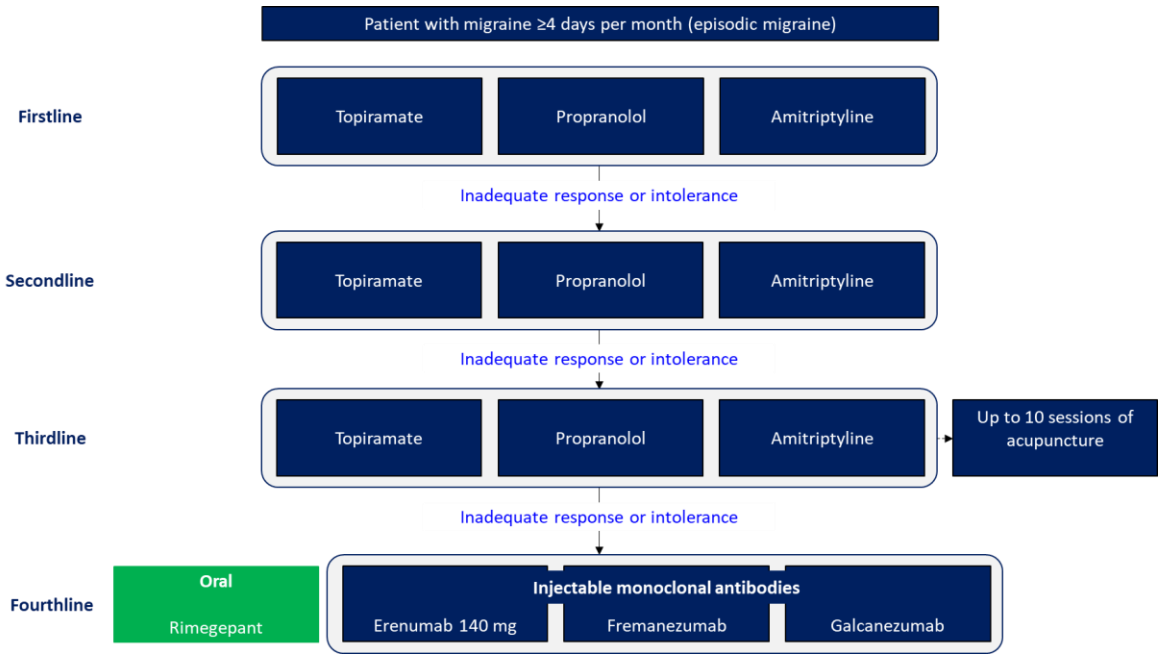
In addition, other challenges associated with CGRP mAbs include the side-effect burden (e.g. constipation has been reported in up to 43% of erenumab patients in clinical practice),[173-176] high rates of discontinuation observed in real-world clinical practice,[170,177,178]

Preventive migraine treatment preferences were explored in a discrete-choice experiment of patients having a mix of EM and CM and the results indicated that patients would value more effective and tolerable treatments and would prefer daily oral medications and monthly injections to more frequent injections (two a month).[179] In another discrete-choice experiment in 506 patients with migraine in the US and Germany,[180] [180] the most apparent difference between treatments was the mode of administration which may be particularly important to patients who have not previously used injectable therapy. Patients significantly preferred oral administration to quarterly infusion ($p<0.01$) and quarterly ($p<0.01$) or monthly ($p=0.02$) injection.[180]

Proposed positioning of rimegepant for the preventive treatment of episodic migraine

Rimegepant is proposed for the preventive treatment of adults with episodic migraine who have four or more migraine attacks per month and have failed three conventional oral treatments. Figure 4 depicts the proposed pathway for migraine prevention and proposed positioning of rimegepant. Based on the current patient pathway, these patients would be eligible to receive one of the injectable mAbs recommended by NICE, such as erenumab, fremanezumab and galcanezumab are deemed the most appropriate comparators. For patients who have failed conventional therapy, rimegepant provides an alternative to currently available injectable therapies. A novel, oral anti-CGRP option may enable patients to receive this type of treatment more quickly and conveniently in the primary care setting rather than having to be referred to secondary care. Such patients can expect to achieve clinically meaningful reduction in MMD and improved quality of life (i.e. improved patient functioning, wellbeing, and activities of daily living) with rimegepant.[181]

Figure 4: Rimegepant in the clinical pathway of care for the preventive treatment of episodic migraine



References: NICE CG150; NICE TA260; NICE TA659; NICE TA682; NICE TA764[4,5,107,142,143]

B.1.4. Equality considerations

Frequent and severe migraine is classified as a disability under the 2010 Equality Act.[182] The addition of rimegepant to the treatment pathways for acute treatment and also prevention of migraine may help to address inequalities of care and reduce disability thus improving equality in migraine management. Frequent and severe migraine is classified as a disability under the 2010 Equality Act.[182]

Given that migraine is about three times more common among women than men,[92] insufficiently managed migraine can have a greater impact on women, particularly in the workplace. In addressing this gendered health impact disparity, it is important to recognise that there is no significant difference in the likelihood of women or men consulting or accessing the health system for headache and migraine. In fact, compounding the greater incidence of migraine in women is that women's pain reports are taken less seriously and they are less likely to be offered treatment than men's.[183] A systematic review of the evidence on gender and consultation for headache and migraine,[184] including UK data, reported that the evidence for greater consultation amongst women was weak and inconsistent, while a separate UK study found that women were no more likely than men to consult a general practitioner in the previous year and, in addition, women were no more likely than men to consult at a given level of severity for a given condition type.[185] Examples of the evidence for gender disparity in pain treatment include a prospective cohort study of

adults with acute pain showing that women were 13% to 25% less likely than men to receive pain treatment and that women waited longer to receive their pain treatment. Further, a study reporting two experiments published in 2021 showed gender bias in the estimation of pain, specifically that perceivers underestimated female patients' pain is compared with male patients and that perceivers prescribed psychotherapy for female and more pain medicine for male patients.[183]

Migraine can have a major impact on absenteeism, presenteeism, and work productivity, which can lead to loss of employment or reduced opportunity for occupational advancement.[186,187] Moreover, migraine is likely to have a greater impact on hourly workers, who may have fewer opportunities to make up work hours missed due to migraine episodes, relative to salaried professional workers.[186] This issue also has a greater impact on women than men: women comprise the majority of the nearly one million UK workers on a zero-hour contract as of September 2021, with 3.6% of female and 2.5% of male workers on such contracts (564,000 women and 433,000 men).[188]

B.2. Clinical effectiveness

Please note that given the appraisal of rimegepant in the acute migraine and episodic migraine prevention populations, this section provides the clinical evidence for the acute and prevention populations as follows:

	Acute treatment of migraine	**Preventive treatment of migraine**
Identification and selection of relevant studies	Section B.2.1.1	Section B.2.1.2
List of relevant clinical effectiveness evidence	Section B.2.2.1	Section B.2.2.2
	Acute	**Prevention**
Summary of methodology of the relevant clinical effectiveness evidence	Section B.2.3 A	Section B.2.3 P
Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence	Section B.2.4 A	Section B.2.4 P
Quality assessment of the relevant clinical effectiveness evidence	Section B.2.5 A	Section B.2.5 P
Clinical effectiveness results for the relevant trials	Section B.2.6 A	Section B.2.6 P
Subgroup analysis	Section B.2.7 A	Section B.2.7 P
Meta-analysis	Section B.2.8 A	Section B.2.8 P
Indirect and mixed treatment comparisons	Section B.2.9 A	Section B.2.9 P
Adverse reactions	Section B.2.10	
Ongoing studies	Section B.2.11	
Innovation	Section B.2.12	
Interpretation of clinical effectiveness and safety evidence	Section B.2.13	

B.2.1. Identification and selection of relevant studies

B.2.1.1. Treatment of acute migraine with rimegepant

A systematic literature review (SLR) was conducted to identify relevant randomised controlled trials (RCTs) in the acute treatment of migraine. The SLR, including search strategy, study selection, and details of selected studies, is described in detail in Appendix D: acute (Section D.1.1.A). A total of 25 publications reporting four unique studies were included in the review (Table 5 [refer also to Appendix D: acute, Section D.1.2.A]).

Table 5. Identified clinical effectiveness evidence: acute treatment of migraine with rimegepant

Study (NCT #)	Primary publication	Linked publications identified in the review*
NCT01430442	Marcus 2014[189]	NA
Study 301 (NCT03235479) **Unpublished:** Data on File - Study 301 clinical study report[138] Data on File – pooled analysis of study 301, study 302, and study 303[190]	ClinicalTrials.gov 2017a;[191]	Blumenfeld 2019;[192] Croop 2020;[193] Hutchinson 2019a;[194] Hutchinson 2019b;[195] Hutchinson 2019c;[196] Jensen 2021a;[197] Jensen 2021b;[198] Levin 2020;[199] Lipton 2019c;[200] Lipton 2019d;[201] Lipton 2020;[202] Mc Allister 2020;[203] Pavlovic 2019;[204] Pavlovic 2020a;[205] Pavlovic 2020b;[206] Pavlovic 2020c;[207] Schim 2020;[208] Smith 2021;[209] Turner 2020[210]
Study 302 (NCT03237845) **Unpublished:** Data on File - Study 302 clinical study report[141] Data on File – pooled analysis of study 301, study 302, and study 303[190]	Lipton 2019a[211]	Croop 2020;[193] Hutchinson 2019a;[194] Hutchinson 2019b;[195] Hutchinson 2019c;[196] Jensen 2021a;[197] Jensen 2021b;[198] Levin 2020;[199] Lipton 2019c;[200] Lipton 2019d;[201] Lipton 2020;[202] Mc Allister 2020;[203] Pavlovic 2019;[204] Pavlovic 2020a;[205] Pavlovic 2020b;[206] Pavlovic 2020c;[207] Schim 2020;[208] Smith 2021;[209] Turner 2020[210]
Study 303 (NCT03461757) **Unpublished:** Data on File - Study 303 clinical study report (final 12 week)[139] Data on File – pooled analysis of study 301, study 302, and study 303[190]	Croop 2019[212]	Blumenfeld 2019;[192] Croop 2020;[193] Hutchinson 2019a;[194] Hutchinson 2019b;[195] Hutchinson 2019c;[196] Jensen 2021a;[197] Jensen 2021b;[198] Levin 2020;[199] Lipton 2019b;[213] Lipton 2019c;[200] Lipton 2019d;[201] Lipton 2020;[202] Mc Allister 2020;[203] Pavlovic 2019;[204] Pavlovic 2020a;[205] Pavlovic 2020b;[206] Pavlovic 2020c;[207] Schim 2020;[208] Smith 2021;[209]

Abbreviations: NA, not applicable

Notes:

*Conference abstracts or clinical trials record

B.2.1.2. Preventive treatment of migraine with rimegepant

A SLR was conducted to identify relevant RCTs in the preventive treatment of migraine. The SLR, including search strategy, study selection, and details of selected studies, is described

in detail in Appendix D: prevention (Section D.6.1.P). A total of 442 publications reporting 22 unique studies evaluating interventions for the prevention of migraine were included in the review (refer to Appendix D: prevention [Section D.7.P] for results). Of the total included studies, a total of five publications reporting one study were identified that evaluated rimegepant for the prevention of migraine (Table 6).

Table 6. Identified clinical effectiveness evidence: prevention of migraine with rimegepant

Study name (Trial ID)	Primary publication	Linked publications identified in the review*
Study 305 (NCT03732638) **Unpublished:** Data on file: BHV3000-305 clinical study report;[214] Data on file: Study BHV3000-305 clinical study report addendum[215]	Croop 2021a[216]	Croop 2021b;[217] Croop 2021c;[218] Croop 2021d;[219] Lipton 2021;[220] ClinicalTrials.gov 2018[221]

Notes:
*Conference abstracts or clinical trials record

B.2.2. List of relevant clinical effectiveness evidence

B.2.2.1. Treatment of acute migraine with rimegepant

The clinical development program that supported rimegepant for the acute treatment of migraine comprised three Phase 3, multicentre, single-dose, placebo-controlled studies of similar design (BHV3000-301,[138] BHV3000-302,[211] BHV3000-303[139,212]) plus an open-label long-term safety study (BHV3000-201)[140,222] (Figure 5).

The Phase 3 trials assessed the efficacy and safety of rimegepant 75 mg in the acute treatment of migraine in adults with at least a one-year history of migraine with or without aura (based on International Classification of Headache Disorders 3rd edition [ICHD-III] beta version diagnostic criteria), a history of two to eight migraine attacks of moderate or severe intensity per month, and fewer than 15 monthly headache days (migraine or non-migraine) over the previous three months.[138-140,211,212,222] The Phase 3, BHV3000-303 study assessed the safety and efficacy of the rimegepant oral dispersible tablet (ODT) formulation, while the two Phase 3, BHV3000-301 and BHV3000-302 studies assessed the safety and efficacy of the rimegepant 75 mg oral tablet formulation.[138-140,211,212] The ODT formulation is bioequivalent to the oral tablet formulation.[223] This ODT formulation can be advantageous for

patients who want quick relief and/or have nausea or vomiting and do not want to drink liquids or would otherwise prefer to avoid swallowing a tablet.[224-226] A pooled analysis from the Phase 3 studies provides sufficient patient numbers to assess the efficacy of rimegepant 75 mg in triptan failure patients (Section B.2.7),[190] which is the population most relevant for the proposed positioning of rimegepant for the acute treatment of migraine (Section B.1.1 and Section B.1.3.3).

The long-term, open-label, safety study, BHV3000-201, assessed the safety and tolerability of the rimegepant 75 mg oral tablet and demonstrated that rimegepant is well-tolerated for long-term use (up to 52 weeks).[140,222,227] As this study was a single arm study, it did not meet eligibility criteria for the SLR but did support the marketing authorisation application.

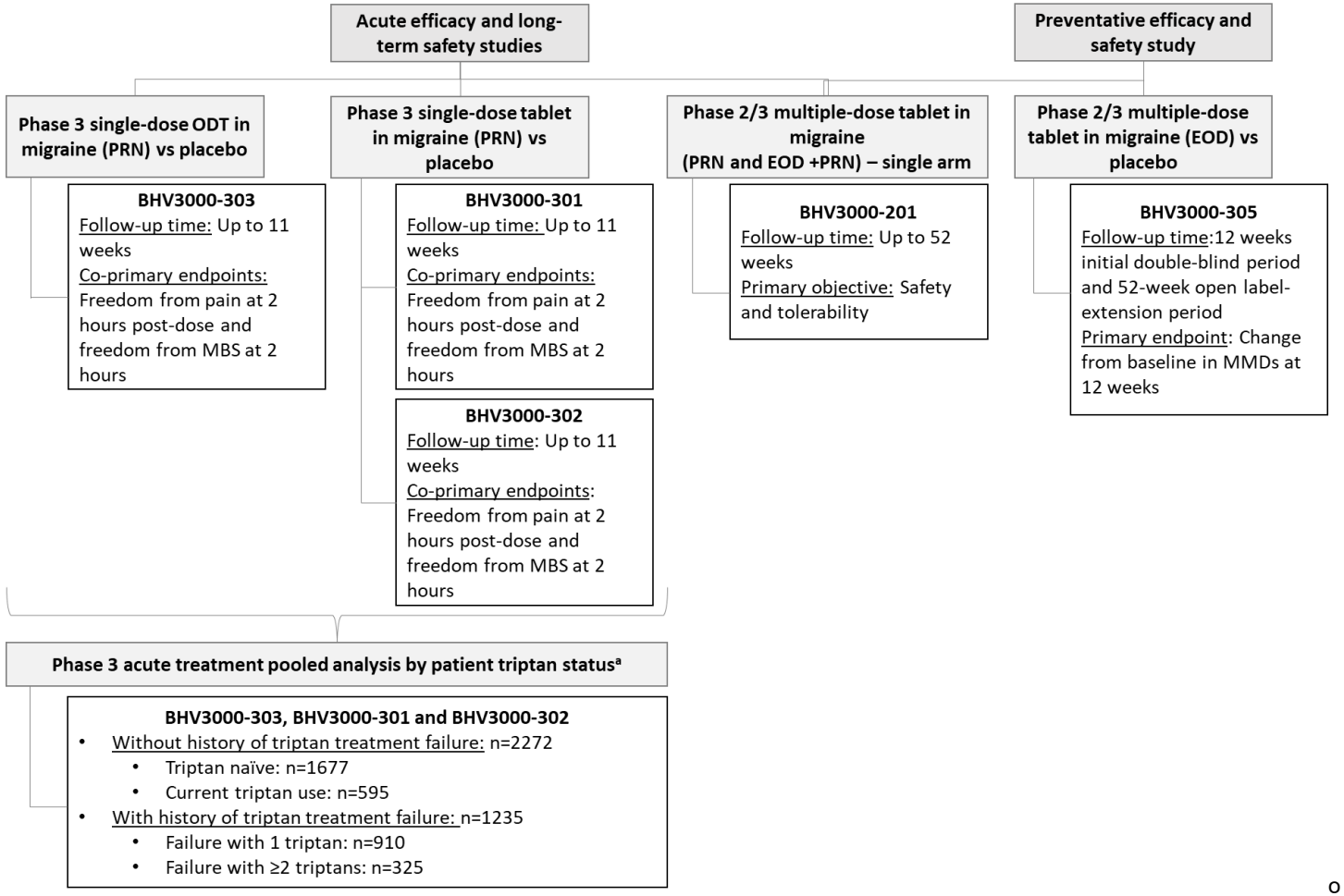
Other completed clinical trials of rimegepant in the treatment of acute migraine not reported in this submission include:

- **CN170-003 (NCT01430442):** Phase 2 study that evaluated the efficacy and safety of six different doses of rimegepant, placebo, or sumatriptan in the treatment of acute migraine.[189] The study was not included in this submission as it was a small dose-finding study in which 75 patients received rimegepant 75 mg tablets,[189] with evidence from the study superseded by the Phase 3 studies of rimegepant in the acute treatment of migraine. In this study, which was not powered to compare rimegepant to sumatriptan, sumatriptan had significantly higher response rates than placebo on primary and secondary outcomes.[189] However, the placebo response rate was relatively high; for example, over half of patients on placebo reported pain relief at two hours post-dose.[189] Response rates on many endpoints were numerically similar for sumatriptan and rimegepant 75 mg, including sustained pain freedom (two to 24 hours post-dose), sustained pain freedom (2-48 hours post-dose), sustained pain relief (two to 24 hours post-dose).[189]

- **BHV3000-310 (NCT04574362):** Phase 3, double-blind, randomised, placebo controlled trial of rimegepant 75 mg for the acute treatment of migraine.[191,228] This study was conducted in 86 sites in China and Korea and completed in January 2022. Collectively, the results from Study BHV3000-310 demonstrated a favourable benefit-risk profile for rimegepant 75 mg ODT in the acute treatment of moderate or severe migraine in Asian patients. Significant efficacy of rimegepant compared to placebo was demonstrated for the co-primary endpoints of freedom from pain and freedom from MBS at two hours post-dose, as well as for all key secondary endpoints. Significant evidence of both early onsets of benefit and durability of response were seen across an array of key secondary

endpoints. Rimegepant 75 mg ODT was safe and well tolerated in adult participants with moderate to severe migraine. The study was identified in the searches on clinical trial registries but has recently completed. It was not included in the main submission as it did not support the marketing authorisation application and was conducted in an Asian population with limited generalisability to the UK clinical practice. Results are summarised in Appendix L.[228]

Figure 5: Summary of rimegepant clinical trial programme for the treatment of migraine included in the submission



o

Abbreviations: EOD, every other day; MBS, most bothersome symptom; MMD, monthly migraine day; ODT, orally dispersible tablet; PRN, as needed;
Notes:
[a]Triptan treatment failure was defined as a self-reported history of triptan discontinuation due to either inadequate efficacy, intolerability or both of any class of triptan medication
References: Study BHV3000-303: Croop 2019;[212] Study BHV3000-301: Data on File Clinical Study Report BHV3000-301[138] Study BHV3000-302: Lipton 2019;[211] Study BHV3000-201: Data on File Clinical Study Report BHV3000-201; [140] Croop 2020b [222] Study BHV3000-305: Croop 2021;[216] Data on File: Clinical Study Report BHV3000-305 (Final Week 12), 2020;[214] Data on File: Clinical Study Report BHV3000-305 (Addendum), 2020;[215]

Table 7: Pivotal clinical effectiveness evidence for rimegepant ODT and oral tablet in the acute treatment of migraine

Study name and number	Phase 3 acute efficacy study with rimegepant ODT	Phase 3 acute efficacy studies with rimegepant tablet		Phase 2/3 long-term safety study with rimegepant tablet
	BHV3000-303 (NCT03461757)[212]	BHV3000-301 (NCT03235479)[138,229]	BHV3000-302 (NCT03237845)[211]	BHV3000-201 (NCT03266588)[140,222]
Study design	Multicentre, randomised, double-blind, placebo-controlled, Phase 3 trial	Multicentre, randomised, double-blind, placebo-controlled, Phase 3 trial		Multicentre, open-label, single arm, long-term, Phase 2/3 trial
Population	• Age ≥18 years • ≥1-year history of migraine with or without aura per ICHD-III (beta version) criteria • Migraine onset before age 50 years • Two to eight moderate-to-severe attacks/month • <15 monthly headache days for past 3 months • Untreated attacks lasting 4 to 72 hours • Ability to distinguish migraine attacks from tension/cluster headaches • If using preventive medication, stable dose for ≥3 months • Patients with contraindications to triptan were not excluded from the study	• Age ≥18 years • 1-year history of migraine (with or without aura) that met ICHD-III (beta version) criteria • Migraine onset before 50 years of age • 2 to 8 moderate-to-severe migraine attacks per month • <15 MHDs for the 3 months prior to screening • Untreated attacks lasting 4 to 72 hours • Ability to distinguish migraine attacks from tension/cluster headaches • If using preventive migraine medication, stable dose for ≥3 months Patients with contraindications to triptan were not excluded from the study		• Age ≥18 years • 1-year history of migraine (with or without aura) that met ICHD-III (beta version) criteria • Migraine onset before 50 years of age • 2 to 14 moderate-to-severe attacks per month (dependent on study group: Group 1 had 2 to 8 attacks per month, Group 2 had 9-14 attacks per month and Group 3 had 4 to 14 attacks per month) • ≥2 migraine days requiring treatment during the baseline assessment period • Untreated attacks lasting 4 to 72 hours • Ability to distinguish migraine attacks from tension/cluster headaches • If using preventive medication, stable dose for ≥3 months • Patients with contraindications to triptan were not excluded from the study
Intervention(s)	75 mg sublingual rimegepant ODT to treat single migraine attacks of moderate to severe pain intensity	Single dose of rimegepant 75 mg tablet to treat a migraine attack of moderate or severe intensity		Group 1 (PRN and historical rate of 2 to 8 moderate to severe migraine attacks per month), and Group 2 (PRN and historical rate of 9 to 14 moderate to severe migraine attacks per month): Rimegepant 75 mg tablet PRN at onset of mild, moderate or severe migraine up to 1 tablet per day for up to 52 weeks Group 1 CGRP mAb subgroup: Continuation of stable dosing of CGRP antagonist mAb

Study name and number	Phase 3 acute efficacy study with rimegepant ODT	Phase 3 acute efficacy studies with rimegepant tablet		Phase 2/3 long-term safety study with rimegepant tablet
	BHV3000-303 (NCT03461757)[212]	**BHV3000-301 (NCT03235479)[138,229]**	**BHV3000-302 (NCT03237845)[211]**	**BHV3000-201 (NCT03266588)[140,222]**
				plus rimegepant treatment as for Group 1 for up to 12-weeks Group 3 (historical rate of 4 to 14 moderate to severe migraine attacks per month): Rimegepant 75 mg tablet EOD and allowed to treat migraine with single dose of rimegepant 75 mg tablet PRN on days not scheduled for dosing for up to 12-weeks
Comparator(s)	Placebo	Placebo		None
Indicate if trial supports application for marketing authorisation	Yes	Yes		Yes
Indicate if trial used in the economic model	Yes	Yes		Yes
Rationale for use/non-use in the model	The trial provides evidence of the clinical efficacy and safety outcomes associated with the use of rimegepant in acute migraine	The trial provides evidence of the clinical efficacy and safety outcomes associated with the use of rimegepant in acute migraine		The trial provides the baseline utilities among patients treated for acute migraine and the change in MMD among acute users with high frequency of MMD
Reported outcomes specified in the decision problem (outcomes highlighted in bold are outcomes used in the economic model)	**Primary endpoints** • Freedom from pain at 2 hours • Freedom from MBS at 2 hours **Secondary endpoints** Reduction in headache pain (including freedom from pain) • Pain relief at 60 minutes • Pain relief at 90 minutes • **Pain relief at 2 hours** • Sustained pain relief from 2 to 24 hours • Sustained pain relief from 2 to 48 hours • Freedom from pain at 90 minutes	**Primary endpoints** • Freedom from pain at 2 hours • Freedom from MBS at 2 hours **Secondary endpoints** Reduction in headache pain (including freedom from pain) • **Pain relief at 2 hours** • Sustained pain relief from 2 to 24 hours • Sustained pain relief from 2 to 48 hours • Sustained freedom from pain from 2 to 24 hours		**Primary objective** • Safety and tolerability (frequency and severity of AEs occurring in ≥5% of patients, SAEs, AEs leading to discontinuation and clinically significant laboratory anomalies) **Secondary objective** • Frequency of elevations in ALT and AST >3X ULN and concurrent with elevations in bilirubin >2x ULN **Exploratory endpoints** • Additional assessment of hepatic AEs and laboratory anomalies

Study name and number	Phase 3 acute efficacy study with rimegepant ODT	Phase 3 acute efficacy studies with rimegepant tablet		Phase 2/3 long-term safety study with rimegepant tablet
	BHV3000-303 (NCT03461757)[212]	**BHV3000-301 (NCT03235479)[138,229]**	**BHV3000-302 (NCT03237845)[211]**	**BHV3000-201 (NCT03266588)[140,222]**
	• Sustained freedom from pain from 2 to 24 hours • Sustained freedom from pain at 2 to 48 hours Freedom from MBS • Freedom from MBS at 90 minutes • Sustained freedom from MBS from 2 to 24 hours • Sustained freedom from MBS from 2 to 48 hours • Freedom from nausea at 2 hours • Freedom from photophobia at 2 hours • Freedom from phonophobia at 2 hours Regain of normal functioning • Ability to function normally at 60 minutes • Ability to function normally at 90 minutes • **Ability to function normally at 2 hours** • Sustained ability to function normally from 2 to 24 hours • Sustained ability to function normally from 2 to 48 hours Prevention of recurrence • Pain relapse from 2 to 48 hours • Use of rescue medication within 24 hours • **Post-hoc analysis: pain intensity from 0 to 48 hours** Supportive and exploratory endpoints[a] Safety and tolerability • Safety and tolerability, including all AEs and SAEs	• Sustained freedom from pain from 2 to 48 hours • Pain relapse from 2 to 48 hours Freedom from MBS • Freedom from photophobia at 2 hours • Freedom from phonophobia at 2 hours • Freedom from nausea at 2 hours Regain of normal functioning • **Ability to function normally at 2 hours** Prevention of recurrence • Rescue medication use ≤24 hours • • **Post-hoc analysis: pain intensity from 0 to 48 hours** **Exploratory (BHV3000-301) or other (BHV3000-302) endpoints:** • Safety and tolerability, including AEs and laboratory assessments		• Daily assessment of migraine severity and frequency • **HRQoL per MSQoL assessment** • Migraine PoM • Satisfaction with medication questionnaire • Score on the Sheehan Suicidality Tracking Scale • HRQoL per MIDAS assessment • Clinical Global Impression of Change per investigator assessment Post-hoc analysis: **Change from baseline in mean MMD**

Study name and number	Phase 3 acute efficacy study with rimegepant ODT	Phase 3 acute efficacy studies with rimegepant tablet		Phase 2/3 long-term safety study with rimegepant tablet
	BHV3000-303 (NCT03461757)[212]	**BHV3000-301 (NCT03235479)[138,229]**	**BHV3000-302 (NCT03237845)[211]**	**BHV3000-201 (NCT03266588)[140,222]**
All other reported outcomes	No additional	No additional		No additional

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CGRP, calcitonin gene-related peptide; EOD, every other day HRQoL, health-related quality of life, ICHD-III, International Classification of Headache Disorders-3rd edition; mAb, monoclonal antibody; MBS, most bothersome symptom; MIDAS, Migraine Disability Assessment Test; MSQoL, Migraine-Specific Quality of Life Questionnaire; ODT, orally dispersible tablet; PoM, preference of medication; PRN, *pro re nata* (as needed); SAE, serious adverse event; ULN, upper limit of normal

Notes:

[a]Supportive analyses: Durability (pain freedom, pain relief, MBS, functional disability, nausea, photophobia, and phonophobia) at 2-24, 3-24, 4-24 hours and 2-48, 3-48, and 4-48 hours; Time to rescue medication; Time to first report of absence of various symptoms (MBS, nausea, photophobia, phonophobia, and return to normal functioning; Endpoints at 3 hours post-dose (freedom from pain, freedom from MBS, freedom from photophobia, freedom from phonophobia, freedom from nausea, pain relief, functional disability scale); and, exploratory efficacy endpoints: Freedom from functional disability at 24 hours post-dose, mITT participants; Pain relief at 15 minutes post-dose, mITT participants; Pain relief at 30 minutes post-dose, mITT participants; pain relief at every timepoint post-dose, mITT participants;

References: Study BHV3000-303: Croop 2019;[212] Study BHV3000-301: Data on File Clinical Study Report BHV3000-301[138] Study BHV3000-302: Lipton 2019;[211] Study BHV3000-201: Data on File Clinical Study Report BHV3000-201; [140] Croop 2020b [222]

B.2.2.2. Preventive treatment of migraine with rimegepant

The clinical evidence for the preventive treatment of migraine is taken from Study BHV3000-305, a pivotal, Phase 2/3, randomised, double-blind, placebo-controlled study that evaluated the efficacy of rimegepant 75 mg tablet administered EOD for up to 12-weeks (Figure 5).[214,216] Table 8 summarises the study design of the BHV3000-305 trial. Data were also available from a long-term open-label Phase 2/3 safety study (Study BHV3000-201).[140,222,230]

Table 8: Pivotal clinical effectiveness evidence for rimegepant in the preventive treatment of migraine

Study	BHV3000-305: Oral rimegepant for preventive treatment of migraine: a Phase 2/3, randomised, double-blind, placebo-controlled trial				
Study design	Multi-centre, randomised, double-blind, placebo-controlled, Phase 2/3 trial				
Population	• Age ≥18 years • ≥1-year history of migraine with or without aura or chronic migraine • Migraine onset before age 50 years • Migraine attacks, on average, lasting 4 to 72 hours if untreated • 4 to 18 migraine attacks of moderate to severe intensity per month within the last 3 months prior to the screening visit • ≥6 but ≤18 migraine days during the 4-week lead-in observation period • Ability to distinguish migraine attacks from tension/cluster headaches • Patients on prophylactic migraine medication (not CGRP mAbs or antagonists) were permitted to remain on 1 medication with possible migraine-prophylactic effects if the dose had been stable for ≥3 months prior to the 4-week observation period, and the dose did not change during the study				
Intervention(s)	75 mg rimegepant taken orally EOD for 12-weeks				
Comparator(s)	Placebo				
Indicate if trial supports application for marketing authorisation	Yes	x	**Indicate if trial used in the economic model**	Yes	x
	No			No	
Rationale for use/non-use in the model	The trial provides the anticipated clinical efficacy and safety outcomes associated with use of rimegepant in migraine prevention				
Reported outcomes specified in the decision problem (outcomes highlighted in bold are outcomes used in the economic model)	Frequency of MMD • **Mean MMD in last 4 weeks of treatment phase (primary)** • Change from baseline in mean MMD as measured over the 12-week double-blind treatment phase • **50% reduction from baseline in mean number of moderate to severe MMD in last 4 weeks of treatment phase** Reduction in acute pharmacologic medication • Mean number of rescue medication days per month in the last 4 weeks of the double-blind treatment phase Safety and tolerability • Frequency of AEs, SAEs, ALT/AST elevations, hepatic-related AEs, and AEs leading to treatment discontinuation HRQoL				

	• Mean change from baseline in MSQoL role function at Week 12 • Mean change from baseline in MIDAS total score at Week 12
All other reported outcomes	None additional

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CGRP, calcitonin gene-related peptide; EOD, every other day; HRQoL, health-related quality of life; mAb, monoclonal antibody; MMD, monthly migraine days, MIDAS, Migraine Disability Assessment; MSQoL, Migraine-Specific Quality of Life Questionnaire; SAE, serious adverse event
References: Croop 2021;[216] Data on File: clinical study report BHV3000-305 (Final Week 12), 2020;[214] Data on File: clinical study report BHV3000-305 (Addendum), 2020;[215]

Acute treatment of migraine

The following sections report the relevant clinical evidence for the treatment of acute migraine (heading prefixed with A:)

B.2.3. A: Summary of methodology of the relevant clinical effectiveness evidence in the acute treatment of migraine

B.2.3.1. A: BHV3000-303, BHV3000-301 and BHV3000-302 (acute): study design and methodology

A summary of study design and methodology used and outcomes assessed in the studies (Study BHV3000-303, Study BHV3000-301, and Study BHV3000-302 and BHV3000-201), are provided in Table 7, Table 9 and Table 10, respectively. Additional information is available in Appendix M and the clinical study reports (CSRs).

Table 9: Summary of study design and methodology for eligible clinical studies evaluating rimegepant in acute treatment of migraine

Study name	Phase 3 acute efficacy studies			Phase 2/3 long-term safety study
	BHV3000-303	**BHV-3000-301**	**BHV3000-302[211]**	**BHV3000-201**
Location	Multicentre: 69 sites across the US	Multicentre: 50 sites across the US	Multicentre: 49 sites across the US	Multicentre: 103 sites across the US
Trial design	Multicentre, randomised, double-blind, placebo-controlled, Phase 3 study	Multicentre, randomised, double-blind, placebo-controlled, Phase 3 study	Multicentre, randomised, double-blind, placebo-controlled, Phase 3 study	Multicentre, open-label, Phase 2/3 study
Duration of study	Estimated duration of 11 weeks: • 3 to 28-day screening period • Occurrence of moderate or severe migraine ≤45 days • EOT follow-up visit ≤7 days	Estimated duration of 11 weeks: • 3 to 28-day screening period • Occurrence of moderate or severe migraine ≤45 days • EOT follow-up visit ≤7 days	Estimated duration of 11 weeks: • 3 to 28-day screening period • Occurrence of moderate or severe migraine ≤45 days • EOT follow-up visit ≤7 days	Estimated duration of 58 weeks: • 30-day screening and baseline assessment period • 12- or 52-week long-term treatment period • EOT follow-up safety visit at 14 ± 2 days
Trial drugs and mode of administration	Rimegepant 75 mg ODT as a single dose vs. matching placebo	Rimegepant 75 mg tablet as a single oral dose vs. matching placebo	Rimegepant 75 mg tablet as a single oral dose vs. matching placebo	Rimegepant 75 mg tablet as a single oral dose to be taken PRN at the onset of mild, moderate or severe migraine up to a maximum 75 mg dose per day for up to 52 weeks Or Rimegepant 75 mg tablet as a single oral dose to be taken EOD or at the onset of mild, moderate or severe migraine up to a maximum 75 mg dose per day for up to 12-weeks
Permitted and disallowed medication	Specified rescue medication use was allowed if patients did not experience migraine symptom relief >2 hours after study medication use. Use of prophylactic medication was allowed in patients who had used stable medication for ≥3	Specified rescue medication use was allowed if patients did not experience migraine symptom relief >2 hours after study medication use. Use of prophylactic medication was allowed in patients who had used stable medication for ≥3	Specified rescue medication use was allowed if patients did not experience migraine symptom relief >2 hours after study medication use and patients could use their SoC therapy >48 hours if needed. Use of prophylactic medication was	Use of prophylactic medication was allowed in patients who had used stable medication for ≥3 months. Previously prescribed SoC medication was also allowed. Use of St John's Wort, butterbur roots, ergotamine medications, non-narcotic

Study name	Phase 3 acute efficacy studies			Phase 2/3 long-term safety study
	BHV3000-303	**BHV-3000-301**	**BHV3000-302[211]**	**BHV3000-201**
	months. Low-dose aspirin for documented CV prophylaxis was allowed. Use of St John's Wort, barbiturates, Modafinil, butterbur roots, ergotamine medications, non-narcotic analgesics, narcotic medication, acetaminophen, marijuana, strong CYP3A4 inhibitors or inducers or muscle relaxants were not allowed.	months. Use of St John's Wort, butterbur roots, ergotamine medications, non-narcotic analgesics, narcotic medication, acetaminophen or marijuana were not allowed.	allowed in patients who had used stable medication for ≥3 months. Use of St John's Wort, ergotamine medications, non-narcotic analgesics, narcotic medication, acetaminophen or marijuana were not allowed.	analgesics, narcotic medication, triptans, acetaminophen, marijuana, strong CYP3A4 inhibitors or inducers, antipsychotics or Lamictal were not allowed.
Pre-specified subgroup analyses	Primary endpoints were evaluated in the following subgroups: • Race (White vs. Black or African American vs. other) • Sex (male/female) • Aura (yes/no) • Headaches per month (<4 vs. ≥4) • Triptan non-responder (yes/no) • CV risk contraindicating triptans (yes/no)	[redacted]	Primary endpoints were evaluated in the following subgroups: • Age (<40 vs. ≥40 years) • Race (White vs. Black or African American vs. other) • Sex (male/female) • Aura (yes/no) • Headaches per month (<median vs. ≥median) • Triptan non-responder (yes/no) • CV risk contraindicating triptans (yes/no)	Exploratory end points of interest were evaluated in the following subgroups: • Age (<40 vs. ≥40 years and <65 vs. ≥65 years) • Sex (male/female) • Sex and age (female <40 years vs. female ≥40 years vs. male <40 years vs. male ≥40) • Race (White vs. Black or African American vs. other including Asian vs. Asian only) • Ethnicity (Hispanic or Latino vs. non-Hispanic or non-Latino) • CV risk contraindicating triptans (yes/no) • Body mass index (<25 mg/m^2 vs. ≥25 to <30 mg/m^2 vs. ≥30 mg/m^2) • Prophylactic migraine medication use (yes/no)

Study name	Phase 3 acute efficacy studies			Phase 2/3 long-term safety study
	BHV3000-303	BHV-3000-301	BHV3000-302[211]	BHV3000-201
				• Time on rimegepant (categorised as quintiles) • Cumulative rimegepant exposure (categorised as quintiles) • Other key rimegepant treatment statistics

Abbreviations: CV, cardiovascular; EOD, every other day; EOT, end of treatment; SoC, standard of care; US, United States; vs, versus
References: Study BHV3000-303: Croop 2019;[212] Study BHV3000-301: Data on File Clinical Study Report BHV3000-301[138] Study BHV3000-302: Lipton 2019;[211] Study BHV3000-201: Data on File Clinical Study Report BHV3000-201; [140] Croop 2020b [222]

Table 10: Summary of outcomes for eligible clinical studies evaluating rimegepant in acute treatment of migraine

Study name	Phase 3 acute efficacy studies			Phase 2/3 long-term safety study
	BHV3000-303	BHV-3000-301	BHV3000-302	BHV3000-201
Primary outcomes:				
• Freedom from pain at 2 hours	✓	✓	✓	
• Freedom from MBS at 2 hours	✓	✓	✓	
Secondary outcomes:				
Reduction in headache pain (including freedom from pain)				
• Pain relief at 60 minutes	✓			
• Pain relief at 90 minutes	✓			
• Pain relief at 2 hours	✓	✓	✓	
• Sustained pain relief from 2 to 24 hours	✓	✓	✓	
• Sustained pain relief from 2 to 48 hours	✓	✓	✓	
• Freedom from pain at 90 minutes	✓			
• Sustained freedom from pain from 2 to 24 hours	✓	✓	✓	
• Sustained freedom from pain at 2 to 48 hours	✓	✓	✓	
Freedom from MBS				
• Freedom from MBS at 90 minutes	✓			
• Sustained freedom from MBS from 2 to 24 hours	✓			

Study name	Phase 3 acute efficacy studies			Phase 2/3 long-term safety study
	BHV3000-303	BHV-3000-301	BHV3000-302	BHV3000-201
• Sustained freedom from MBS from 2 to 48 hours	✓			
• Freedom from nausea at 2 hours	✓	✓	✓	
• Freedom from photophobia at 2 hours	✓	✓	✓	
• Freedom from phonophobia at 2 hours	✓	✓	✓	
Function				
• Ability to function normally at 60 minutes	✓			
• Ability to function normally at 90 minutes	✓			
• Ability to function normally at 2 hours	✓	✓	✓	
• Sustained ability to function normally from 2 to 24 hours	✓			
• Sustained ability to function normally from 2 to 48 hours	✓			
Prevention of recurrence				
• Pain relapse from 2 to 48 hours	✓	✓	✓	
• Use of rescue medication within 24 hours	✓	✓	✓	
Safety and tolerability				
• Safety and tolerability, AEs and laboratory assessments	✓	✓	✓	✓[a]

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CV, cardiovascular; CYP3A4, Cytochrome P450 3A4; EOT, end of treatment; MBS, most bothersome symptom; ODT, orally dispersible tablet; SAE, serious adverse event; SoC, standard of care; ULN, upper limit of normal

Notes

✓ Outcomes reported

[a]Safety and tolerability were assessed as the primary endpoint with additional liver-specific safety events assessed as secondary endpoints.

References: Study BHV3000-303: Croop 2019;[212] Study BHV3000-301: Data on File Clinical Study Report BHV3000-301[138] Study BHV3000-302: Lipton 2019;[211] Study BHV3000-201: Data on File Clinical Study Report BHV3000-201; [140] Croop 2020b [222]

B.2.4. A: Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence in the acute treatment of migraine

A summary of trial populations and statistical analysis across the four eligible clinical studies of rimegepant for the acute treatment of migraine is provided in Table 11. The hypothesis and statistical analyses conducted for the BHV3000-301 and BHV3000-302 studies were similar to the BHV3000-303 study, although there were slight differences in the categorisation of patients as treatment failures

Table 11: BHV3000-303, BHV3000-301, BHV3000-302 and BHV3000-201 (acute): Trial populations and statistical analyses

	Phase 3 acute efficacy studies			Phase 2/3 long-term safety study
	BHV3000-303[139,212]	**BHV3000-301**[138,229]	**BHV3000-302**[211]	**BHV3000-201**[140]
Trial populations				
ITT set	mITT (n=1351): All patients who underwent randomisation, had a migraine attack of moderate to severe pain intensity, took a dose of study treatment and had ≥1 efficacy assessment after dose administration Used for all efficacy endpoints	mITT (n=1084): All patients who underwent randomisation, had a migraine attack of moderate to severe pain intensity, took a dose of study treatment and had ≥1 efficacy assessment after dose administration Used for all efficacy endpoints	mITT (n=1072): All patients who underwent randomisation, had a migraine attack of moderate to severe pain intensity, took a dose of study treatment and had ≥1 efficacy assessment after dose administration Used for all efficacy endpoints	NA
Safety analysis set	Safety population (n=1375): All patients who underwent randomisation and took a dose of study drug	Safety population (n=1095): All patients who underwent randomisation and took a dose of study drug	Safety population (n=1086): All patients who underwent randomisation and took a dose of study drug	Treated patients (n=1800): All patients who took any dose of study drug Follow-up patients (n=1693): All patients whose last contact date was in the 2 weeks after EOT
Statistical analyses				
Hypothesis objective	To test whether there is a difference between rimegepant 75 mg and placebo in the number of patients who experienced freedom from pain and freedom from MBS at 2 hours (co-primary endpoints) after taking drug upon experiencing	To test whether there is a difference between rimegepant 75 mg and placebo in the number of patients who experienced freedom from pain and freedom from MBS at 2 hours (co-primary endpoints) after taking drug upon experiencing	To test whether there is a difference between rimegepant 75 mg and placebo in the number of patients who experienced freedom from pain and freedom from MBS at 2 hours (co-primary endpoints) after taking drug upon experiencing	NA

	Phase 3 acute efficacy studies			Phase 2/3 long-term safety study
	BHV3000-303[139,212]	BHV3000-301[138,229]	BHV3000-302[211]	BHV3000-201[140]
Trial populations				
	a migraine attack of moderate or severe pain intensity	a migraine attack of moderate or severe pain intensity	a migraine attack of moderate or severe pain intensity	
Statistical tests	The co-primary endpoints were analysed by Cochran-Mantel-Haenszel tests at a 2-sided alpha level of 0.05 and stratified by preventive medication use (yes/no). Patients with missing data at 2 hours post-dose, those who used rescue medication within 2 hours of study treatment were categorised as having failed on treatment Secondary endpoints were tested in a hierarchical gatekeeping approach to control the type I error rate at 0.05	The co-primary endpoints were analysed by Cochran-Mantel-Haenszel tests at a 2-sided alpha level of 0.05 and stratified by preventive medication use (yes/no). Patients with missing data at 2 hours post-dose, those who used rescue medication within 2 hours of study treatment and those who reported their MBS after taking study treatment were categorised as having failed on treatment Secondary endpoints were tested in a hierarchical gatekeeping approach to control the type I error rate at 0.05	The co-primary endpoints were analysed by Cochran-Mantel-Haenszel tests at a two-sided alpha level of 0.05 and stratified by preventive medication use (yes/no). Patients with missing data at 2 hours post-dose were categorised as having failed on treatment. Patients who used rescue medication were categorised as having failed on treatment at the time the medication was taken. Sensitivity analyses were performed that took missing data into account Secondary endpoints were tested in a hierarchical gatekeeping approach to control the type I error rate at 0.05	Safety endpoints were described using summary statistics
Sample size, power calculations	Power calculations were based on the BHV3000-301 and BHV3000-302 Phase 3 studies and a Phase 2b study of rimegepant A sample of 600 patients in each treatment group was estimated to provide 95% power to detect a significant difference between the treatment groups for each of the two co-primary endpoints and 90% power to detect a significant difference jointly across both co-primary endpoints	Power calculations were based on a Phase 2b study of rimegepant A sample of 500 patients in each treatment group was estimated to provide 95% power to detect a significant difference between the treatment groups for each of the two co-primary endpoints and 90% power to detect a significant difference jointly across both co-primary endpoints	Power calculations were based on a Phase 2b study of rimegepant A sample of 500 patients in each treatment group was estimated to provide 95% power to detect a significant difference between the treatment groups for each of the two co-primary endpoints and 90% power to detect a significant difference jointly across both co-primary endpoints	A sample size of approximately 2000 patients was estimated to detect AEs that occur at a rate greater than 15 cases per 10,000 people based on a 1-sided 95% CI A subpopulation sample of 800 patients with greater exposure to study drug due to a higher frequency of migraine attacks was estimated to detect AEs that occur at a rate greater than 37.5 cases per 10,000 people based on a 1-sided 95% CI

	Phase 3 acute efficacy studies			Phase 2/3 long-term safety study
	BHV3000-303[139,212]	**BHV3000-301**[138,229]	**BHV3000-302**[211]	**BHV3000-201**[140]
Trial populations				
Data management, patient withdrawals	Patients were withdrawn if they: • Experienced an AE, laboratory anomaly or intercurrent illness whereby continued study participation was not beneficial to the patient per investigator assessment • Loss ability to freely provide or withdrawal of informed consent • Became pregnant A data monitoring committee was not used in the single-dose study. Data management was performed by an independent CRO according to their written SOP	Patients were withdrawn if they: • Experienced an AE, laboratory anomaly or intercurrent illness whereby continued study participation was not beneficial to the patient per investigator assessment • Loss of ability to freely provide or withdrawal of informed consent • Became pregnant Data management was performed by an independent CRO according to their written SOP	Patients were withdrawn if they: • Did not experience a migraine attack of sufficient severity to mandate administration of study treatment ≤45 days of study entry A data and safety monitoring committee was not used in the study because rimegepant was previously shown to be safe and well tolerated	Patients were withdrawn if they: • Did not experience a migraine requiring treatment by Week 8 of the open-label treatment period • Experienced an AE, laboratory anomaly or intercurrent illness whereby continued study participation was not beneficial to the patient per investigator assessment • Had a non-0 score on the Sheehan Suicidality Tracking Scale • Had 6 missed evening reports in 2 months (sequential or non-sequential) indicating poor compliance with study procedures and visits • Loss of ability to freely provide or withdrawal of informed consent • Became pregnant Data management was performed by an independent CRO according to their written SOP

Abbreviations: AE, adverse event; CI, confidence interval; CRO, contract research organisation; EOT, end of treatment; ICF, informed consent form; ID, identification; IWRS, interactive web response system; MBS, most bothersome symptom; MedDRA, Medical Dictionary for Regulatory Activities; mITT, modified intent-to-treat; NA, not applicable; PT, preferred term; SAEs, serious adverse events; SoC, system organ class; SOP, standard operating procedures

References: Study BHV3000-303: Croop 2019;[212] Study BHV3000-301: Data on File Clinical Study Report BHV3000-301[138] Study BHV3000-302: Lipton 2019;[211] Study BHV3000-201: Data on File Clinical Study Report BHV3000-201; [140] Croop 2020b [222]

B.2.5. A: Quality assessment of the relevant clinical effectiveness evidence for treatment in the acute treatment of migraine

A summary of quality assessments across the three eligible randomised clinical studies of rimegepant for the acute treatment of migraine is provided in Table 12. Modified criteria from the CRD handbook (Box 1.5) for assessment of risk of bias in the included RCTs were used to assess study quality.[231] A summary of quality assessment of the open-label safety study for the treatment of migraine is provided in Table 12. Full quality assessments of each study can be found in Appendix D: acute (Section D.5.A).

Table 12: Overview of quality assessment of eligible randomised controlled trials that evaluated rimegepant for the acute treatment of migraine

	Phase 3 acute efficacy studies		
	BHV3000-303	**BHV3000-301**	**BHV3000-302**
Was randomisation carried out appropriately?	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes
What conflict of interests are declared by the authors of the study publication?	Conflicts of interest were reported by study authors	Conflicts of interest were reported by study authors	Conflicts of interest were reported by study authors

Abbreviations: CRO, contract research organisation; IWRS, interactive web response system; MBS, most burdensome symptom; mITT, modified intent-to-treat; NA, not applicable
References: Study BHV3000-303: Croop 2019;[212] Study BHV3000-301: Data on File Clinical Study Report BHV3000-301[138] Study BHV3000-302: Lipton 2019;[211]

B.2.6. A: Clinical effectiveness results for the relevant trials for treatment in the acute treatment of migraine

The following sections present results for the trial populations for Studies BHV3000-303, BHV3000-301, and BHV3000-302. Results supporting rimegepant's anticipated positioning are provided in Section B.2.7.1.1.

B.2.6.1. A: Participant disposition (acute)

B.2.6.1.1. A: BHV3000-303, BHV3000-301, and BHV3000-302 (acute)

Participant disposition for each of the 3 randomised control trials is provided in Appendix D: acute (Section D.4.A).

B.2.6.1.2. A: BHV3000-201 (acute)

Participant disposition is provided in Appendix D: acute (Section D.4.A).

B.2.6.2. A: Baseline characteristics (acute)

B.2.6.2.1. A: BHV3000-303 (acute)

A total of 1,466 patients were randomised in Study BHV3000-303, with 1,375 patients experiencing a qualifying migraine event within the study period and 1,351 patients evaluable for efficacy (669 on rimegepant and 682 on placebo).[212]

Rimegepant ODT and placebo groups were well matched on demographic variables and appeared well-balanced between treatment arms in terms of age, sex, ethnicity, weight, height, or body mass index (BMI) (Table 13).[212]

Participants had a mean age of 40·2 years (SD 12·0), and most were female (85%) and white (75%). [212] Participants had a mean weight of 84·8 kg (SD 23·2) and a mean body-mass index of 30·9 kg/m² (SD 8·1).[212] The primary migraine type was migraine without aura in 70% of participants and migraine with aura in 30% of participants.[212] The mean history of moderate to severe attacks per month was 4·6 (SD 1·8), and untreated attacks lasted a mean of 29·5 hours (SD 21·6).[212] Historically, the most bothersome symptom was photophobia for 770 (57%) participants, nausea for 317 (23%), and phonophobia for 261 (19%).[212] For the treated attack, the most bothersome symptom was photophobia for 733 (54%) participants, phonophobia for 209 (15%), and nausea for 384 (28%).[212]

B.2.6.2.2. A: BHV3000-301 (acute)

A total of 1,162 patients were randomised in the BHV3000-301 study; 1,095 patients received a dose of study drug, and therefore comprised the safety population, and 1,084 patients comprised the modified intent-to-treat (mITT) population for efficacy analyses.[138] The demographic and disease characteristics were well-balanced between the treatment groups.[138]

B.2.6.2.3. A: BHV3000-302 (acute)

A total of 1,186 patients were randomised in the BHV3000-302 study; 1,086 patients received a dose of study drug, and therefore comprised the safety population, and 1,072 patients comprised the mITT population for efficacy analyses.[211] The demographic and disease characteristics between the treatment groups were similar, (Table 13).[211]

B.2.6.2.4. A: BHV3000-201 (acute)

A total of 1,800 patients received ≥1 dose of the rimegepant 75 mg tablet in the BHV3000-201 study; 1,693 comprised the follow-up population, and 1,197 completed study treatment.[140] Most participants (89.4%) were female; median age was 43 years and 3.7% were ≥65 years.[222]

Table 13: Baseline demographics and disease characteristics across eligible clinical studies of rimegepant for the acute treatment of migraine

Characteristic	Phase 3 acute efficacy studies						Phase 2/3 long-term safety study
	mITT population		mITT population		mITT population		Treated population
	BHV3000-303		BHV3000-301		BHV3000-302		BHV3000-201
	Rimegepant (n=669)	Placebo (n=682)	Rimegepant (n=543)	Placebo (n=541)	Rimegepant (n=537)	Placebo (n=535)	Rimegepant (n=1,800)
Age in years, mean (SD)	40.3 (12.1)	40.0 (11.9)	41.9 (12.3)	41.3 (12.1)	40.2 (11.9)	40.9 (12.1)	43.1 (12.2)
Sex, n (%)							
Males	101 (15)	103 (15)	79 (14.5)	78 (14.4)	58 (10.8)	63 (11.8)	191 (10.6)
Females	568 (85)	579 (85)	464 (85.5)	463 (85.6)	479 (89.2)	472 (88.2)	1,609 (89.4)
Race, n (%)							
White	496 (74)	521 (76)	417 (76.8)	444 (82.1)	394 (73.4)	399 (74.6)	1,475 (81.9)
Black or African American	141 (21)	125 (18)	107 (19.7)	80 (14.8)	111 (20.7)[b]	118 (22.1)[b]	250 (13.9)
Asian	8 (1)	19 (3)	6 (1.1)	7 (1.3)	8 (1.5)	8 (1.5)	32 (1.8)
Multiple	7 (1)	9 (1)	10 (1.8)	7 (1.3)	14 (2.6)	5 (0.9)	28 (1.6)
American Indian or Alaska Native	4 (1)	3 (<1)	1 (0.2)	3 (0.6)	4 (0.7)	5 (0.9)	10 (0.6)
Native Hawaiian or other Pacific Islander	11 (2)	5 (1)	2 (0.4)	0	6 (1.1)	0	5 (0.3)
Missing	2 (<1)	0	-	-	-	-	0 (0)
Body mass index in kg/m^2, mean (SD)	31.1 (8.2)	30.6 (8.0)	[redacted]	[redacted]	31.0 (7.9)	31.8 (8.5)	29.4 (7.5)
Migraine history							
Attacks per month, mean (SD)	4.6 (1.8)[a]	4.5 (1.8)[a]	[redacted]	[redacted]	4.5 (1.9)	4.6 (1.8)	6.7 (3.1)[a]
Duration in hours of untreated attacks, mean (SD)	28.7 (21.5)	30.4 (21.7)	[redacted]	[redacted]	32.0 (22.5)	32.9 (21.7)	33.9 (22.3)
Migraine with aura, n (%)	189 (28)	220 (32)	190 (35.0)	183 (33.8)	[redacted]	[redacted]	600 (33.3)
Migraine without aura, n (%)	480 (72)	462 (68)	353 (65.0)	358 (66.2)	[redacted]	[redacted]	1,200 (66.7)
MBS for treated attack, n (%)							
Photophobia	359 (54)	374 (55)	[redacted]	[redacted]	277 (51.6)	279 (52.1)	NR
Phonophobia	108 (16)	101 (15)	[redacted]	[redacted]	72 (13.4	92 (17.2)	NR
Nausea	189 (28)	195 (29)	[redacted]	[redacted]	169 (31.5)	148 (27.7)	NR

Abbreviations: ITT, intention-to-treat; MBS, most bothersome symptom; mITT, modified intent-to-treat; NR, not reported; SD, standard deviation
Notes:
[a]Restricted to moderate and severe attacks; [b]Race categorised in Study BHV3000-302 as Black
References: Study BHV3000-303: Croop 2019;[212] Study BHV3000-301: Data on File Clinical Study Report BHV3000-301[138] ClinicalTrial.gov NCT03235479;[232] Study BHV3000-302: Lipton 2019;[211] Study BHV3000-201: Data on File Clinical Study Report BHV3000-201; [140] Croop 2020b [222]

B.2.6.3. A: Efficacy outcomes in the acute treatment of migraine

B.2.6.3.1. A: Co-primary endpoint: Freedom from pain at two hours post-dose and freedom from MBS at two hours post-dose (acute)

A: BHV3000-303 (acute)

Rimegepant 75 mg demonstrated rapid onset of pain relief and return to normal function along with sustained effects with a single dose in the acute treatment of migraine in the BHV3000-303 study.[212] Rimegepant achieved statistical significance on both co-primary endpoints of freedom from pain and freedom from MBS at two hours post-dose (Table 14).[212]

- For freedom from pain at two hours post-dose, the therapeutic gain (risk difference) for rimegepant was 10.4%; 142 (21.2%) patients in the rimegepant group achieved freedom from pain versus 74 (10.9%) in the placebo group (p<0.0001).[212]
- For freedom from MBS at two hours post-dose, the therapeutic gain for rimegepant was 8.3%; 235 (35.1%) patients in the rimegepant group achieved freedom from MBS versus 183 (26.8%) in the placebo group (p=0.0009).[212]

A: BHV3000-301 (acute)

In a modified intention-to-treat (mITT) analysis, significant efficacy was demonstrated on both of the coprimary endpoints of freedom from pain and freedom from MBS at two hours post-dose (Table 14):

- For freedom from pain at two hours post-dose, the therapeutic gain (risk difference) for rimegepant was 4.91% (104 [19.2%] rimegepant participants vs 77 [14.2%] placebo participants; p=0.0298).[138,232]
- For freedom from MBS at two hours post-dose, the therapeutic gain for rimegepant was 8.90% (199 [36.6%] rimegepant participants vs 150 [27.7%] placebo participants; p=0.0016).[138,232]

A: BHV3000-302 (acute)

In a modified intention-to-treat (mITT) analysis, significant efficacy was demonstrated on both of the coprimary endpoints of freedom from pain and freedom from MBS at two hours post-dose (Table 14).

- For freedom from pain at two hours post-dose, the therapeutic gain (risk difference) for rimegepant was 7.6% (95% CI, 3.3 to 11.9; p<0.001: 105 [19.6%] rimegepant participants vs 64 [12.0%] placebo participants.[211]

- For freedom from MBS at two hours post-dose, the therapeutic gain (risk difference) for rimegepant was 12.4% (95% CI, 6.9 to 17.9; p<0.001: 202 [37.6%] rimegepant participants vs 135 [25.2%] placebo participants.[211]

B.2.6.3.2. A: Secondary endpoints (acute)

A: BHV3000-303 (acute)

Rimegepant was superior to placebo on 19 of 21 secondary endpoints, including pain relief and ability to function normally at 60 minutes post-dose, freedom from pain and freedom from most bothersome symptom at 90 minutes post-dose, rescue medication use within 24 hours, and sustained freedom from pain and pain relief from two hours to 24 hours and two hours to 48 hours post-dose; the only exceptions were freedom from nausea and pain relapse (Table 14).[212] Because of the non-significant result on two-hours freedom from nausea and the pre-planned hierarchical gate-keeping procedure for the analysis of efficacy, statistical inferences cannot be drawn for this endpoint and the subsequent endpoint of pain relapse from two hours to 48 hours post-dose.

Participants treated with rimegepant were more likely to have relief of migraine headache pain during the observation period than participants treated with placebo.[212] The percentage of participants reporting pain relief post-dose was significantly better for rimegepant than for placebo at minutes 60 (p<0·05), 90 (p<0·001) and 120 (p<0·001).[212]

A: BHV3000-301 (acute)

Secondary efficacy endpoints were tested hierarchically. Significant results were achieved on freedom from photophobia, freedom from phonophobia, and pain relief at two hours post-dose. The secondary endpoint of freedom from nausea at two hours post-dose was not significant and therefore it, and all endpoints listed afterwards in the hierarchy, were not considered significant (Table 14).[138,232] All 11 secondary endpoints had numerical differences in favour of rimegepant.[138,232]

A: BHV3000-302 (acute)

Secondary efficacy endpoints were tested hierarchically. Significant results were achieved on freedom from photophobia, freedom from phonophobia, and pain relief at two hours post-dose.[211] The secondary endpoint of freedom from nausea at two hours post-dose was not significant and therefore it, and all endpoints listed afterwards in the hierarchy, were not considered significant (Table 14). All 11 secondary endpoints had numerical differences in favour of rimegepant.[211]

B.2.6.3.3. Exploratory objectives: outcomes research (acute)

A: BHV3000-303 (acute)

Patient preference of medication at 24 hours post-dose (mITT participants) indicated [redacted]% ([redacted]) of rimegepant-treated participants preferred rimegepant over their previous medication, compared with [redacted]% ([redacted]) of placebo-treated participants (Table 15).[212]

Median Migraine Quality of Life Questionnaire (MQoLQ) score indicated more favourable results for rimegepant than for placebo (Table 15).[212]

A: BHV3000-301 (acute)

Patient preference of medication at 24 hours post-dose (mITT participants) indicated [redacted]% ([redacted]) of rimegepant-treated participants preferred rimegepant over their previous medication, compared with [redacted]% ([redacted]) of placebo-treated participants (Table 15).[138,232]

Median MQoLQ score indicated more favourable results for rimegepant than for placebo (Table 15).[138,232]

A: BHV3000-302 (acute)

Patient preference of medication at 24 hours post-dose (mITT participants) indicated [redacted]% ([redacted]) of participants who provided a response, preferred rimegepant compared with [redacted]% ([redacted]) in the placebo-treated participants (Table 15).[211]

Median MQoLQ score indicated more favourable results for rimegepant than for placebo (Table 15).[211]

.

Table 14. Primary and secondary endpoint results for mITT participants in acute treatment studies BHV3000-303, BHV3000-301 and BHV3000-302

	BHV3000-303			BHV3000-301			BHV3000-302		
	Rimegepant, n/N (%)	Placebo, n/N (%)	Absolute difference, percentage points (95% CI); p-value	Rimegepant, n/N (%)	Placebo, n/N (%)	Absolute difference, percentage points (95% CI); p-value	Rimegepant, n/N (%)	Placebo, n/N (%)	Absolute difference, percentage points (95% CI); p-value
Co-primary endpoints									
Freedom from pain at 2 hours	142/669 (21.2)	74/682 (10.9)	10.4 (6.5, 14.2) p<0.0001	104/543 (19.2)	77/541 (14.2)	4.9 (0.5, 9.3) p=0.0298	105/537 (19.6)	64/535 (12.0)	7.6 (3.3, 11.9) p=0.0006
Freedom from MBS at 2 hours	235/669 (35.1)	183/682 (26.8)	8.3 (3.4, 13.2) p=0.0009	199/543 (36.6)	150/541 (27.7)	8.9 (3.4, 14.4) p=0.0016	202/537 (37.6)	135/535 (25.2)	12.4 (6.9, 17.9) p<0.0001
Secondary endpoints									
Pain relief at 2 hours post-dose	397/669 (59.3)	295/682 (43.3)	16.1 (10.8, 21.3) p<0.05	304/543 (56.0)	247/541 (45.7)	10.3 (4.4, 16.2) p=0.0006	312/537 (58.1)	229/535 (42.8)	15.3 (9.4, 21.2) p<0.0001
Ability to function normally at 2 hours post-dose	255/669 (38.1)	176/682 (25.8)	12.3 (7.4, 17.2) p<0.05	181/543 (33.3)	118/541 (21.8)	[redacted]	175/537 (32.6)	125/535 (23.4)	9.2 (3.9, 14.6) Nominal p=0.0007
Sustained pain relief from 2 to 24 hours post-dose	320/669 (47.8)	189/682 (27.7)	20.1 (15.1, 25.2) p<0.05	211/543 (38.9)	151/541 (27.9)	[redacted]	229/537 (42.6)	142/535 (26.5)	16.1 (10.5, 21.7) Nominal p<0.0001
Sustained freedom from MBS, 2 to 24 hours post-dose	181/669 (27.1)	121/682 (17.7)	9.3 (4.9, 13.7) p<0.05	Not assessed			Not assessed		
No use/use of rescue medication within 24 hours post-dose[b]	574/669 (85.8)	483/682 (70.8)	15.0 (10.7, 19.3) p<0.05	111/543 (20.4)	172/541 (31.8)	[redacted]	113/537 (21.0)	198/535 (37.0)	−16.0 (−21.3, −10.6) Nominal p<0.0001

	BHV3000-303			BHV3000-301			BHV3000-302		
	Rimegepant, n/N (%)	**Placebo, n/N (%)**	**Absolute difference, percentage points (95% CI); p-value**	**Rimegepant, n/N (%)**	**Placebo, n/N (%)**	**Absolute difference, percentage points (95% CI); p-value**	**Rimegepant, n/N (%)**	**Placebo, n/N (%)**	**Absolute difference, percentage points (95% CI); p-value**
Sustained ability to function normally, 2 to 24 hours post-dose	198/669 (29.6)	115/682 (16.9)	12.7 (8.3, 17.2) p<0.05	Not assessed			Not assessed		
Sustained pain relief, 2 to 48 hours post-dose	282/669 (42.2)	172/682 (25.2)	16.9 (12.0, 21.9) p<0.05	183/543 (33.7)	129/541 (23.9)	[redacted]	195/537 (36.3)	121/535 (22.6)	13.7 (8.3, 19.1) Nominal p<0.0001
Sustained freedom from MBS, 2 to 48 hours post-dose	155/669 (23.2)	112/682 (16.4)	6.7 (2.5, 11.0) p<0.05	Not assessed			Not assessed		
Sustained ability to function normally, 2 to 48 hours post-dose	174/669 (26.0)	105/682 (15.4)	10.6 (6.3, 14.9) p<0.05	Not assessed			Not assessed		
Freedom from photophobia at 2 hours post-dose	198/593 (33.4)	150/611 (24.5)	8.8 (3.7, 13.9) p<0.05	164/470 (34.9)	120/483 (24.8)	10.2 (4.4, 15.9) p=0.0005	183/489 (37.4)	106/477 (22.3)	15.1 (9.4, 20.8) p<0.0001
Ability to function normally at 90 mins post-dose	202/669 (30.2)	145/682 (21.3)	8.9 (4.3, 13.6) p<0.05	Not assessed			Not assessed		
Pain relief at 90 minutes post-dose	332/669 (49.6)	254/682 (37.2)	12.4 (7.1, 17.6) p<0.05	Not assessed			Not assessed		
Sustained pain freedom, 2 to 24 hours post-dose	105/669 (15.7)	38/682 (5.6)	10.1 (6.9, 13.4) p<0.05	76/543 (14.0)	44/541 (8.1)	[redacted]	66/537 (12.3)	38/535 (7.1)	5.2 (1.7, 8.7) Nominal p=0.0040
Freedom from MBS at 90 minutes post-dose	183/669 (27.4)	147/682 (21.5)	5.8 (1.2, 10.4) p<0.05	Not assessed			Not assessed		

	BHV3000-303			BHV3000-301			BHV3000-302		
	Rimegepant, n/N (%)	**Placebo, n/N (%)**	**Absolute difference, percentage points (95% CI); p-value**	**Rimegepant, n/N (%)**	**Placebo, n/N (%)**	**Absolute difference, percentage points (95% CI); p-value**	**Rimegepant, n/N (%)**	**Placebo, n/N (%)**	**Absolute difference, percentage points (95% CI); p-value**
Pain freedom at 90 minutes post-dose	101/669 (15.1)	50/682 (7.3)	7.8 (4.4, 11.1) p<0.05	Not assessed			Not assessed		
Freedom from phonophobia at 2 hours post-dose	188/451 (41.7)	135/447 (30.2)	11.5 (5.3, 17.7) p<0.05	133/345 (38.6)	113/366 (30.9)	7.7 (0.8, 14.6) p=0.0299	133/362 (36.67)	100/374 (26.8)	9.9 (3.2, 16.6) p=0.0039
Sustained pain freedom from 2 to 48 hours post-dose	90/669 (13.5)	37/682 (5.4)	8.0 (4.9, 11.1) p<0.05	63/543 (11.6)	39/541 (7.2)	[redacted]	53/537 (9.9)	32/535 (6.0)	3.9 (0.7, 7.1) Nominal p=0.0181
Pain relief at 60 minutes post-dose	246/669 (36.8)	213/682 (31.2)	5.5 (0.5, 10.6) p<0.05	Not assessed			Not assessed		
Ability to function normally at 60 minutes post-dose	149/669 (22.3)	108/682 (15.8)	6.4 (2.3, 10.6) p<0.05	Not assessed			Not assessed		
Freedom from nausea at 2 hours post-dose	203/397 (51.0)	194/430 (45.2)	5.9 (-0.9, 12.7) p>0.05 (NS)	149/318 (46.9)	134/322 (41.6)	5.2 (−2.4, 12.9) p=0.1815	171/355 (48.1)	145/336 (43.3)	4.8 (−2.7, 12.2) p=0.2084
No pain relapse/pain relapse from 2 to 48 hours post-dose[c]	90/142 (63.4)	37/74 (50.0)	13.3 (-0.4, 27.1) p=NR	41/104 (40.1)	38/77 (50.0)	[redacted]	52/105 (49.6)	32/64 (50.0)	−0.4 (−15.8, 15.1) Nominal p=0.9648

Abbreviations: CI, confidence interval; MBS, most bothersome symptom; mITT, modified intent-to-treat; NR = not reported; NS = not significant
Percentages are Cochran-Mantel-Haenszel estimates
[a]Secondary endpoints are listed in the hierarchical testing order for Study BHV3000-303
[b]Data reported as no use of rescue mediation ≤24 hours post-dose in BHV3000-303 and as use of rescue medication ≤24 hours post-dose in BHV3000-301 and BHV3000-302.
[c]Data reported as no pain relapse from 2 to 48 hours post-dose in BHV3000-303 and as pain relapse from 2 to 48 hours post-dose in BHV3000-301 and BHV3000-302.
References: Study BHV3000-303: Croop 2019;[212] Study BHV3000-301: Data on File Clinical Study Report BHV3000-301;[138] ClinicalTrial.gov NCT03235479;[232] Study BHV3000-302: Lipton 2019a[211]

Table 15. Outcomes research endpoints for mITT participants in acute treatment studies BHV3000-303, BHV3000-301 and BHV3000-302

	BHV3000-303		BHV3000-301		BHV3000-302	
	Rimegepant 75 mg N=669	**Placebo N=682**	**Rimegepant 75 mg N=543**	**Placebo N=541**	**Rimegepant 75 mg N=537**	**Placebo N=535**
Preference of medication at 24 hours post-dose (PoM)[a]						
Participants who provided a response, n (%)	N=	N=	N=	N=	N=	N=
Preferred study treatment						
Preferred previous treatment						
No preference						
Participants who responded to treatment, n (%)	N=	N=	N=	N=	N=	N=
Preferred study treatment						
Preferred previous treatment						
No preference						
Migraine specific quality of life questionnaire (MQoLQ) at 24 hours post-dose, continuous analysis						
Median total score (min, max)						

Abbreviations: CI, confidence interval; MBS, most bothersome symptom; mITT, modified intent-to-treat; MQoLQ, Migraine Quality of Life Questionnaire; NR = not reported; NS = not significant; PoM = preference of medicine

Notes:

[a]Migraine preference of medicine (PoM) scale: The PoM is a subject-rated, 5-point scale that measures preference of the study medication compared to the previous medications to treat migraine pain. The eDiary was used to evaluate the PoM

References: Study BHV3000-303: Croop 2019;[212] Study BHV3000-301: Data on File Clinical Study Report BHV3000-301;[138] ClinicalTrial.gov NCT03235479;[232] Study BHV3000-302: Lipton 2019a[211]

B.2.6.3.4. A: Study BHV3000-201 (acute)

The primary objective of the BHV3000-201 study was to evaluate the long-term safety of the rimegepant 75 mg tablet formulation, with efficacy outcomes restricted to exploratory analyses.[140,222,230]

Study BHV3000-201 was a Phase 2/3, open-label long-term safety trial of rimegepant 75 mg oral tablet for the acute treatment of migraine. The study was conducted between August 30, 2017 and July 15, 2019. The total sample size of 1,800 treated in the long-term treatment (LTT) period: 1,033 (57.4%) participants in the PRN (2 to 8 moderate to severe migraine attacks per month) group, 481 (26.7%) participants in the PRN (9 to 14 moderate to severe migraine attacks per month) group, and 286 (15.9%) participants in the scheduled EOD + PRN group.[140,222,230]

The exploratory efficacy objectives of this study were to assess the effects of repeated dosing of rimegepant on migraine-related disability, MSQ, MMD, absenteeism, presenteeism, and lost time due to migraine (LTM).[222,230,233-242]

A: Reduction in MMD Frequency of Repeated Acute Treatment

A post-hoc analysis of Study BHV3000-201 evaluated the reduction in MMD observed with rimegepant PRN for the acute treatment of migraine and assessed if any benefits observed might support a hypothesis that intermittent CGRP-receptor blockade could result in reductions in MMD over time.[237] The analysis was conducted in the 1,044 participants with six or more MMD at baseline.[237] Median time to a ≥30% reduction was 12-weeks (95% CI 4 to 40 weeks) and median time to ≥50% reduction was 32 weeks (IQR 12 to NR weeks).[237] Changes were non-linear with greater reductions in the first weeks of treatment, followed by a stable rate over the remainder of the follow up period, and the change pattern was consistent across the three MMD cluster groups.[237] By Week 52, a ≥30% reduction in baseline MMD was observed in 78.6% of patients and a ≥50% reduction in baseline MMD was observed in 63.3% of patients.[237] These findings highlight that a large percentage of patients presenting with migraine frequencies of six or more per month may achieve clinically significant reductions in MMD with treatment over a reasonable period of time.[237]

A: Absenteeism, Presenteeism and Lost Productivity

Table 16 shows baseline mean (standard error) absenteeism, presenteeism, and lost productivity time and mean (95% CI) changes from baseline at Weeks 12, 24, 36, 52. Improvements vs. baseline were clinically relevant and statistically significant at all timepoints ($p<0.0001$).[187]

Table 16: BHV-3000-201 - Absenteeism, Presenteeism, and Lost Productivity Time Over 52 Weeks

		Change from Baseline, Mean (95% CI)			
	Baseline Mean (SE)	**Week 12**	**Week 24**	**Week 36**	**Week 52**
Absenteeism[a] (days)	17.7 (0.5)	−6.7 (−7.5 −5.9)	−7.8 (−8.7, −6.9)	−8.0 (−9.1, −6.9)	−7.9 (−9.0, −6.8)
Presenteeism[a] (days)	16.2 (0.4)	−5.9 (−6.6, −5.1)	−6.4 (−7.3, −5.6)	−6.8 (−7.7, −5.9)	−6.9 (−7.8, −5.9)
Lost productivity time[a] (days)	25.8 (0.6)	−9.6 (−10.7, −8.5)	−11.0 (−12.2, −9.7)	−11.4 (−12.8, −10.0)	−11.3 (−12.8, −9.9)

Abbreviations: CI, confidence interval; SE, standard error
Notes:
[a]Absenteeism, presenteeism and lost productivity time were assessed at baseline and Weeks 12, 24, 36, and 52 using the validated Migraine Disability Assessment Instrument. Absenteeism and presenteeism were assessed from Items 1 and 2 and lost productivity time was derived from the formula, lost productivity time = absenteeism + presenteeism x 0.5
References: L'Italien 2020[187]

A: Patient Preference and Satisfaction, Clinical Global Impression of Change

An analysis of Study BHV-3000-201 investigated patient preference and satisfaction with medication, as well as clinical global impression of change (CGI-C), an observer-rated scale administered by the investigator, in 1,514 patients treated with rimegepant 75 mg PRN.[242] At Week 24 and Week 52, it was found that 78.7% and 79.8% of rimegepant patients, respectively, preferred rimegepant over their previous migraine medications, and the majority (89.4% at Week 24 and 90.5% at Week 52) reported being satisfied with rimegepant (defined as completely satisfied, very satisfied, or somewhat satisfied).[242] The investigator-administered CGI-C scale demonstrated that 88.8% and 90.9% of patients treated with rimegepant were considered improved at Weeks 24 and 52, respectively, compared with study entry.[242]

A: Use of Analgesics and Antiemetics:

Another post-hoc analysis of Study BHV3000-201 explored the relationship between rimegepant for the acute treatment of migraine attacks and the use of over-the-counter (OTC) or prescription analgesics and antiemetics during the 30-day observation period and over time in the rimegepant long-term treatment period.[235] Of the 1,800 participants treated (PRN [n=1514], EOD+PRN [n=286]), 89.4% were female, and mean age was 43 years. The most commonly used analgesics were ibuprofen, fixed combination acetaminophen/aspirin/caffeine, acetaminophen, and naproxen (select analgesics). The most commonly used antiemetics were ondansetron, promethazine, dimenhydrinate, meclizine, and prochlorperazine (select antiemetics).[235] During the first 12-weeks of

rimegepant treatment, an increase in patients reporting freedom from using select analgesics and antiemetics was observed (19.9% during the observation period, 44.6% from Weeks 1 to 4, 58.3% at Weeks 5 to 8, and 61.6% from Weeks 9 to 12).[235] During Weeks 9 to 12, 56.5% of patients who had been using analgesics and antiemetics in the observation period reported a 100% reduction in use, and through Weeks 49 to 52, this proportion had increased to 61.3%.[235] These results were observed both in patients taking rimegepant PRN and those who received rimegepant on an EOD + PRN basis.[235] With long-term rimegepant treatment, the majority of patients were able to avoid using common analgesic and antiemetic medications.[235]

B.2.7. A: Subgroup analysis in the acute treatment of migraine

B.2.7.1. A: BHV3000-303, BHV3000-301, and BHV3000-302 (acute)

A summary of results for co-primary efficacy outcomes by the following pre-specified subgroups in the final scope: headaches per month (<4 vs. ≥4) and cardiovascular risk contraindicating triptans (yes/no) are provided in Appendix E: acute.

A summary of results for efficacy outcomes by the following pre-specified subgroups: age (<40 vs. ≥40 years); race (White vs. Black or African American vs. other); sex (male/female); aura (yes/no); triptan non-responder (yes/no); and cardiovascular risk contraindicating triptans (yes/no) are also provided in Appendix E: acute.

Subgroup analysis in patients for whom ≥2 prior treatments with triptan have failed (acute) is provided in Section B.2.7.1.1.

B.2.7.1.1. A: Patients for whom ≥2 prior treatments with triptan have failed (acute)

A summary of the clinical effectiveness results for the primary and secondary endpoints for the subgroup of patients relevant for the decision problem, i.e. patients for whom ≥2 prior treatment with triptan have failed are presented in this section.

Data across the three Phase 3 trials (Study BHV3000-303, Study BHV3000-301, Study BHV3000-302) were pooled to facilitate a post-hoc analysis by triptan treatment history). The definition used for treatment failure of triptans in the post-hoc pooled analysis differed to the definition used for the individual Phase 3 studies (see Table 18for a summary of the differences). Of note, whilst both definitions used self-reported data from trial participants, the inclusion of treatment failure for reasons of intolerability as well as efficacy, and removing the requirement to have failed on all routes of administration in the post-hoc

pooled analysis increased the clinical relevance compared with the pre-specified analyses in the individual Phase 3 studies, and provides the rationale for the use of the post-hoc pooled analysis as the basis for the efficacy outcome in the economic model.

Table 17. A summary of the differences between the definitions of failure of prior treatment with ≥2 triptans in the pre-specified analyses from individual Phase 3 studies (Study BHV3000-303, Study BHV3000-301, Study BHV3000-302) and the post-hoc pooled analysis

	Pre-specified analyses in Phase 3 studies in patients who failed ≥2 prior treatments with triptan.	**Post-hoc pooled analysis in patients who failed ≥2 prior treatments with triptan.**
Reasons included for treatment failure	Efficacy only.	Either efficacy or intolerability.
Route of administration	Subjects had to fail all routes of administration tried for a single molecular entity (i.e. analysis was failure per molecular entity).	Subjects did not need to fail on all routes of administration (i.e. analysis was failure per product, not per molecular entity).

Of the 3,507 participants in the three trials (rimegepant n=1,749, placebo n=1,758), 2,272 (64.8%) had no history of triptan treatment failure, and 1,235 (35.2%) had a history of treatment failure with 1 or ≥2 triptans (Table 18).[190] The differences in definitions of prior triptan failure between the analyses of the single trials and the post-hoc pooled analysis mean that sample size of the pooled analysis (rimegepant n= 148; placebo n= 177) was larger than the sum of the sample sizes from the three individual Phase 3 studies (rimegepant n=78; placebo n=104).

Baseline characteristics are provided in Table 19.

Table 18: Historical use of discontinued triptans mITT participants in Study BHV3000-301, Study BHV3000-302, and Study BHV3000-303

Discontinued triptans	**Rimegepant 75 mg N=1,749**	**Placebo N=1,758**	**Overall N=3,507**
None n (%)	1,151 (65.8)	1,121 (63.8)	2,272 (64.8)
1 n (%)	450 (25.7)	460 (26.2)	910 (25.9)
≥2 n (%)	148 (8.5)	177 (10.1)	325 (9.3)

Abbreviations: mITT, modified intention to treat
References: Data on File: Pooled analysis of BHV3000-301, BHV3000-302 and BHV3000-303 (final version), 2021;[190,197,198]

Treatment response to rimegepant was superior to placebo across the subgroups for the coprimary endpoints (Table 20), with pairwise comparisons demonstrating no difference in response between the subgroups (Table 21).[190,197] Data by prior triptan treatment failure are

also summarised (no historical use of discontinued triptans ["no historical use of triptan failure", where no discontinued triptan could include patients who had either never taken a triptan or had taken a first triptan but had not failed treatment], historical use of one discontinued triptan ["failed one triptan"], and historical use of two discontinued triptans ["failed ≥2 triptans"]).[190,197] These data generally show that rimegepant provides benefit to patients versus placebo across a variety of endpoints even if they have previous treatment failure on triptans (Table 20).[190,197] Overall, these data suggest that response to rimegepant is independent of response to previous triptans, and would therefore provide an efficacious treatment for patients with limited treatment options.[190,197] In addition, the proportion of patients treated with rimegepant responding with pain freedom at two hours post-dose was remarkably consistent (around 20%) across the subgroups ("no historical use of discontinued triptans", "failed one triptan", and "failed ≥2 triptans").[190,197]

Table 19: Baseline characteristics for mITT participants in acute treatment from studies BHV3000-303, BHV3000-301 and BHV3000-302 stratified by historical discontinuation of triptans

	No historic use of discontinued triptan ("no historic use of triptan failure")[b]		Historic use of 1 discontinued triptan ("failed 1 triptan")		Historic use of 2 discontinued triptans ("failed ≥2 triptans")	
	Rimegepant n/N (%)	Placebo n/N (%)	Rimegepant n/N (%)	Placebo n/N(%)	Rimegepant n/N (%)	Placebo n/N (%)
N	[redacted]	[redacted]	**450**	**460**	**148**	**177**
Age in years, mean (SD)	[redacted]	[redacted]	42.4 (11.8)	42.0 (11.5)	44.5 (10.9)	43.8 (10.7)
Males, n (%)	[redacted]	[redacted]	46 (10.2)	41 (8.9)	9 (6.1)	14 (7.9)
Females, n (%)	[redacted]	[redacted]	404 (89.8)	419 (91.1)	139 (93.9)	163 (92.1)
Race, n (%)						
White	[redacted]	[redacted]	359 (79.8)	398 (86.5)	132 (89.2)	160 (90.4)
Black or African American	[redacted]	[redacted]	69 (15.3)	52 (11.3)	12 (8.1)	13 (7.3)
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiple	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Native Hawaiian or other Pacific Islander	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Body mass index in kg/m^2, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Migraine history						
Attacks per month, mean (SD)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Duration in hrs of untreated attacks, mean (SD)	[redacted]	[redacted]	33.7 (22.8)	33.6 (21.6)	37.6 (23.1)	34.5 (22.1)
Migraine with aura, n (%)	[redacted]	[redacted]	165 (36.7)	166 (36.1)	42 (28.4)	65 (36.7)
Migraine without aura, n (%)	[redacted]	[redacted]	285 (65.3)	294 (63.9)	106 (71.6)	112 (63.3)
MBS for treated attack, n (%)						
Photophobia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Phonophobia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; hrs, hours; MBS, most bothersome symptom; mITT, modified intent-to-treat
Notes:
[a]Moderate or severe; [b]No discontinued triptan could include patients who had either never taken a triptan or had taken a first triptan but had not failed treatment
References: Data on File: Pooled analysis of BHV3000-301, BHV3000-302 and BHV3000-303 (final version), 2021;[190,197,198]

Table 20: Primary and secondary endpoint results for mITT participants in acute treatment from studies BHV3000-303, BHV3000-301 and BHV3000-302 stratified by historical discontinuation of triptans[a]

	Rimegepant n/N (%)	Placebo n/N (%)	Risk difference (95% CI; p value)
Primary endpoints	**"No historic use of triptans failure"**		
Pain freedom at 2 hours post-dose	[redacted]	[redacted]	[redacted]
Freedom from MBS at 2 hours post-dose	[redacted]	[redacted]	[redacted]
Secondary endpoints			
Pain relief at 2 hours post-dose	[redacted]	[redacted]	[redacted]
Functional disability at 2 hours post-dose	[redacted]	[redacted]	[redacted]
Sustained pain relief 2 to 24 hours post-dose	[redacted]	[redacted]	[redacted]
Rescue Medication Use within 24 hours post-dose	[redacted]	[redacted]	[redacted]
Sustained pain relief 2 to 48 hours post-dose	[redacted]	[redacted]	[redacted]
Freedom from photophobia at 2 hours post-dose[c]	[redacted]	[redacted]	[redacted]
Sustained pain freedom from 2 to 24 hours post-dose	[redacted]	[redacted]	[redacted]
Freedom from phonophobia at 2 hours post-dose[c]	[redacted]	[redacted]	[redacted]
Sustained pain freedom from 2 to 48 hours post-dose	[redacted]	[redacted]	[redacted]
Freedom from nausea at 2 hours post-dose[c]	[redacted]	[redacted]	[redacted]
Pain relapse from 2 to 48 hours post-dose[d]	[redacted]	[redacted]	[redacted]
Primary endpoints	**Failed 1 triptan**		
Pain freedom at 2 hours post-dose	93/450 (20.7)	57/460 (12.4)	8.3 ([redacted]; p=0.0007)
Freedom from MBS at 2 hours post-dose	163/450 (36.2)	112/460 (24.4)	11.8 ([redacted]; p<0.0001)
Secondary endpoints			
Pain relief at 2 hours post-dose	[redacted]	[redacted]	[redacted]
Functional disability at 2 hours post-dose	[redacted]	[redacted]	[redacted]
Sustained pain relief 2 to 24 hours post-dose	[redacted]	[redacted]	[redacted]
Rescue Medication Use within 24 hours post-dose	[redacted]	[redacted]	[redacted]
Sustained pain relief 2 to 48 hours post-dose	[redacted]	[redacted]	[redacted]
Freedom from photophobia at 2 hours post-dose[c]	[redacted]	[redacted]	[redacted]
Sustained pain freedom from 2 to 24 hours post-dose	[redacted]	[redacted]	[redacted]
Freedom from phonophobia at 2 hours post-dose[c]	[redacted]	[redacted]	[redacted]

	Rimegepant n/N (%)	Placebo n/N (%)	Risk difference (95% CI; p value)
Sustained pain freedom from 2 to 48 hours post-dose	[redacted]	[redacted]	[redacted]
Freedom from nausea at 2 hours post-dose[c]	[redacted]	[redacted]	[redacted]
Pain relapse from 2 to 48 hours post-dose[d]	[redacted]	[redacted]	[redacted]
Primary endpoints	**Failed ≥2 triptans**		
Pain freedom at 2 hours post-dose	30/148 (20.0)	18/177 (10.2)	9.8 ([redacted]; p=0.0131)
Freedom from MBS at 2 hours post-dose	64/148 (43.0)	38/177 (21.5)	21.5 ([redacted]; p<0.0001)
Secondary endpoints			
Pain relief at 2 hours post-dose	[redacted]	[redacted]	[redacted]
Functional disability at 2 hours post-dose	[redacted]	[redacted]	[redacted]
Sustained pain relief 2 to 24 hours post-dose	[redacted]	[redacted]	[redacted]
Rescue Medication Use within 24 hours post-dose	[redacted]	[redacted]	[redacted]
Sustained pain relief 2 to 48 hours post-dose	[redacted]	[redacted]	[redacted]
Freedom from photophobia at 2 hours post-dose[c]	[redacted]	[redacted]	[redacted]
Sustained pain freedom from 2 to 24 hours post-dose	[redacted]	[redacted]	[redacted]
Freedom from phonophobia at 2 hours post-dose[c]	[redacted]	[redacted]	[redacted]
Sustained pain freedom from 2 to 48 hours post-dose	[redacted]	[redacted]	[redacted]
Freedom from nausea at 2 hours post-dose[c]	[redacted]	[redacted]	[redacted]
Pain relapse from 2 to 48 hours post-dose[d]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; MBS, most bothersome symptom; mITT, modified intent-to-treat
Notes:
[b]Data are presented in the hierarchical testing order used in BHV3000-303
[c]Based on mITT participants who have the symptom at on-study migraine attack onset
[d]Based on mITT participants who have pain freedom at two hours post-dose
[e]Stratified by prophylactic migraine medication use with CMH weighting. Participants who are missing data at the time point or using rescue medication at or before the time point are classified as failures for all endpoints except probability of using rescue medication

References: Data on File: Pooled analysis of BHV3000-301, BHV3000-302 and BHV3000-303 (final version), 2021;[190,197,198]

Table 21: Primary and secondary endpoints compared pairwise between historical use of discontinued triptan subgroups using logistic regression models (mITT participants in Study BHV3000-301, Study BHV3000-302, and Study BHV3000-303)

	None[a] vs 1	None versus ≥2	1 versus ≥2
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Primary endpoints			
Pain freedom at 2 hours post-dose	[redacted]	[redacted]	1.03 (0.65, 1.63)
Freedom from MBS at 2 hours post-dose	[redacted]	[redacted]	0.75 (0.51, 1.09)
Secondary endpoints			
Pain relief at 2 hours post-dose	[redacted]	[redacted]	[redacted]
Functional disability at 2 hours post-dose	[redacted]	[redacted]	[redacted]
Sustained pain relief 2 to 24 hours post-dose	[redacted]	[redacted]	[redacted]
Rescue Medication Use within 24 hours post-dose	[redacted]	[redacted]	[redacted]
Sustained pain relief 2 to 48 hours post-dose	[redacted]	[redacted]	[redacted]
Freedom from photophobia at 2 hours post-dose[c]	[redacted]	[redacted]	[redacted]
Sustained pain freedom from 2 to 24 hours post-dose	[redacted]	[redacted]	[redacted]
Freedom from phonophobia at 2 hours post-dose[c]	[redacted]	[redacted]	[redacted]
Sustained pain freedom from 2 to 48 hours post-dose	[redacted]	[redacted]	[redacted]
Freedom from nausea at 2 hours post-dose[c]	[redacted]	[redacted]	[redacted]
Pain relapse from 2 to 48 hours post-dose[c]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; MBS, most bothersome symptom; OR, odds ratio; mITT, modified intent-to-treat
Notes:
Values highlighted in **bold** are statistically significant at p≤0.05
Models include class predictors variables for historical use of discontinued triptans (none, 1, and >= 2) and prophylactic migraine medication use (yes, no).
Participants who are missing data at the time point or using rescue medication at or before the time point are classified as failures for all endpoints except probability of using rescue medication.
* Presented in the hierarchical order tested in Study BHV3000-303
[a]No discontinued triptan could include patients who had either never taken a triptan or had taken a first triptan but had not failed treatment
[b]Based on mITT participants who have the symptom at on-study migraine attack onset
[c]Based on mITT participants who have pain freedom at 2 hours post-dose
dp≤0.05
References: Data on File: Pooled analysis of BHV3000-301, BHV3000-302 and BHV3000-303 (final version), 2021;[190,197,198]

B.2.8. A: Meta-analysis of evidence in the acute treatment of migraine

Direct evidence for the efficacy of rimegepant versus placebo can be drawn from the pooled analysis of Study BHV3000-301, Study BHV3000-302, and Study BHV3000-303, therefore no meta-analysis or indirect comparison were conducted.

B.2.9. A: Indirect and mixed treatment comparisons in the acute treatment of migraine

Given the positioning of rimegepant in the clinical pathway and absence of relevant comparator triptan trials,[3] no network meta-analysis (NMA) was required.

Preventive treatment of migraine

The following sections report the relevant clinical evidence for the preventive treatment of migraine (heading prefixed with P:)

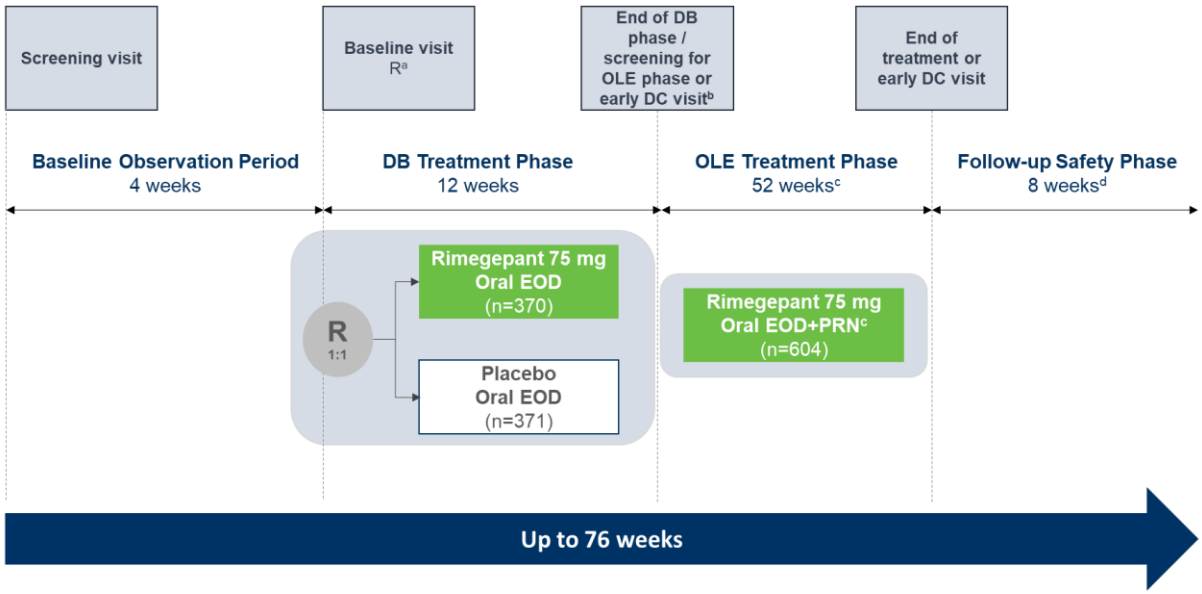
B.2.3. P: Summary of methodology of the relevant clinical effectiveness evidence in migraine prevention

B.2.3.1. P: BHV3000-305 (prevention): Study design and methodology

BHV3000-305 was a Phase 2/3 randomised, double-blind, placebo-controlled prevention study to assess efficacy and safety of rimegepant 75 mg tablet EOD for 12-weeks in patients with episodic and chronic migraine (four to 18 migraine attacks per month).[216] The study consisted of four phases (Figure 6):[216]

1. Screening phase, which included a screening visit and a 28-day baseline migraine observation period.
2. 12-week double-blind treatment phase.
3. 52-week open-label extension phase.
4. Eight-week follow-up safety phase.

Figure 6: BHV3000-305 study design



Abbreviations: DB, double-blind; DC, discontinuation; EOD, every other day; EOT, end of treatment; OLE, open-label extension; OP, observation period; R, randomisation
Notes:
[a]After completing the 28-day OP, participants returned to the clinic for the Baseline visit, during which their eligibility for continued participation in the study was assessed. If eligible, participants were randomised and entered the 12-week DBT phase (Weeks 1 through 12), during which they were instructed to take 1 tablet of blinded study drug (rimegepant 75 mg or placebo) every other calendar day. If participants had a migraine during the DBT phase of the study, if needed, they could treat the migraine with their standard of care medication and were instructed to continue to take study medication on their regular schedule (scheduled dosing days only
[b]End of DB phase, screening for OLE phase or early DC visit. Assess eligibility of participant to enter OLE phase and start study medication or if ineligible for OLE phase participant to return study medication
[c]During the OLE phase, participants were instructed to take 1 tablet of rimegepant 75 mg every other calendar day. If participants had a migraine on a day that they were not scheduled to dose with rimegepant, they could take 1 tablet of rimegepant 75 mg on that calendar day to treat a migraine. Therefore, during the OLE phase, participants could take a maximum of 1 rimegepant 75 mg tablet per calendar day for this 52-week period.
[d]After completing the OLE phase, participants were to return to the clinic for an EOT visit. There were follow-up safety visits 2 and 8 weeks after the EOT visit for assessment of liver function tests. Participants who did not complete the DBT phase and/or did not enter or complete the OLE phase were to complete the EOT visit, the 2-week follow-up safety visit, and the 8-week follow-up safety visit after their early discontinuation
References: Croop 2021;[216] Data on File: Module 2.7.3 Summary of Clinical Efficacy (Rimegepant Preventive Treatment of Migraine BHV3000)[243]

During the four-week observation period, patients documented the occurrence and severity of migraine attacks using an eDiary; they used a paper diary to record use of all migraine treatments and daily menstrual cycle information for women. Four days preceding the baseline (randomisation) visit, participants returned to the study site for a pre-randomisation (laboratory) visit. This visit included safety laboratory tests, a serum pregnancy test for women of childbearing potential, and assessment of eDiary compliance.[216]

After the four-week observation period, eligible patients (Table 22) were randomised 1:1 using an IWRS to double-blind treatment with oral rimegepant 75 mg tablets or matching placebo every other day for 12-weeks at one of 92 study centres in the USA.[216] Patients continued to document the occurrence and severity of migraine attacks in the eDiary and recorded the use of standard migraine drugs and menstrual cycle information (women only)

in the paper diary. Beyond the study medication, patients could continue using one protocol-specified migraine preventive drug (e.g., topiramate, amitriptyline, or propranolol) if the dose was stable for ≥3 months before the start of the screening period and was expected to remain stable throughout the study. Patients recorded use of rescue medication in a paper diary during the 12-week double-blind treatment phase. Acceptable rescue medications included triptans, NSAIDs, paracetamol ≤1,000 mg/day for ≤2 consecutive days (including a fixed combination containing paracetamol 250 mg, aspirin 250 mg, and caffeine 65 mg [based on guidance from the American Headache Society (AHS) and the American Academy of Family Physicians (AAFP), patients with mild to moderate symptoms should be prescribed oral NSAIDs and combination analgesics containing caffeine as first-line acute therapy[15,16,39,101]]), baclofen, antiemetics, and muscle relaxants. At the baseline and Week 12 visits, patients completed paper-based versions of the Migraine Specific Quality of Life Questionnaire (MSQoL) V2.1 and Migraine Disability Assessment (MIDAS). Patients were allowed to continue in an open-label extension study for an additional 12 months.[216]

Table 22: Inclusion and exclusion criteria for prevention Study BHV3000-305

Inclusion criteria
• Age ≥18 years • ≥1-year history of migraine with or without aura or chronic migraine per ICHD-III criteria • Migraine onset at age <50 years • Migraine attacks, on average, lasting 4 to 72 hours if untreated • 4 to 18 migraine attacks of moderate to severe intensity per month within the last 3 months prior to the screening visit   • This criterion was amended in protocol amendment 3 to change the allowance for the number of migraine attacks for eligibility during the 3 months prior to screening from 4-14 migraine attacks to 4-18 migraine attacks. • ≥6 migraine days during the observation period • ≤18 headache days during the observation period • Ability to distinguish migraine attacks from tension/cluster headaches • Patients on prophylactic migraine medication were permitted to remain on 1 medication with possible migraine-prophylactic effects if the dose has been stable for ≥3 months prior to the screening visit, and the dose was not expected to change during the course of the study
Exclusion Criteria
• History of basilar migraine or hemiplegic migraine • Headaches occurring ≥19 days per month (migraine or non-migraine) in any of the 3 months prior to the screening visit • History of non-response to any >2 of the 8 drug categories for the preventive treatment of migraine. No response was defined as no reduction in headache frequency, duration or severity after treatment for ≥6 weeks per investigator assessment but did not include lack of sustained response to treatment or intolerance to treatment • History of drug use or allergy that would make participation unsuitable • Women who are pregnant, breastfeeding, or unwilling or unable to avoid pregnancy • A history of treatment for, or evidence of, alcohol or drug abuse within the past 12 months • An ECG or laboratory test finding that raised safety or tolerability concerns

• Any medical condition that might interfere with study assessments or expose patients to undue risk of a significant AE per investigator assessment • Other: suicidal patients, patients involuntary incarcerated or detained, and patients involved in other clinical studies within 30 days prior to the screening visit or enrolment in any other multiple dose rimegepant clinical study

Abbreviations: AE, adverse event; ECG, electrocardiogram; ICHD-III, International Classification of Headache Disorders-3rd edition
References: Croop 2021[216]

Patients who received ≥1 dose of their assigned study medication and who had ≥14 days of data in the screening period and ≥14 days of data for at least one four-week interval during the double-blind treatment phase were analysed for efficacy.[216] Those who received ≥1 dose of study medication were analysed for safety.[216]

The primary efficacy endpoint of this study was the change from the observation period in the mean number of MMD in the last month (Weeks 9 to 12) of the double-blind treatment phase.[216]

B.2.4. P: Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence in migraine prevention

B.2.4.1. P: BHV3000-305 (prevention): Trial populations and statistical analyses

Table 23 summarises the trial populations analysed and statistical methodology performed in Study BHV3000-305.

Table 23: Trial populations and statistical analyses of the preventive treatment studies (BHV3000-305)

Study	BHV3000-305
Populations for analysis	The following participant populations were evaluated for the Week 12 analysis: • **Modified intent-to-treat (mITT) participants:** Enrolled participants who were randomised only once and received at least one dose of double-blind study medication (rimegepant or placebo), i.e., participants with a non-missing double-blind treatment (DBT) start date (referred to as full analysis set in the protocol) − **Evaluable mITT participants:** mITT participants with ≥14 days eDiary efficacy data in both the OP and at least one month (i.e. four-week interval) in the DBT phase (efficacy analysis set) − **Open-label rimegepant mITT participants:** mITT participants who received at least one dose of open-label rimegepant, i.e., participants with a non-missing open-label rimegepant start date. ▪ **Evaluable open-label rimegepant mITT participants:** Open-label rimegepant mITT participants with ≥14 days of eDiary efficacy data (not necessarily consecutive) in both the OP and at least one month (i.e., four-week interval) in the OLE phase. • **Treated participants:** Enrolled participants who received at least one dose of study drug (double blind or open-label), i.e., participants with a non-missing study drug start date • **Open-label rimegepant-treated participants:** Enrolled participants who received at least one dose of open-label rimegepant, i.e., participants with a non-missing open-label rimegepant start date. • **Double-blind or open-label rimegepant treated participants:** Enrolled participants who received at least one dose of rimegepant (double-blind or open-label); i.e., participants with a non-missing double-blind or open-label rimegepant start date (safety analysis set) • **Follow-up participants:** Treated participants whose last contact date was in the follow-up safety analysis period.
Statistical analyses	
Hypothesis objective	To test whether there is a superior difference between rimegepant 75 mg EOD and placebo in the number of patients who experienced a change in the mean MMD in Week 9 to 12 vs. the baseline period
Statistical tests	The primary endpoint was analysed by using a generalised linear mixed-effect model that included the patient as a random effect and the number of MMD in the baseline period as a covariate. Included in the model were fixed effects for treatment group, stratification factor, study month in the double-blind treatment phase and month-by-treatment group interaction MMD were based on between assessment visit intervals (4-weeks) with data prorated to account for missing diary data in patients with ≥14 days eDiary data during any reporting period Secondary endpoints were tested in a hierarchical gatekeeping approach to control the type I error rate at 0.05
Exploratory endpoints	There were 13 exploratory endpoints in the study (refer to Study 305 CSR [final, 12 week]).[214]
Efficacy subgroups	For mITT participants, the following efficacy subgroups were analysed for the reduction in migraine days per month: • Age (years): <40, ≥40; <65 , ≥65 • Sex: female, male

Study	BHV3000-305
	• Race: White, Black or African American, Other Including Asian, Asian • Ethnicity: Hispanic or Latino, Not Hispanic or Latino • Baseline body mass index (BMI; kg/m^2): <25, ≥25 to <30, ≥30 • Historical number of moderate or severe migraine attacks per month: <6, ≥6; <8, ≥8; <12, ≥12; <15, ≥15 • Historical primary migraine type: migraine with aura, migraine without aura • Historical chronic migraine: yes, no • Prophylactic migraine medication use at randomisation (i.e., IWRS randomization strata): yes, no • Total migraine days per month in the OP: <14, ≥14 (post hoc analysis)
Sample size, power calculations	With a sample size of roughly 800 participants randomised, and 400 participants per treatment group, it was expected that there would be roughly 370 participants per treatment group in the evaluable mITT population. Assuming rimegepant provides roughly a one-day advantage over placebo on the primary endpoint and a common standard deviation (SD) of 3.75 days, then the study will have roughly 95% power on the primary endpoint. The estimates for the change in migraine days per month and the SD are consistent with publicly available information from another investigational CGRP antagonist for this indication.[244]
Data management, patient withdrawals	Patients were withdrawn if they: • Experienced an AE, laboratory anomaly or intercurrent illness whereby continued study participation was not beneficial to the patient per investigator assessment • [redacted]Patients with poor compliance were considered for discontinuation.[redacted] • Loss of ability to freely provide or withdrawal of informed consent • Had a laboratory abnormality meeting exclusion criterion in the baseline assessment period • Became pregnant A data and safety monitoring committee was not used in the study because rimegepant was previously shown to be safe and well tolerated. Data management was performed by an independent CRO according to their written SOP

Abbreviations: AE, adverse event; CGRP, calcitonin gene-related peptide; CMH, Cochran-Mantel-Haenszel; CRO, contract research organisation; CRF, case report form; DBT, double blind treatment; eDiary, electronic diary; EOD, every other day; GLM, generalised linear model; GLMEM, generalised linear mixed effect model; IWRS, interactive web response system; MedDRA, Medical Dictionary for Regulatory Activities mITT, modified intent-to-treat; MMD, monthly migraine days; OP, observation period; PT, preferred term; SAE, serious adverse event; SD, standard deviation; SOC, system organ class; SOP, standard operating procedure; TEAE, treatment emergent adverse event
References: Croop 2021;[216] Data on File: clinical study report BHV3000-305 (Final Week 12), 2020;[214] Data on File: clinical study report BHV3000-305 (Addendum), 2020;[215]

B.2.5. P: Quality assessment of the relevant clinical effectiveness evidence in migraine prevention

Study BHV3000-305[214,216] was a well-designed Phase 2/3 study with appropriate randomisation via an IWRS and double blinding of patients and study investigators.

An overview of the quality assessment for the Phase 2/3 preventive treatment study for rimegepant (Study BHV3000-305[214,216]) is provided in Table 24. A full quality assessment of this study can be found in Appendix D: prevention (Section D.10.P).

Table 24: Overview of quality assessment of Study BHV3000-305 for rimegepant for preventive treatment of migraine

	BHV3000-305
Was the randomisation method adequate?	Yes
Was the allocation adequately concealed?	Yes
Were the groups similar at the onset of the study in terms of prognostic factors, for example severity of disease?	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes
What conflict of interests are declared by the authors off the study publication?	Conflicts of interest were reported by study authors

Abbreviations: RCT, randomised controlled trial
References: Croop 2021;[216] Data on File: clinical study report BHV3000-305 (Final Week 12), 2020[214]

B.2.6. P: Clinical effectiveness results for the relevant trials in migraine prevention

B.2.6.1. P: BHV3000-305 (prevention): Participant disposition

Participant disposition for the DBT phase and open-label phase is provided in Appendix D: prevention (Section D.9.P).

B.2.6.2. P: BHV3000-305 (prevention): Baseline characteristics

Among treated patients (n=741), demographic variables and disease characteristics were well balanced across the rimegepant and placebo groups (Table 25).[214,216]

The treated population (n=741) had a mean age of 41·2 (SD 13·1) years (Table 25).[216] 613 (83%) participants were women and 604 (82%) were of white race (Table 25).[216] Mean body-mass index was 26·4 (3·8) kg/m^2.[216] The treated population (n=741) reported a history of

moderate or severe attacks per month of mean 7·8 (SD 2·7).[216] A total of 446 (60%) participants had a primary migraine type without aura, and 173 (23%) were assessed as having chronic migraine by history (Table 25). Without treatment, attacks lasted for a median of 24 (IQR 12–48) h.[216] During the observation period, efficacy-evaluable participants in the rimegepant (n=348) and placebo (n=347) groups had a mean of 10·3 (SD 3·2) and 9·9 (3·0) migraine days per month, respectively (Table 25).[216]

Table 25: Baseline demographics and disease characteristics in the study of rimegepant for preventive treatment of migraine (BHV3000-305): DBT population

Characteristic	BHV3000-305 double-blind treated population	
	Rimegepant (n=370)	Placebo (n=371)
Age in years, mean (SD)	41.3 (13.0)	41.1 (13.1)
Gender, n (%)		
Women	300 (81)	313 (84)
Men	70 (19)	58 (16)
Race, n (%)		
White	295 (80)	309 (83)
Black or African American	62 (17)	49 (13)
Asian	1 (<1)	7 (2)
Multiple	6 (2)	2 (1)
American Indian or Alaska Native	6 (2)	1 (<1)
Native Hawaiian or other Pacific Islander	0	3 (1)
Weight (kg)	73.5 (13.3)	72.3 (13.0)
Height (cm)	165.9 (8.7)	165.9 (8.5)
BMI in kg/m^2, mean (SD)	26.6 (3.8)	26.2 (3.9)
Migraine history		
Age at disease onset in years, median (IQR)	18 (14, 28)	18 (13, 28)
Moderate or severe attacks per month, mean (SD)	7.8 (2.8)	7.8 (2.7)
Duration in hours of untreated attacks, median (IQR)	24 (12, 48)	24 (12, 48)
History of chronic migraine n (%)		
Yes	78 (21)	95 (26)
No	292 (79)	276 (74)
Primary migraine type n (%)		
Without aura	220 (59)	226 (61)
With aura	150 (41)	145 (39)
MMD in the observation period, mean (SD)	10.3 (3.2)	9.9 (3.0)

Abbreviations: BMI, body mass index; IQR, interquartile range; SD, standard deviation
References: Croop 2021[216]

The double-blind or open-label rimegepant treated population (n=[redacted]) had similar demographics and disease characteristics regardless of the original treatment assignment and were similar to the overall treated population.[215]

Table 26: Baseline demographics and disease characteristics in the study of rimegepant for preventive treatment of migraine (BHV3000-305): by DB treatment allocation

	DB Rimegepant / OLE rimegepant (n=[redacted])	Placebo / OLE rimegepant (n=[redacted])
Age in years, mean (SD)	41.3 (13.0)	[redacted]
Gender, n (%)		
Women	300 (81)	[redacted]
Men	70 (19)	[redacted]
Race, n (%		
White	295 (80)	[redacted]
Black or African American	62 (17)	[redacted]
Asian	1 (<1)	[redacted]
Multiple	6 (2)	[redacted]
American Indian or Alaska Native	6 92)	[redacted]
Native Hawaiian or other Pacific Islander	0	[redacted]
Weight (kg)	73.5 (13.3)	[redacted]
Height (cm)	165.9 (8.7)	[redacted]
BMI in kg/m^2, mean (SD)	26.6 (3.8)	[redacted]
Migraine history		
Age at disease onset in years, median (IQR)	18 (14, 28)	NR
Moderate or severe attacks per month, mean (SD)	7.8 (2.8)	NR
Duration in hours of untreated attacks, median (IQR)	24 (12, 48)	NR
History of chronic migraine n (%)		
Yes	78 (21)	NR
No	292 (79)	NR
Primary migraine type n (%)		
Without aura	220 (59)	NR
With aura	150 (41)	NR
MMD in the observation period, mean (SD)	10.3 (3.2)	NR

Abbreviations: BMI, body mass index; IQR, interquartile range; OLE, open label extension; SD, standard deviation
References: Data on File: Clinical Study Report BHV3000-305, 2020 [214,215]

B.2.6.3. P: BHV3000-305 (prevention): DBT (to Week 12) efficacy outcomes

B.2.6.3.1. P: Primary endpoint: Change in mean number of total MMD in the last month of the double-blind treatment phase (Weeks 9 to 12) vs. baseline (prevention)

Rimegepant was superior to placebo with regard to the primary endpoint of change in the mean number of MMD during Weeks 9 to 12 (Table 28).[216]

The least squares mean difference between the rimegepant and placebo treatment groups was −0.8 days (95% CI −1.46 to −0.20; p=0.0099), with reductions of 4.3 days (−4.8 to −3.9) for rimegepant and 3.5 days (−4.0 to −3.0) for placebo.[216]

Table 27: Primary endpoint results for mITT participants in prevention Study BHV3000-305

	Rimegepant (n=348)	Placebo (n=347)
n	348	347
LSM (95% CI)	−4.3 (−4.83, −3.87)	−3.5 (−4.00, −3.04)
Difference from placebo (95% CI)	−0.8 (−1.46, −0.20)	---
p-value	0.0099*	---

Abbreviations: CI, confidence interval; LSM, least squares mean
Notes:

*Significant p value in hierarchical testing

[a]GLMEM: change from baseline in number of total MMD is dependent variable; patient is random effect; number of total MMD in the baseline period is covariate; treatment group, prophylactic migraine medication use at randomisation, month, and month-by-treatment group interaction are fixed effects.
References: Croop 2021[216]

B.2.6.3.2. P: Secondary endpoints (prevention)

Rimegepant also displayed statistically significant superiority over placebo for the following secondary endpoints (Table 28):[216]

- Number and percentage of participants who have a ≥50% reduction from observation period in the mean number of moderate or severe MMD on treatment in the last month of the double-blind treatment phase.[216]
- Change from baseline in the mean number of MMD over the entire double-blind treatment phase (Weeks 1 to 12).[216]

The secondary endpoint of rescue medication days per month in the last month of the double-blind treatment phase did not reach statistical significance (p>0.05); due to the hierarchical nature of the analysis plan for efficacy, no further statistical testing was done.[216]

Of note, the nominal p-values corresponding to the secondary endpoints of change from the baseline period in mean number of total MMD in the first month (Weeks 1 through 4) and MSQoL restrictive role function domain score change from baseline at Week 12 were <0.05 (Table 28).[216]

Table 28: Secondary endpoint results for mITT participants in prevention Study BHV3000-305

	Rimegepant (n=348)	Placebo (n=347)
Secondary endpoints		
Proportion of patients with ≥50% reduction in mean number of moderate or severe MMD in the last month of the double-blind treatment phase (Weeks 9 through 12) vs. baseline		
Response rate (n/N)	171/348	144/347
Stratified risk[b] (95% CI)	49.1% (43.9, 54.3)	41.5% (36.3, 46.7)
Difference from placebo (95% CI)	7.6% (0.2, 14.9)	-
p-value	0.0438*	-
Change in mean number of total MMD during the double-blind treatment phase (Weeks 1 through 12) vs. baseline[a]		
n	348	347
LSM (95% CI)	−3.6 (−3.97, −3.17)	−2.7 (−3.14, −2.34)
Difference from placebo (95% CI)	−0.8 (−1.34, −0.31)	-
p-value	0.0017*	-
Rescue medication days per month in the last month of the double-blind treatment phase (Weeks 9 through 12)[c]		
n	348	347
LSM (95% CI)	3.7 (3.29, 4.15)	4.0 (3.53, 4.39)
Difference from placebo (95% CI)	−0.2 (−0.80, 0.31)	-
p-value	0.3868†	-
Change in mean number of total MMD in the first month of the double-blind treatment phase (Weeks 1 through 4) vs. baseline[a]		
n	348	347
LSM (95% CI)	−2.9 (−3.32, −2.46)	−1.7 (−2.15, −1.29)
Difference from placebo (95% CI)	−1.2 (−1.72, −0.61)	-
p-value	<0.0001†	-
MSQoL restrictive role function domain score at the last week of the double-blind treatment phase (Week 12) vs. baseline[d]		
n	269	266
LSM (95% CI)	18.0 (15.54, 20.56)	14.6 (12.07, 17.10)
Difference from placebo (95% CI)	3.5 (0.23, 6.70)	-
p-value	0.0358†	-

	Rimegepant (n=348)	Placebo (n=347)
MIDAS total score change at the last week of the double-blind treatment phase (Week 12) vs. baseline[e]		
n	269	266
LSM (95% CI)	−11.8 (−15.41, −8.21)	−11.7 (−15.29, −8.10)
Difference from placebo (95% CI)	−0.1 (−4.74, 4.51)	-
p-value	0.9616[†]	-

Abbreviations: CI, confidence interval; eDiary, electronic diary; GLM, generalised linear model; GLMEM, generalised linear mixed effects model; LSM, least-squares mean; MIDAS, Migraine Disability Assessment; mITT, modified intent-to-treat; MMD, monthly migraine days; MSQoL, Migraine Specific Quality of Life Questionnaire; vs, versus
Notes:
Evaluable participants were those with ≥ 14 days of eDiary efficacy data (not necessarily consecutive) in both the baseline period and ≥ 1 month (4-week interval) in the double-blind treatment phase.
* Significant p-value in hierarchical testing
[†]Nominal p-value in hierarchical testing
[a]GLMEM: change from baseline in number of total MMD is dependent variable; patient is random effect; number of total MMD in the baseline period is covariate; treatment group, prophylactic migraine medication use at randomisation, month, and month-by-treatment group interaction are fixed effects.
[b]Stratified by prophylactic migraine medication use at randomisation using Cochran-Mantel Haenszel weighting.
[c]GLMEM: number of rescue medication days per month is dependent variable; patient is random effect; treatment group, prophylactic migraine medication use at randomisation, month, and month-by-treatment group interaction are fixed effects.
[d]GLM: Week 12 change from baseline in domain score is dependent variable; baseline domain score is covariate; treatment group and prophylactic migraine medication use at randomisation are fixed effects.
References: Croop 2021[216]

At Week 12: 50.0% of rimegepant-treated participants were reported to have very much improved or much improved, compared with 37.6% of placebo-treated participants; 58.6% of rimegepant-treated participants preferred their current study medication over their previous medication, compared with 45.4% of placebo-treated participants; and, 49.2% of rimegepant-treated participants were completely or very satisfied with their medication, compared with 39.3% of placebo-treated participants (Table 29).[214,215]

Table 29: Other assessments for mITT participants in prevention Study BHV3000-305

	Rimegepant N=370	Placebo N=371
Clinical Global Impression – change scale		
N	[redacted]	[redacted]
Improved	[redacted]	[redacted]
Preference of medication improvement categories at Wk 12 – treated subjects		
N	[redacted]	[redacted]
Prefer study medication	[redacted]	[redacted]
About the same as previous medication	[redacted]	[redacted]
Prefer previous medication	[redacted]	[redacted]
Satisfaction with medication		
N	[redacted]	[redacted]

	Rimegepant N=370	Placebo N=371
Completely or very satisfied	[redacted]	[redacted]

References: Data on File: Clinical Study Report BHV3000-305, 2020[214,215]

B.2.6.4. P: BHV3000-305 (prevention): Open-label (to Week 64) efficacy outcomes

The 52-week open-label phase of the BHV3000-305 study extended the duration and exposure of rimegepant treatment.[215] The median duration on rimegepant treatment was [redacted] weeks, with a median average exposure of [redacted] tablets per month.[215] Rimegepant was taken for up to 12 months by [redacted] patients (62%) and for up to 15 months by [redacted] patients ([redacted]%).[215]

There was one exploratory efficacy endpoint for the open-label extension phase: To evaluate the reduction in the number of migraine days per month by severity (total; moderate or severe) in each month and the entire course of the OLE phase.[215]

[redacted] Medication days per month on non-scheduled dosing days of open-label rimegepant evaluable open-label rimegepant mITT participants are provided in Table 30.

Figure 7: Longitudinal Plot of Total Migraine Days per Month Mean Change From the Observational Period Over Time on OLE Rimegepant - Evaluable OLE Rimegepant mITT Participants

Abbreviations: CI, confidence interval; DB, double-blind; mITT, modified intent-to-treat; OLE, open-label extension; OP, observation period (baseline); PBO, placebo; RIM, Rimegepant
Notes:
Evaluable participants are those with >= 14 days of eDiary efficacy data (not necessarily consecutive) in both the Observational Period (OP) and >= 1 month (4- week interval) in the OLE Phase
Month 1 corresponds to the first month of the open-label period, whereby all patients had received 4 months of study treatment (i.e., rimegepant or placebo).
References: Data on File: clinical study report BHV3000-305 (Addendum), 2020;[215]

Figure 8: Longitudinal Plot of Moderate or Severe Migraine Days per Month Mean Change From the Observational Period Over Time on OLE Rimegepant - Evaluable OLE Rimegepant mITT Participants

Abbreviations: CI, confidence interval; DB, double-blind; mITT, modified intent-to-treat; OLE, open-label extension; OP, observation period (baseline); PBO, placebo; RIM, Rimegepant
Notes:
Evaluable participants are those with >= 14 days of eDiary efficacy data (not necessarily consecutive) in both the Observational Period (OP) and >= 1 month (4- week interval) in the OLE Phase
Month 1 corresponds to the first month of the open-label period, whereby all patients had received 4 months of study treatment (i.e., rimegepant or placebo).
References: Data on File: clinical study report BHV3000-305 (Addendum), 2020[215]

Table 30: Medication days per month on non-scheduled dosing days of open-label rimegepant evaluable open-label rimegepant mITT participants

	Rimegepant N=289 Mean (SD)	Placebo N=290 Mean (SD)
Any medication (rimegepant or rescue medication[a]	[redacted]	[redacted]
Acute migraine medication (rimegepant, triptan or ergotamine)[b]	[redacted]	[redacted]
Rimegepant only[b]	[redacted]	[redacted]
Rescue medication only	[redacted]	[redacted]
Rimegepant and rescue medication[b]	[redacted]	[redacted]
Triptan and ergotamine only[b]	[redacted]	[redacted]

Abbreviations: SD, standard deviation
Notes:
Evaluable participants are those with >=14 days of eDiary efficacy data (not necessarily consecutive in both the observational period and >=1 month (four-week interval) in the open-label extension phase
[a]Rescue medication: Triptan ergotamine or other
[b]Migraine days

B.2.7. P: Subgroup analysis in migraine <u>prevention</u>

A summary of results for efficacy outcomes by the following pre-specified subgroups: age (<40 vs. ≥40 years and <65 vs. ≥65 years); race (White vs. Black or African American vs.

Other Including Asian, Asian); sex (male/female); ethnicity (Hispanic or Latino, Not Hispanic or Latino), baseline body mass index (BMI; kg/m^2) (<25, ≥25 to <30, ≥30), historical primary migraine type (aura yes/no); headaches per month (<6, ≥6; <8, ≥8; <12, ≥12; <15, ≥15); historical chronic migraine (yes, no), and prophylactic migraine medication use at randomisation (i.e., IWRS randomisation strata) (yes, no), and total migraine days per month in the OP (<14, ≥14 [post hoc analysis]) are provided in Appendix E: prevention (Section E. 2.P).

As noted in Table 1, the licence for rimegepant is for episodic migraine and, as such, no data are presented for chronic migraine in the submission. It was not possible to analyse according to the number of previous preventive treatments as these data were not collected in the trial. Real-world data available from the US, where rimegepant was approved by the FDA for the prevention of migraine in May 2021, show that over [redacted]% of prescriptions are in patients who have previously been on at least one alternative prevention agent.

B.2.8. P: Meta-analysis of evidence in migraine prevention

There is a single RCT evaluating rimegepant for migraine prevention and data from a long-term open-label Phase 2/3 safety study (Study BHV3000-201). Meta-analysis was therefore not conducted.

B.2.9. P: Indirect and mixed treatment comparisons in migraine prevention

B.2.9.1. P: Network meta-analysis (prevention)

B.2.9.1.1. P: Rationale for NMA (prevention)

The proposed positioning of rimegepant in the UK treatment pathway is for patients with EM who have at least four MMD, but fewer than 15 MHD, and have failed three or more conventional preventive therapies. As per the NICE scope, this is where the three injectable mAbs – erenumab (140 mg monthly), galcanezumab (120 mg monthly), and fremanezumab (225 mg monthly and 675 mg quarterly) – are currently positioned, and as such, the mAbs are the comparators of interest for the indirect treatment analysis.

A clinical SLR was conducted to identify relevant RCTs for comparing the efficacy and safety of rimegepant to the relevant comparators in migraine prevention (see Appendix D: prevention [Section D.6.P and Section D.7.P]). No trials directly comparing rimegepant to mAbs were identified via the clinical SLR. The efficacy and safety of rimegepant for the preventive treatment of EM was demonstrated in a placebo-controlled

randomised trial (BHV3000-305).[216] The evidence base for the mAbs also consists of placebo-controlled trials. In the absence of any direct comparisons, it was therefore necessary to indirectly compare rimegepant with mAbs via an NMA using the placebo arms of the trials as a common comparator. NMAs are used for indirect comparisons and evidence synthesis by combining data from RCTs so each intervention can be compared to each of the other interventions.[245] This method preserves randomisation and produces estimates that are internally consistent.[245]

The objective of this NMA was to indirectly compare the efficacy of rimegepant with comparators listed in the decision problem (Section B.1.1) (erenumab, galcanezumab, and fremanezumab) in adult patients with EM who have a history of treatment failure to three or more conventional preventive therapies (e.g., anticonvulsants, beta-blockers, antidepressants; see Section B.1.1). The efficacy outcomes of interest included: (1) proportion achieving ≥50% reduction from baseline in MMD, and (2) mean CFB in MMD.

B.2.9.1.2. P: NMA methods (prevention)

Fixed- and random-effects models were conducted for each outcome (with and without adjustments for baseline risk) and compared via the deviance information criterion (DIC). A Bayesian framework was used to fit all NMA models in accordance with NICE Decision Support Unit (DSU) guidelines.[245]

NMA estimates of treatment effects were measured as proportion achieving ≥50% reduction in MMD from baseline, and CFB in MMD, relative to placebo. The 50% responder results were expressed in terms of odds ratio (OR), with 95% credible intervals (CrI) for achieving ≥50% response while CFB in MMD results were expressed as mean differences in MMD, with 95% CrI. For a given intervention, higher positive values for OR indicate a more favourable effect (e.g., greater probability of response) whereas lower negative values for mean difference in MMD indicate a more favourable effect (e.g., greater reduction in MMD).

A binomial likelihood model incorporating a logit link was used for the ≥50% reduction in baseline MMD outcome, while a normal likelihood model incorporating an identity link was used for the change from baseline in MMD outcome.

For each efficacy outcome, selection of the base case was based on goodness of fit statistics (DICs) across the various models fit. When two DICs are similar (<3 units difference), the standard approach is to select the less complex model.

Uninformative priors were used for all parameters including trial baselines, treatment effects, between-trial standard deviation, and meta-regression covariates. Model convergence was assessed via Gelman-Rubin plots, trace plots, and parameter density plots (Appendix D: prevention [Section D.8.9.P]). For each model, two chains of 100,000 iterations were run (with an additional burn-in of 50,000 being discarded), thinning to retain every 10th iteration. Further details can be found in Appendix D: prevention (Section D.8.9.P).

B.2.9.1.3. P: Studies included in NMA (prevention)

The studies included in the NMA evidence synthesis were restricted to Phase 2/3 or Phase 3 RCTs on the interventions of interest, among EM or mixed EM/CM study populations. If mixed populations were reported, the EM-subgroup was used if results were presented separately and EM/CM was a stratification factor, to align with the NICE decision problem and proposed positioning. The prevention clinical SLR informed the current evidence base, as described in Appendix D: prevention (Section D.6.P and Section D.7.P).

The scope of the prevention clinical SLR (Appendix D: prevention) was broader than that of the current NMA – specifically the NMA was restricted to Phase 2/3 or Phase 3 RCTs, that reported the endpoints of interest, and included mAb doses that are not currently recommended by NICE. Therefore, additional criteria (see Appendix: prevention, Section D.8.1.P) were applied to the 22 primary publications included in the prevention SLR, and additional screening of full text articles was conducted by two independent reviewers (see Appendix D: prevention, Section D.8.1.P, Figure 5). A total of 10 studies were included in the NMA (Appendix D: prevention, Section D.8.1.P). A description of the studies that were excluded can be found in Section B.2.9.2 and Appendix D: prevention (Section D.8.4.P).

A summary of studies included in the NMA are listed in Table 31. To clarify, secondary sources are studies from the same data cut as the primary sources, which contributed additional details in order to align on endpoint definitions, as described in Section B.2.9.1.4. The quality of all included trials was assessed using the quality assessment tool developed by the University of York's CRD, as recommended by NICE, [231] as is reported in Appendix D (Appendix D: prevention, Section D.8.3.P). Risk of bias was low in all trials informing the evidence base, therefore no adjustments were made in this regard.

Table 31 Summary of included studies, migraine prevention NMA

Intervention and dose (UK relevant only)	Trial	Endpoints*	Primary and (secondary) sources*
Erenumab (140 mg monthly)	STRIVE	Percent with ≥50% MMD reduction from baseline	Goadsby 2017[246]

Intervention and dose (UK relevant only)	Trial	Endpoints*	Primary and (secondary) sources*
	NCT02456740	CFB in MMD	
	EMPOwER NCT03333109	Percent with ≥50% MMD reduction from baseline CFB in MMD	Wang 2021[247]
	LIBERTY NCT03096834	Percent with ≥50% MMD reduction from baseline CFB in MMD	Reuter 2018[248]
Fremanezumab (225 mg monthly and 675 mg quarterly)	HALO EM NCT02629861	Percent with ≥50% MMD reduction from baseline CFB in MMD	Dodick 2018[249]
	NCT03303105	Percent with ≥50% MMD reduction from baseline CFB in MMD	Sakai 2021[250]
	FOCUS NCT03308968	Percent with ≥50% MMD reduction from baseline CFB in MMD	Ferrari 2019[251]
Galcanezumab (120 mg monthly)	EVOLVE-1 NCT02614183	Percent with ≥50% MMD reduction from baseline CFB in MMD	Stauffer 2018[252] (Detke 2020[253])
	EVOLVE-2 NCT02614196	Percent with ≥50% MMD reduction from baseline CFB in MMD	Skljarevski 2018[254] (Detke 2020)[253]
	CONQUER NCT03559257	Percent with ≥50% MMD reduction from baseline CFB in MMD	Mulleners 2020[255]
Rimegepant 75 mg EOD	NCT03732638	Percent with ≥50% MMD reduction from baseline CFB in MMD	Croop 2021[216] (Data on File: clinical study report BHV3000-305, 2020;[214])

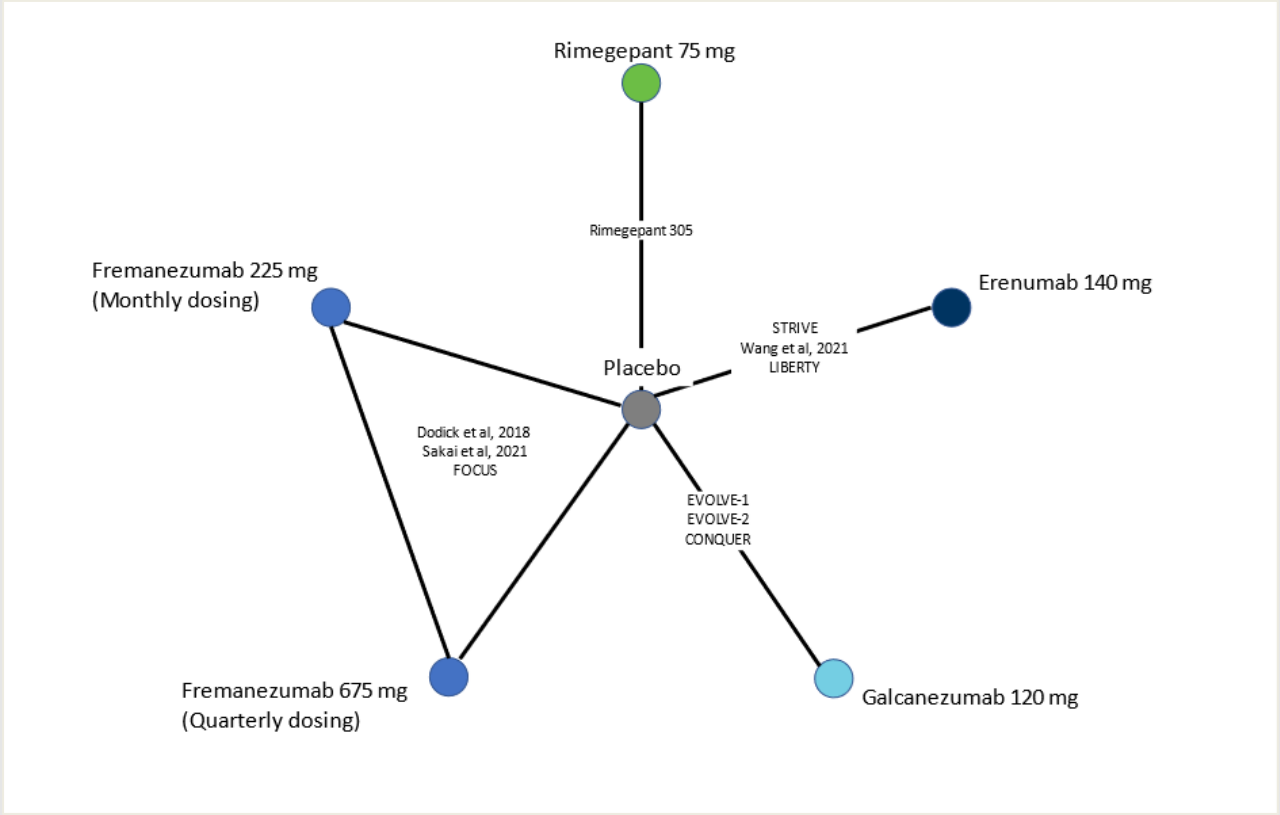
Abbreviations: CFB=change from baseline; EM=episodic migraine; EOD=every other day; MMD=monthly migraine day; NMA=network meta-analysis
Notes:
*Secondary sources are from the same data cut as the primary sources

Consistent with prior NICE TAs in migraine prevention,[4,142,143] efficacy outcomes of interest for the NMA included the number of participants achieving ≥50% reduction in MMD from baseline (50% responder rate), averaged over the 12-week DBT phase, and change from baseline (CFB) in MMD at Week 12.[256] The 50% responder rate is required for the economic analysis of rimegepant in migraine prevention, while the mean CFB in MMD endpoint is recommended as the primary efficacy endpoint in RCTs of migraine preventive therapies.[256]

A migraine day is defined as a day with headache lasting at least 30 minutes without intake of analgesics and meeting ICHD-3 criteria for migraine, or a migraine that successfully responds to acute treatment with a migraine-specific medication.[256]

The network diagram for both efficacy endpoints is presented in Figure 9.

Figure 9: Network diagram



No additional trials were included outside of the decision comparator set. All trials including outcomes that were deemed relevant to the outcomes of interest were included in the synthesis comparator set (see Section B.2.9.1.4).

Since multiple doses of fremanezumab are currently recommended by NICE, data from the clinical trials were retained, as reported, for use in the NMAs (i.e., separate doses were not pooled and remained as distinct nodes in the NMA). As all closed loops in the network were formed by single trials, which are assumed to have internal consistency, no edge-splitting was possible in the network, and therefore no opportunity for inconsistencies to arise (Figure 9).

B.2.9.1.4. P: Assessment of study comparability (prevention)

An integral step of conducting an NMA involves a feasibility assessment, in which the similarity or homogeneity of the study design and patient populations are examined. Differences in prognostic factors do not invalidate the NMA as by definition, the variables are expected to affect the treatment arms equally due to trial randomisation; this is accounted for by the fact that the NMA is conducted on the relative scale. However, difference in treatment effect modifiers may be problematic if the levels of these variables differ across included study populations.

P: Patient population (prevention)

A descriptive assessment of baseline patient characteristics between the included studies is presented in Table 32 for the comparators and doses relevant to the UK.

Mean age ranged from 37.1 to 46.8, percent female ranged from 80.0 to 89.0, and disease duration ranged from 11.2 to 24.3 years (Table 32). The EMPOwER trial (erenumab) had a slightly lower mean age and lower corresponding disease duration than other included studies, however these variables were evenly distributed across study arms within the trial and were not considered to be prognostic factors and not treatment effect modifiers.[247]

Mean MMD at baseline ranged from 8.2 to 9.5 for the 8 studies that included EM patients only or reported this subgroup separately (Table 32). The rimegepant trial included a small proportion of CM patients, which is reflected in the slightly higher mean MMD at baseline of 10.3 and 10.1, for rimegepant and placebo arms respectively. The use of a mixed (EM + CM) population from rimegepant 305 resulted from migraine status not being a stratification factor in trial randomisation and the CM population representing a small subset of the overall trial cohort. Hence, the perceived bias of using the mixed population was deemed less than the bias of using a subgroup that broke randomization. The FOCUS trial of fremanezumab in refractory patients also enrolled a mixture of EM and CM patients which contributes to the higher mean baseline MMD of 14.3 and 14.1 for fremanezumab and placebo arms (Table 32). In the FOCUS trial we were unable to restrict to the EM subgroup, in order to align outcome definitions with other trials in the network, and instead the mITT cohort (40% EM and 60% CM) was included in the NMA. This analysis is based on the assumption that baseline MMD is a prognostic factor and does not modify the migraine preventive treatment effect.

Eight of the included studies were conducted primarily in North America and Europe,[216,246,248,251-255,257] however, one study (Sakai et al.), enrolled patients from Japan and

South Korea,[250] and the EMPOwER study enrolled patients from Asia, Middle East, Latin America.[247] Based on review of the literature, location of study and race of participants were not thought to be treatment effect modifiers for preventive migraine therapies.

The evidence base consists of studies enrolling populations at earlier levels of the preventive treatment pathway (experience with <2 classes of conventional preventive therapies) and those who have failed two to four classes of migraine preventive therapies. In seven of the 10 studies, patients were excluded based on prior treatment history, although criteria differed across studies.[216,246,247,250,252,254,257] In contrast, in the three refractory mAb trials: LIBERTY, FOCUS, and CONQUER, 100% of patients had failed two to four classes of migraine prophylactic medications.[248,251,255] The proportion of patients with *any* prior preventive treatment use was reported in eight of the 10 included studies and ranged from 9.5% to 100.0%.[216,246-248,251-255] Sensitivity analysis to explore the impact of this was not feasible as detailed information regarding prior treatment history was not recorded during BHV3000-305. Therefore, treatment history heterogeneity is an acknowledged limitation of the NMA. An assumption of this analysis is that the relative treatment effect of preventive therapies does not differ based on line of therapy,

Typically, concomitant use of a single preventive therapy was permitted in the included trials if the dose had been stable in the month leading up to study enrolment. This is with exception to the refractory mAb trials which excluded patients on concurrent prophylactic medications.[248,251,255] The proportion of current preventive treatment users was available from seven of 10 studies and ranged from 0.0% to 21.4%.[216,246,248-251,255]

Table 32: Baseline patient characteristics for included studies, migraine prevention NMA

Trial	Study arm	Pts treated (n)	Mean Age (SD) years	Sex (% Female)	Race (% White)	Migraine with aura (%)	EM (%)	Mean migraine duration, years (SD)	Mean MMD (SD) at baseline	Preventive treatment, prior use (%)	Preventive treatment, current use (%)
STRIVE NCT02456740 Goadsby 2017[246]	**ERE 140**	319	40.4 (11.1)	85.3	NR	NR	100	NR	8.3 (2.5)	38.9	2.5
	PBO	319	41.3 (11.2)	85.9	NR	NR		NR	8.2 (2.5)	41.1	3.1
EMPOwER NCT03333109 Wang 2021[247]	**ERE 140**	224	37.1 (9.6)	82.1	15.6	73.7	100	11.2 (9.7)	8.3 (3.1)	53.1	NR
	PBO	338	38.0 (10.1)	83.1	17.8	67.2		12.6 (10.2)	8.4 (2.8)	53.0	NR
LIBERTY NCT03096834 Reuter 2018[248]	**ERE 140**	121	44.6 (10.5)	80.0	93.0	35.0	100	NR	9.2 (2.6)	100.0	0.0
	PBO	125	44.2 (10.6)	82.0	92.0	36.0		NR	9.3 (2.7)	100.0	0.0
HALO EM NCT02629861 Dodick 2018[249]	**FRE 225**	290	42.9 (12.7)	84.1	NR	NR	100	20.7 (12.9)	8.9 (2.6)	NR	21.4
	FRE 675	291	41.1 (11.4)	86.3	NR	NR		20.0 (12.1)	9.3 (2.7)	NR	19.9
	PBO	294	41.3 (12.0)	84.0	NR	NR		19.9 (11.9)	9.1 (2.7)	NR	21.1
NCT03303092 Sakai 2021[250]	**FRE 225**	121	44.4 (9.5)	83.5	NR	NR	100	22.0 (12.9)	8.6 (2.5)	NR	19.8
	FRE 675	119	41.9 (10.1)	84.9	NR	NR		18.3 (11.4)	8.7 (2.5)	NR	19.3
	PBO	117	44.2 (10.7)	85.5	NR	NR		19.4 (13.3)	9.0 (2.8)	NR	18.8
FOCUS NCT03308968 Ferrari 2019[251]	**FRE 225**	283	45.9 (11.1)	84.0	93.0	NR	40	24.0 (13.7)	14.1 (5.6)*	100.0	0.0
	FRE 675	276	45.8 (11.0)	83.0	95.0	NR		24.3 (12.8)	14.1 (5.6)*	100.0	0.0
	PBO	279	46.8 (11.1)	84.0	94.0	NR		24.3 (13.6)	14.3 (6.1)*	100.0	0.0

Trial	Study arm	Pts treated (n)	Mean Age (SD) years	Sex (% Female)	Race (% White)	Migraine with aura (%)	EM (%)	Mean migraine duration, years (SD)	Mean MMD (SD) at baseline	Preventive treatment, prior use (%)	Preventive treatment, current use (%)
EVOLVE-1 NCT02614183 Stauffer 2018[252]	**GAL 120**	213	40.9 (11.9)	85.0	79.3	NR	100	12.1 (13.0)	9.2 (3.1)	62.4	NR
	PBO	443	41.3 (11.4)	83.6	82.2	NR		19.9 (12.3)	9.1 (3.0)	59.4	NR
EVOLVE-2 NCT02614196 Skljarevski 2018[254]	**GAL 120**	231	40.9 (11.2)	85.3	71.9	NR	100	19.9 (11.7)	9.1 (2.9)	68.0	NR
	PBO	461	42.3 (11.3)	85.3	70.5	NR		21.2 (12.8)	9.2 (3.0)	64.6	NR
CONQUER NCT03559257 Mulleners 2020[255]	**GAL 120 (EM)**	137	45.9 (11.2)	82.0	86.0	47.0	100^	21.7 (12.7)	9.5 (3.0)	100.0	0.0
	PBO (EM)	132	46.3 (11.8)	89.0	87.0	42.0		22.9 (13.1)	9.2 (2.7)	100.0	0.0
NCT03732638 Croop 2021[216]	**RIM 75**	370	41.3 (13.0)	81.0	80.0	41.0	77	18.0 (range: 14-28)	10.3 (3.2)	[redacted]**	[redacted]**
	PBO	371	41.1 (31.1)	84.0	83.0	39.0		18.0 (range: 13-28)	10.1 (3.1)	[redacted]**	[redacted]**

Abbreviations: EM=episodic migraine, ERE=erenumab; FRE=fremanezumab; GAL=galcanezumab; MMD=monthly migraine day; NR=not reported; PBO=placebo; RIM=Rimegepant
Notes:
*note that baseline characteristics in FOCUS trial were only reported for mITT population, EM subgroup not reported separately
**BHV300-305 CSR
^EM subgroup only (stratified by EM/CM)

P: Trial endpoints (prevention)

Among the included trials, we observed heterogeneity in the methods used to calculate the migraine preventive efficacy endpoints of interest, as described in Table 33. To summarise, some studies reported the 50% responder endpoint as calculated from the observation period to Weeks 9-12 ("at 12-weeks"),[246-249] while others calculated the 50% responder endpoint from the observation period as averaged over Weeks 1-12, or the entire DBT period ("average over 12-weeks").[249-251,255]. Furthermore, there were differences in the DBT duration, while most reported endpoints at 12-weeks the galcanezumab EVOLVE-1 and EVOLVE-2 trials reported outcomes at 24-weeks.[252,254]

Table 33: Endpoint definitions reported in randomised controlled trials of migraine preventive therapies

Endpoint	Calculation method		Definition selected for NMA*
	At 12-weeks	Average over 12-weeks	
Percent with ≥50% MMD reduction from baseline	≥50% reduction in mean number of migraine days per month during weeks 9–12	≥50% reduction in mean number of migraine days per month over the 12-week period	**Average over 12-weeks**
CFB in MMD	CFB in MMD from OP to weeks 9-12	CFB in MMD from OP, averaged over the 12-week period	**At 12-weeks**

Abbreviations: CFB=change from baseline; EOD=every other day; NMA=network meta-analysis; OP=observation period
Notes:
*Based on the most commonly used definitions across included studies, and the ability to manually calculate average from monthly 50% responder rates.

Efforts were taken to align efficacy endpoint definitions across included trials, regarding both timepoint measured (e.g., 12-weeks vs 24-weeks), and method of calculation, based on the most frequently reported method for each endpoint (Table 33). This involved digitising figures from publications and review of secondary publications related to the primary RCTs, to ensure consistency in calculation methods used for the NMA efficacy endpoints. Furthermore, for the 50% responder endpoint, when responder rate was presented by month, the average over 12-weeks was manually calculated from the monthly rates:

$$\frac{([\%\ responders\ in\ month\ 1] + [\%\ responders\ in\ month\ 2] + [\%\ responders\ in\ month\ 3])}{3}$$

The availability of endpoint data in the included trials, and the studies that required manual calculation of the 50% responder endpoint are summarised in Table 34.

Table 34: Availability of efficacy endpoint definitions among included trials, migraine prevention NMA

Intervention and dose (UK relevant only)	Trial	CFB in MMD		Percent with ≥50% MMD reduction from baseline	
		At 12-weeks*	Average over 12-weeks	At 12-weeks	Average over 12-weeks*
Erenumab (140 mg monthly)	STRIVE NCT02456740 Goadsby 2017[246]	Yes	No	Yes	Yes (Imputed from Goadsby 2017[248])
	EMPOwER NCT03333109 Wang 2021[247]	Yes	No	Yes	Yes (Imputed from Wang 2021[247]
	LIBERTY NCT03096834 Reuter 2018[248]	Yes	No	Yes	Yes (Imputed from Reuter 2018[248])
Fremanezumab (225 mg monthly and 675 mg quarterly)	HALO EM NCT02629861 Dodick 2018[249]	Yes	Yes	Yes	Yes
	NCT03303092 Sakai 2021[250]	Yes	Yes	No	Yes
	FOCUS NCT03308968 Ferrari 2019[251]	Yes**	Yes	No	Yes**
Galcanezumab (120 mg monthly)	EVOLVE-1 NCT02614183 Stauffer 2018[252]	Yes	No	No	Yes (Imputed from Detke 2020[253])
	EVOLVE-2 NCT02614196 Skljarevski 2018[254]	Yes	No	No	Yes (Imputed from Detke 2020[253])
	CONQUER NCT03559257 Mulleners 2020[255]	Yes	Yes	No	Yes
Rimegepant 75 mg EOD	NCT03732638 Croop 2021[216]	Yes	Yes	No	Yes (From BHV3000-305 CSR)

Abbreviations: CFB=change from baseline; EOD=every other day; MMD=monthly migraine day
Notes:
*Shading indicates endpoint definitions used in the NMA
**Note that these outcomes were only available for the mITT subgroup, not reported for the EM subgroup

All data relevant for the treatment comparators (erenumab, galcanezumab, fremanezumab) were identified and collected from the prevention clinical SLR reported in Appendix D: prevention (Section D.8.1.P), and supplemented by further review of the secondary publications as needed (e.g., post-hoc analyses). The galcanezumab EVOLVE-1 and EVOLVE-2 trials primary publications reported the 50% responder rate at 24-weeks only.[252,254] Therefore, this data was supplemented by a post-hoc analysis by Detke et al. 2020, which reported 50% responder rate by month, for Months 1-6.[253] The average over 12-weeks was calculated using the monthly reported data for Months 1-3 (Table 34).

The FOCUS trial of fremanezumab enrolled a mix of patients with EM and CM (39.3% and 60.7% respectively). While we intended to use data from the EM subgroup for this trial, the mITT population was the only population that allowed us to have aligned outcome definitions with other trials in the network, (CFB in MMD at 12-weeks and 50% responder rate averaged over 12-weeks, (Table 34).[251] Therefore, we selected the mITT population, as the bias introduced by using a different endpoint definition was thought to be a greater validity risk than the introduction of patients with higher MMD (a characteristic which was balanced across treatment arms).

Data for rimegepant were identified and collected from the SLR and supplemented by the BHV3000-305 clinical study report (CSR) for the proportion achieving ≥ 50% reduction in baseline MMD. Data from the CSR were required to align with the definitions used in all of the mAb trials which reported ≥50% MMD reduction in *any* severity of migraine averaged over the 12-week DBT (Table 33), compared to Croop et al. 2021 which reported reduction in *moderate or severe* migraines, from baseline to Weeks 9-12 (Table 35).[216]

Table 35: Comparison of 50% responder endpoint definitions for rimegepant vs placebo, when considering moderate or severe migraines only and any migraine severity

Endpoint definition	n (%)		Source
	Rimegepant (n=348)	Placebo (n=347)	
≥50% reduction in mean number of moderate or severe migraine days per month during weeks 9–12	171 (49%)	144 (41%)	Croop et al.[216]
≥50% reduction in mean number of any severity of migraine days per month overall double-blind treatment period	[redacted]	[redacted]	(Data on File: clinical study report BHV3000-305, 2020;[214])

P: Magnitude of placebo response (prevention)

Heterogeneity in placebo responses was observed across trials for both outcomes (Table 36). For ≥50% reduction in baseline MMD, placebo responses ranged from 8.6% in FOCUS[251] to 36.4% in EMPOwER[247] (Table 36). Similarly, for CFB in MMD, placebo responses ranged from −0.2 in LIBERTY[248] to −3.5 in Croop et al. 2021[216] (Table 36).

Table 36: Change from baseline and ≥50% reduction in MMD, raw efficacy data from included trials, migraine prevention NMA

Trial	Treatment	N	CFB in MMD, mean (SD)	≥50% reduction in MMD, n (%)
STRIVE NCT02456740 Goadsby 2017[246]	PBO	316	-1.70 (0.21)	[redacted]*
	ERE 140	318	-3.51 (0.21)	[redacted]*
EMPOwER NCT03333109 Wang 2021[247]	PBO	330	-3.10 (0.25)	[redacted]*
	ERE 140	219	-4.79 (0.30)	[redacted]*
LIBERTY NCT03096834 Reuter 2018[248]	PBO	124	-0.20 (0.40)	[redacted]*
	ERE 140	119	-1.80 (0.40)	[redacted]*
HALO EM NCT02629861 Dodick 2018[249]	PBO	290	-2.69 (0.28)	81 (27.93)
	FRE 225	287	-3.89 (0.28)	137 (47.74)
	FRE 675	288	-3.70 (0.30)	128 (44.44)
NCT03303092 Sakai 2021[250]	PBO	116	-1.59 (0.44)	13 (11.21)
	FRE 225	121	-4.33 (0.38)	50 (41.32)
	FRE 675	117	-3.88 (0.44)	53 (45.30)
FOCUS NCT03308968 Ferrari 2019[251]	PBO	278	-0.58 (0.35)	24 (8.63)
	FRE 225	283	-4.09 (0.36)	97 (34.28)
	FRE 675	276	-3.40 (0.39)	95 (34.42)
EVOLVE-1 NCT02614183 Stauffer 2018[252]	PBO	433	-2.99 (0.27)	[redacted]*
	GAL 120	213	-4.66 (0.54)	[redacted]*
EVOLVE-2 NCT02614196 Skljarevski 2018[254]	PBO	461	-2.19 (0.22)	[redacted]*
	GAL 120	231	-3.77 (0.26)	[redacted]*
CONQUER NCT03559257 Mulleners 2020[255]	PBO	132	-0.59 (0.39)	23 (17.42)
	GAL 120	137	-2.80 (0.36)	57 (41.61)
NCT03732638	PBO	347	-3.50 (0.20)	[redacted]**

Trial	Treatment	N	CFB in MMD, mean (SD)	≥50% reduction in MMD, n (%)
Croop 2021[216]	RIM 75	348	-4.30 (0.26)	[redacted]**

Abbreviations: CFB=change from baseline; ERE=erenumab; FRE=fremanezumab; GAL=galcanezumab; MMD=monthly migraine day; PBO=placebo; RIM=Rimegepant
Notes:
*imputed from monthly 50% responder rates, for Months 1-3
**From BHV300-305 CSR

There are several factors that can affect the placebo response across trials, and over time. Firstly, higher frequency of drug administration (which is highest for rimegepant EOD compared to the monthly and quarterly administration schedules for the mAbs), can contribute to a larger placebo effect, which is consistent with what was observed in the current evidence base (Table 36). However, the invasiveness of the treatment may also influence placebo response. In this case we would expect that the injectable therapies would confer a larger placebo effect compared to orals, due to higher level of treatment invasiveness, however this is not the case in the current analysis, as the largest placebo effect was observed for the oral therapy rimegepant (mean CFB in MMD of -3.5 for placebo arm; Table 36).

Another trend that was observed was that the placebo response was the lowest for the 100% refractory trials (LIBERTY, FOCUS, and CONQUER; Table 36).[248,251,255] Clinical feedback from the advisory board indicated that patients who have experienced lack of response or intolerability to two to four prior preventive therapies, may in turn have lower expectations for the benefits of a subsequent study drug (consistent with expectancy therapy for placebo response).[258]

Placebo effect in studies of migraine preventive therapies has also been demonstrated to increase over time. An SLR that included 73 RCTs of migraine preventive therapies found a positive correlation between mean CFB in MMD in the placebo arm and year of publication (Figure 10).[259] A plausible explanation for the disparate correlation between oral and injection placebo study results and publication year might be recency of the latter and a narrower temporal distribution.[260] Oral studies are less current and distributed across a longer period.[260] In the current analysis, publication dates ranged from 2017 to 2021, and it is unclear if this difference in publications dates would have had any substantial effect on placebo. However, collectively, these considerations provided the rationale to conduct models adjusting for baseline risk in the NMA. Random-effects and baseline risk adjusted models can account for between-trial heterogeneity to a certain extent, however it should be noted that it is not expected for these models to completely account for all the underlying population differences between included trials.

Figure 10: Relationship between mean change in the placebo arm and year of publication

Reference: Data on File: Interim Meta-analysis Results (Continuous Outcomes) Placebo Response SLR for Migraine Prevention[259]

B.2.9.2. P: Excluded studies (prevention)

The scope of the prevention clinical SLR (Appendix D: prevention [Section D.6.P]), was broader than that of the current NMA. PICOS criteria were applied to the 22 primary publications included in the prevention SLR (see Appendix D: prevention [Section D.7.P]). Twelve of the 22 studies were excluded: Three erenumab studies from the broader SLR were excluded from the NMA because they only studied the 70 mg dose, which did not receive recommendation by NICE (see Appendix D: prevention [Section D.8.1.P]), five studies were excluded that were not Phase 2/3 or Phase 3 RCTs, and four were excluded that only reported safety outcomes. A detailed description of the studies excluded from the NMA can be found in Appendix D: prevention (Section D.8.4.P).

B.2.9.3. P: Selection of base case (prevention)

Different models were fit for each of the two efficacy outcomes. A brief description of these types of models is provided below:

- **Fixed effects model:** Assumes that there is one underlying treatment effect size for each treatment comparison, and that each trial comparing a specific set of treatments, estimates an equivalent effect size.

- **Random effects model:** Allows for the underlying treatment effect size for each treatment comparison to vary by instead assuming a distribution around each treatment comparison parameter. Evidence contributed from each trial comparing a specific set of treatments is not assumed to be equivalent, and instead the combined treatment effect estimates the mean effect from a distribution.

- **Baseline adjusted models (meta-regression):** Baseline risk adjustment is a technique which is known to account for cross-trial variability in multiple (measured and unmeasured) confounders.[261,262] This technique was used in the current analysis in order to account for difference in placebo effect that was observed across the included trials.

In Table 37, the goodness of fit statistics (DICs) across the various models fit for each outcome are summarised and were used to select base case models.

Table 37: Model fit statistics across outcomes

Model	≥50% reduction in baseline MMD			Change from baseline in MMD		
	Dbar	pD	DIC	Dbar	pD	DIC
FE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FE – Baseline adjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RE – Baseline adjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Dbar = deviance; DIC = deviance information criterion; FE = fixed-effects; MMD = monthly migraine days; pD = effective number of parameters; RE = random-effects
Notes:
Bolded values indicate chosen base case model

B.2.9.3.1. P: Proportion achieving ≥50% reduction from baseline, selection of base case (prevention)

The fixed-effects baseline-adjusted model was selected for the base case for the ≥50% reduction in baseline MMD outcome due to the large differences observed in placebo response across the trials and the baseline-adjusted models fitting better than the non-adjusted models in terms of DIC (Table 37). In addition, the regression coefficients [estimate (95% CrI)] were [redacted]. Fixed-effects were chosen over random-effects because there was a negligible difference in the DICs between the FE – Baseline adjusted and RE – Baseline

adjusted models, and a large decrease in the between-study standard deviation, sd [median (95% CrI)] was observed between [redacted]. This indicates that most of the heterogeneity is accounted for in the baseline risk adjustment and adding an additional layer of complexity with the random-effects is not necessary. However, given that the random-effects baseline-adjusted model had the lowest DIC, the results from this model are presented as a sensitivity analysis (Table 40).

B.2.9.3.2. P: Change from baseline in monthly migraine days, selection of base case (prevention)

For change from baseline in MMD, the random-effects model was selected as it had the lowest DIC and the regression coefficients were not statistically significant in either of the baseline risk-adjusted models [redacted]. However, given observed heterogeneity of placebo responses and the DICs between the RE and RE – Baseline adjusted models being similar, results from the RE – Baseline adjusted model are also displayed as a sensitivity analysis (Table 41).

B.2.9.4. P: Base case results (prevention)

Results for rimegepant versus competing active therapies across all models are displayed in Figure 11 and Figure 12. Base case models are outlined in the red boxes in the figures.

Figure 11: Summary of model results for ≥50% reduction in baseline monthly migraine days – rimegepant vs comparators

Abbreviations: Adj = adjusted; BL = baseline; CrI = credible interval; DIC = deviance information criterion; ERE = erenumab; FE = fixed effects; FRE = fremanezumab; GAL = Galcanezumab; PBO = placebo; MMD = monthly migraine days; RE = random-effects; RIM = Rimegepant
Notes:
Base case models are outlined in the red boxes in the figures.
Estimates are odds ratios (95% CrI). Bolded values are significant at a 5% level. Base case analyses are outlined with red box.

Figure 12: Summary of model results for change from baseline in monthly migraine days – rimegepant vs comparators

Abbreviations: Adj = adjusted; BL = baseline; CrI = credible interval; DIC = deviance information criterion; ERE = erenumab; FE = fixed effects; FRE = fremanezumab; GAL = Galcanezumab; PBO = placebo; MMD = monthly migraine days; RE = random-effects; RIM = Rimegepant
Notes:
Base case models are outlined in the red boxes in the figures.
Estimates are mean differences (95% CrI). Bolded values are significant at a 5% level. Base case analyses are outlined with red box.

Cross tables for the base case results are presented in Table 38 for mean change from baseline in MMD and in Table 39 for proportion achieving ≥50% reduction from baseline MMD. For change from baseline in MMD, in the base case model, all active therapies except rimegepant 75 mg showed [redacted] versus placebo (Table 38). All comparisons for other active therapies showed [redacted].

Table 38: Change from baseline in monthly migraine days, base case, random-effects model (reported MDs with 95% CrIs)

PBO					
	ERE_140				
		GAL_120			
			FRE_225		
				FRE_675	
					RIM_75

Abbreviations: CrI, credible interval; ERE, erenumab; FRE, fremanezumab; GAL, galcanezumab; PBO, placebo; RIM, Rimegepant
Notes:
Estimates are mean differences (95% CrI). Bolded values are significant at a 5% level.

For the proportion achieving ≥50% reduction from baseline MMD endpoint, in the base case model, all active therapies showed [redacted] versus placebo (Table 39). There were no substantial differences between treatments with only the CrI for rimegepant 75 mg vs galcanezumab 120 mg not crossing one ([redacted]).

Table 39: Proportion achieving 50% reduction from baseline MMD, base case, fixed-effect baseline adjusted model (reported ORs with 95% CrIs)

PBO					
	ERE_140				
		GAL_120			
			FRE_225		
				FRE_675	
					RIM_75

Abbreviations: CrI, credible interval; ERE, erenumab; FRE, fremanezumab; GAL, galcanezumab; PBO, placebo; RIM, Rimegepant
Notes:
Estimates are odds ratios (95% CrI). Bolded values are significant at a 5% level.

The between trial heterogeneity parameter for this model sd [median (95% CrI)] was [redacted]. In the 305 study, the difference between rimegepant and placebo was -0.8 days (-4.3 days for rimegepant and – 3.5 days for placebo; p = 0.0099). Note that while the

estimate from the NMA remains similar, rimegepant compared to placebo is no longer statistically significant using the 95% credible interval, -0.80 (-2.31 , 0.70). This is due partially to the fact that random effects were used which by nature increased the width of the credible intervals. Using the fixed effect model, the change from baseline between rimegepant and placebo was -0.80 (-1.44, -0.14).

B.2.9.5. P: Sensitivity analyses (prevention)

Sensitivity analyses are displayed for alternative fitting models using the same data as in the base case, and for models excluding the 100% Asian population trial (Sakai et al, 2021).[250] Models excluding the 100% Asian population trial were presented due to potential differences in the management of migraine.

In the alternative fitting model for proportion achieving ≥50% reduction, sensitivity analysis showed [redacted] results to the base case except that the estimate of rimegepant 75 mg vs galcanezumab 120 mg was [redacted] (Table 40).

In the alternative fitting model for CFB in MMD, results of the sensitivity analysis showed similar results in terms of statistical significance and direction of association; however, point estimates varied relative to the base case results, indicating a high degree of variability in these estimates.

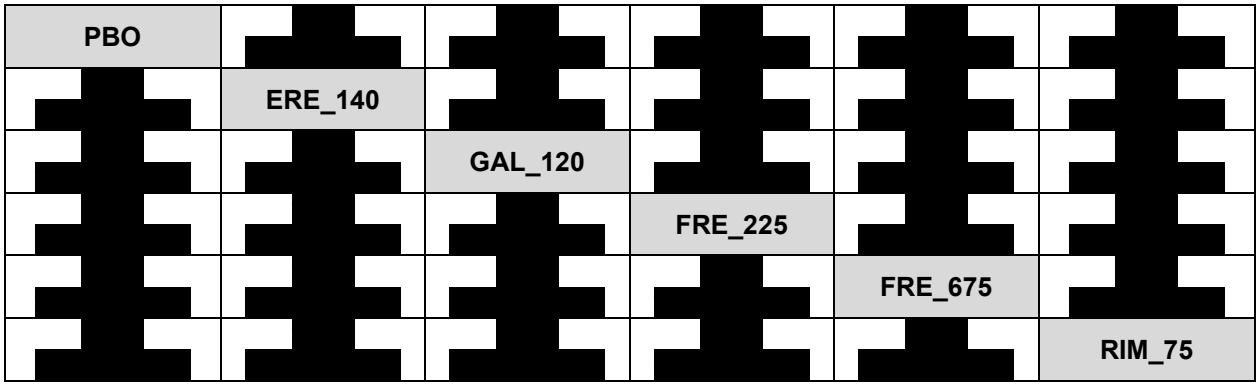
Table 40: Proportion achieving ≥50% reduction from baseline MMD, sensitivity analysis, random-effects baseline-adjusted model (reported ORs with 95% CrIs)

PBO					
	ERE_140				
		GAL_120			
			FRE_225		
				FRE_675	
					RIM_75

Abbreviations: CrI, credible interval; ERE, erenumab; FRE, fremanezumab; GAL, galcanezumab; PBO, placebo; RIM, Rimegepant
Notes:
Estimates are odds ratios (95% CrI). Bolded values are significant at a 5% level.

The between-trial heterogeneity parameter for this model, sd [median (95% CrI)] was: [redacted].

Table 41: Change from baseline in monthly migraine days, sensitivity analysis, random-effects baseline-adjusted model (reported MDs with 95% CrIs)

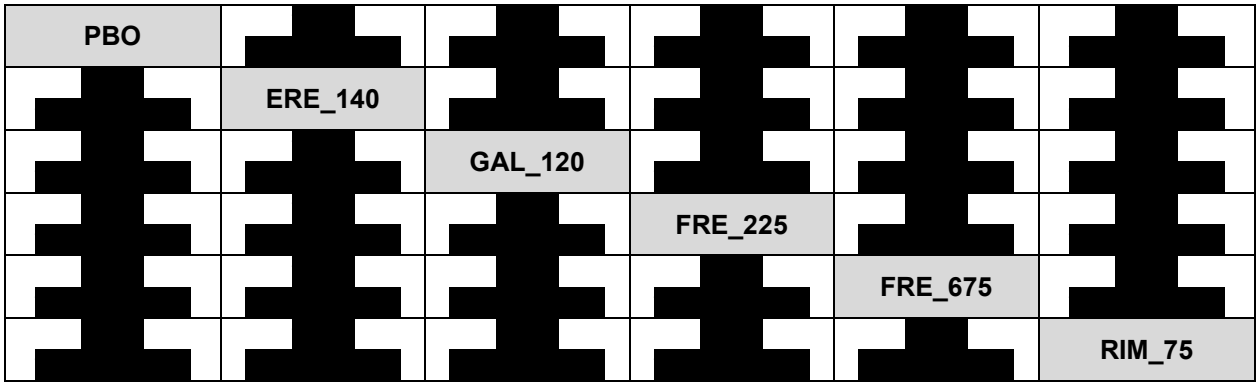


Abbreviations: CrI, credible interval; ERE, erenumab; FRE, fremanezumab; GAL, galcanezumab; PBO, placebo; RIM, Rimegepant
Notes:
Estimates are mean differences (95% CrI). Bolded values are significant at a 5% level.

The between-trial heterogeneity parameter for this model, sd [median (95% CrI)] was: [redacted].

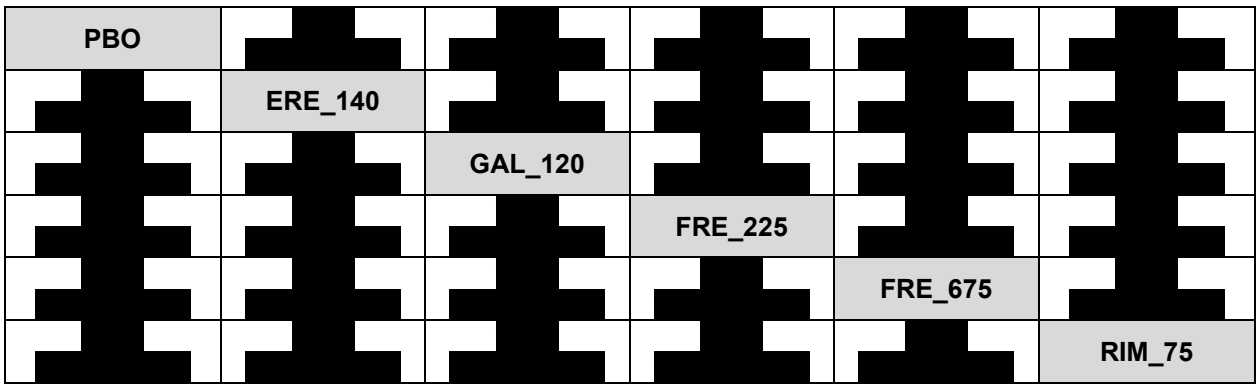
Models excluding Sakai et al, 2021 are presented for the proportion achieving ≥50% reduction from baseline MMD (fixed-effects baseline-adjusted model, Table 42**)** and CFB in MMD endpoints (random-effects model, Table 43). When compared to the base case analyses, for both outcomes, [redacted] when the Sakai et al. fremanezumab trial (which was conducted in Japan and South Korea) is excluded from the analysis**.**

Table 42: Proportion achieving 50% reduction from baseline MMD, sensitivity analysis (removing Sakai et al, 2021), fixed-effect baseline adjusted model (reported ORs with 95% CrIs)



Abbreviations: CrI, credible interval; ERE, erenumab; FRE, fremanezumab; GAL, galcanezumab; PBO, placebo; RIM, Rimegepant
Notes:
Estimates are odds ratios (95% CrI). Bolded values are significant at a 5% level.

Table 43: Change from baseline in monthly migraine days, sensitivity analysis (removing Sakai et al, 2021), random-effects model (reported MDs with 95% CrIs)



Abbreviations: CrI, credible interval; ERE, erenumab; FRE, fremanezumab; GAL, galcanezumab; PBO, placebo; RIM, Rimegepant
Notes:
Estimates are mean differences (95% CrI). Bolded values are significant at a 5% level.

The between-trial heterogeneity parameter for this model, sd [median (95% CrI)] was: [redacted].

Due to the adoption of response as the *average over 12-weeks* rather than specifically *at 12-weeks* in the NMA, we compared the odds ratios for the two-endpoint definitions versus placebo, when data were available for both in a single study publication (Figure 13). This was conducted to assess the extent to which the relative effect may be influenced by this approach.

This comparison shows consistency in odds ratios across the approaches (Figure 13). To the extent that point estimates differ, the ORs for mAbs appear to benefit from the estimation of effects over the period (*average over 12-weeks)* rather than specifically *at 12-weeks*.

Figure 13: Comparison of at 12-weeks vs over 12-weeks response in individual studies

Abbreviations: CI, confidence interval; OR, odds ratio

B.2.9.6. P: Statistical assessment of heterogeneity and response (prevention)

Statistical heterogeneity was assessed using the between-trial heterogeneity parameter (sd) for each outcome. Regarding the proportion achieving ≥50% reduction from baseline outcome, the fixed-effects baseline adjusted model was deemed best fitting in terms of DIC (Table 37). As discussed in Section B.2.9.3 there was a large decrease in sd when moving from the random-effects model to the random-effects baseline adjusted model (with the lower bound of the 95% CrI being zero). This is indicative of the baseline adjusted model sufficiently accounting for the between-trial heterogeneity without the need for added complexity of a random-effects model. For change from baseline in monthly migraine days, the random-effects model was chosen as it had the lowest DIC (Table 37). Thus, in this model, the between-trial heterogeneity was directly accounted for using the sd parameter

rather than using the baseline risk adjustment parameter, as in the model for the ≥50% reduction outcome.

B.2.9.7. P: Heterogeneity between results of pairwise comparisons and inconsistencies between direct and indirect evidence (prevention)

As all closed loops in the network were formed by single trials (Figure 9), which are assumed to have internal consistency. No edge-splitting was possible in the network, and therefore there were no opportunities for inconsistencies to arise.

B.2.9.8. P: Uncertainties in the indirect and mixed treatment comparisons (prevention)

Uncertainties and limitations of the analysis include the following:

- The pivotal rimegepant prevention trial and many key mAb trials were conducted in a mix of patients with and without prior migraine preventive treatment experience. In order to retain the largest evidence base possible, which would allow for the fitting of more complex NMA models to account for between-trial heterogeneity and baseline risk differences, no restriction of prior preventive treatment failure was applied to the NMA inclusion criteria. Therefore, a key underlying assumption of this analysis is that the relative treatment effect results from study populations with a range of prior treatment experience can be used to estimate efficacy in patients who have failed ≥3 preventive treatments, and that including these populations in the NMA does not invalidate the results. [redacted] (see Appendix D [Section D.8.5.P]). This may suggest that the rimegepant 305 trial would provide a conservative estimate of treatment effect for a refractory population.

- The migraine population of interest is those with EM (<15 MMD); however, mixed EM/CM study populations were included in the SLR. The rimegepant trial included a small proportion of patients with a history of CM (23%); it was not possible to restrict the analysis to the EM-only subgroup without breaking randomisation, as this was not a pre-specified stratification factor for randomisation in Study BHV3000-305(prevention).[216] The perceived bias of using the mixed population was deemed less than the bias of using a subgroup that broke randomisation. The fremanezumab FOCUS trial consisted of 60.7% CM patients, and while migraine frequency strata were defined pre-randomization, the 50% responder outcome and CFB at 12-weeks outcomes were only

reported for the mITT (EM+CM) population.[251] All other trials in the network were conducted in 100% EM populations or reported endpoints for the EM subgroup separately when the EM/CM strata were defined pre-randomisation. We assume that the presence of CM patients in the rimegepant and fremanezumab samples does not have a substantial effect on the relative efficacy observed in the NMA.

- As presented in Table 33 and Table 34, we observed inconsistencies in the methods used to calculate the migraine preventive efficacy endpoints of interest. However, efforts were made to align on these endpoints, and the average over 12-weeks endpoint was calculated manually for the 50% responder outcome when necessary.
- As presented in Table 36, heterogeneity was observed in regard to the placebo effect across studies. The absolute placebo effect across studies ranged from [redacted]. To address this heterogeneity, a baseline-adjusted analysis was performed. [redacted].

While random-effects and baseline risk adjusted models can account for between-trial heterogeneity to a certain extent, it is not expected for these models to completely account for all the underlying population differences between included trials. We acknowledge the limitations in the assumptions taken and consider this is the best estimation of relative treatment effects that can obtained with the currently available evidence base and for the target population of interest.

The NMA results have shown rimegepant to be an efficacious preventive treatment compared to placebo and not substantially different, in the proportion of patients achieving ≥50% MMD reduction or change from baseline in MMD, when compared to the relevant comparators.

The proportion of patients achieving >50% reduction in MMD was only [redacted] when comparing rimegepant versus galcanezumab in the base case, but not in the sensitivity analysis.

Acute and preventive treatment of migraine

The following sections report the relevant safety evidence for the treatment of acute migraine and preventive treatment of migraine, ongoing studies, innovation and interpretation of evidence

B.2.10. Adverse reactions

B.2.10.1. BHV3000-303, BHV3000-301, BHV3000-302 (acute): Safety profile of rimegepant in the Phase 3 acute treatment of migraine studies (ODT and tablet formulations)

A total of 3,553 patients received a single dose of rimegepant 75 mg (N=1,771) or placebo (N=1,782) across the Phase 3 acute treatment studies (BHV3000-303, BHV3000-301 and BHV3000-302).[190,197] Two bioequivalent formulations were evaluated in the Phase 3 studies, a ODT formulation in BHV3000-303[139,212] and a tablet formulation in BHV3000-301[138] and BHV3000-302[211] (Section B.2.2.1 [acute] and Section B.2.2.2 [prevention]). These studies were similar in design and demonstrated that rimegepant 75 mg was well tolerated and had a safety profile similar to that of placebo (Table 44).[190,222] Most AEs were mild or moderate in intensity, not related to study therapy, and resolved without treatment.[190,222]

B.2.10.2. BH3000-201 (acute): Long-term safety profile of rimegepant for the acute treatment of migraine (tablet formulation)

In addition to the Phase 3 acute treatment studies (BHV3000-303, BHV3000-301 and BHV3000-302), the BHV3000-201 study[140,222,227] provides long-term safety data for the acute treatment of migraine with rimegepant 75 mg dosed as PRN with ≤1 dose per day for up to 52 weeks.[140,227] Patients in Group 1 (2 to 8 migraines per month with PRN dosing, N=1,033) received rimegepant for a mean of [redacted] weeks (SD: [redacted]) and with a mean dose of [redacted] (SD: [redacted]) tablets per four weeks.[140,227] Patients in Group 2 (9 to 14 migraines per month with PRN dosing, N=481) received rimegepant for a mean of [redacted] weeks (SD: [redacted]) and with a mean dose of [redacted] (SD: [redacted]) tablets per four weeks. Patients in Group 3 (scheduled EOD and PRN N=286) received rimegepant for a mean of [redacted] weeks (SD: [redacted]) and with a mean dose of [redacted] (SD: [redacted]) tablets per four weeks.[140,227] Across all patients who received rimegepant in the BHV3000-201 study (N=1,800), 954 ([redacted]%) took rimegepant for ≥[redacted] weeks.[140,227]

The majority of AEs in the BHV3000-201 study were of mild or moderate severity and deemed unrelated to treatment per investigator assessment (Table 45).[140,222,227] No single AE related to rimegepant occurred in ≥2% of overall participants.[140,222,227] There were no clinically meaningful differences or trends in on-treatment AEs across enrolment

groups.[140,222,227] On-treatment AEs related to rimegepant over the up to one-year time period were reported in 20.0% of participants.[140,222,227] There was no clinically meaningful difference in the AEs related to rimegepant when assessed across enrolment groups.[140,222,227] Most AEs related to rimegepant were mild to moderate in intensity – No AEs of drug hypersensitivity related to rimegepant were reported.[140,222,227] SAEs were reported in 47 (2.6%) participants; none were considered by the investigator to be related to rimegepant – SAEs considered by the investigator to be possibly (1 SAE) or unlikely (9 SAEs) related to rimegepant were reported in 10 (0.6%) participants – All other SAEs were considered by the investigator to be unrelated to rimegepant.[140,222,227] Overall only 2.7% of patients had AEs leading to discontinuation of treatment.[140,222,227] No deaths were reported.[140,222,227]

Table 44. Safety profile of single-dose rimegepant 75 mg in the Phase 3 acute treatment of migraine studies: Study BHV3000-303, Study BHV3000-302, Study BHV3000-301, and pooled analysis of Study BHV3000-303, Study BHV3000-301, and Study BHV3000-302

	Pooled single-dose, Phase 3 studies		BHV3000-303		BHV3000-301		BHV3000-302	
	RIM (N=1,771)	Placebo (N=1,782)	RIM (N=682)	Placebo (N=693)	RIM (N=546)	Placebo (N=549)	RIM (N=543)	Placebo (N=543)
Study population			Treated participants		Treated participants		Treated participants	
On-treatment AEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	93 (17.1)	77 (14.2)
Reported in ≥1% in any group								
UTI	NR	NR	[redacted]	[redacted]	NR	NR	8 (1.5)	6 (1.1)
Nausea	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	10 (1.8)	6 (1.1)
Dizziness	NR	NR	[redacted]	[redacted]	4 (0.7)	2 (0.4)	NA	NA
On-treatment severe AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1 (0.2)	2 (0.4)
Reported in >1 participant								
Diarrhoea	NR	NR	[redacted]	[redacted]	NA	NA	[redacted]	[redacted]
On-treatment AEs related to study drug	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Reported in ≥1% of any group								
Nausea	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
On treatment serious AE			[redacted]	[redacted]			1 (0.2)	2 (0.4)
On treatment serious AE related to study drug			[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
On treatment AE leading to study drug discontinuation			[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Deaths			[redacted]	[redacted]	[redacted]	[redacted]	NR	NR

Abbreviations: AE, adverse event; NA, not applicable; NR, not reported; UTI, urinary tract infection
References: Study BHV3000-303: Croop 2019;[212] Study BHV3000-301: Data on File Clinical Study Report BHV3000-301[138] Study BHV3000-302: Lipton 2019;[211] Croop 2020b;[222] Data on File: Pooled analysis of BHV3000-301, BHV3000-302 and BHV3000-303 (final version), 2021;[190,197,198]

Table 45. Safety profile of long-term treatment with rimegepant 75 mg in Study BHV3000-201

Incidence, n (%)	Group 1: PRN 2-8[a] (N=1,033)	Group 2: PRN 9-14[a] (N=481)	Group 3: Scheduled EOD + PRN[a] (N=286)	Overall (N=1,800)
Any AE	[redacted]	[redacted]	[redacted]	[redacted]
Any severe AE	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related AE[b]	[redacted]	[redacted]	[redacted]	[redacted]

Incidence, n (%)	Group 1: PRN 2-8[a] (N=1,033)	Group 2: PRN 9-14[a] (N=481)	Group 3: Scheduled EOD + PRN[a] (N=286)	Overall (N=1,800)
SAE	[redacted]	[redacted]	[redacted]	[redacted]
SAE related to study drug[b]	[redacted]	[redacted]	[redacted]	[redacted]
AE leading to study drug discontinuation	24 (2.3)	16 (3.3)	8 (2.8)	48 (2.7)
Hepatic-related AE	[redacted]	[redacted]	[redacted]	[redacted]
Severe hepatic-related AE	[redacted]	[redacted]	[redacted]	[redacted]
Hepatic-related SAE	[redacted]	[redacted]	[redacted]	[redacted]
Hepatic-related AE leading to study drug discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
AEs associated with potential abuse	[redacted]	[redacted]	[redacted]	[redacted]
Cardiovascular AE	[redacted]	[redacted]	[redacted]	[redacted]
Suicidality AE	[redacted]	[redacted]	[redacted]	[redacted]
AEs reported in ≥2% overall				
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; EOD+ PRN, scheduled EOD+PRN, every other day dosing plus as needed on nonscheduled dosing days for up to 12-weeks; PRN, *pro re nata* (as needed) dosing; SAE, serious adverse event

Notes:

[a]Treatment groups were as follows: (1) PRN 2-8: historical rate of 2-8 moderate to severe migraine attacks per month with dosing as needed (PRN) up to a maximum of 1 tablet of rimegepant 75 mg per day; (2) PRN 9-14: historical rate of 9-14 migraine attacks per month with dosing as needed (PRN) up to a maximum of 1 tablet of rimegepant 75 mg per day; (3) Scheduled EOD dosing with as needed (PRN) dosing to treat a migraine attack of any severity on non-schedule days

[b]Events were considered related to treatment if the relationship was not reported or rated as unlikely related, possibly related or related per investigator assessment.

Refereces: Data on File Clinical Study Report BHV3000-201; [140] Croop 2020b [222]

B.2.10.3. BHV3000-305 (prevention): Safety profile of rimegepant (tablet formulation)

In Study BHV3000-305 study, the use of rimegepant 75 mg EOD for the prevention of migraine was well tolerated and demonstrated a safety profile similar to that of placebo (Table 46).[216] Most AEs were mild or moderate in intensity, not related to study therapy, and resolved without treatment (Table 46).[216]

Table 46: Summary of adverse events in the safety population (Study BHV3000-305): DB population (to Week 12)

Incidence, n (%)	Rimegepant (n=370)	Placebo (n=371)
Any AE	133 (36%)	133 (36%)
Mild AE	92 (25%)	91 (25%)
Moderate AE	64 (17%)	62 (17%)
Treatment-related AE	40 (11%)	32 (9%)
SAE	3 (1%)	4 (1%)
Treatment-related SAE	0	1 (<1%)
AE leading to discontinuation	7 (2%)	4 (1%)
AEs reported by ≥2% of patients treated with rimegepant, n (%)		
Nasopharyngitis	13 (4%)	9 (2%)
Nausea	10 (3%)	3 (1%)
Urinary tract infection	9 (2%)	8 (2%)
Upper respiratory tract infection	8 (2%)	10 (3%)

Abbreviations: AE, adverse event; DB, double blind; SAE, serious adverse event
References: Croop 2021[216]

Overall the median time on double-blind or open-label rimegepant was [redacted] weeks.[215] The median average rimegepant exposure was [redacted] tablets per month.[215] The median cumulative rimegepant exposure was [redacted] tablets. [redacted] participants ([redacted]%) received rimegepant for at least 12 months, and [redacted] participants ([redacted]%) received rimegepant for at least 15 months.[215]

The open-label treatment phase of Study BHV3000-305, in which patients received rimegepant for up to 64 weeks, provided evidence of the long-term safety of rimegepant 75 mg tablets.[215] During the double-blind or open-label periods, for the [redacted] DB or OLE rimegepant-treated participants ([redacted] of whom received rimegepant during the DBT phase, and [redacted] of whom received placebo during the DBT phase).[215]

During the double-blind and open-label periods of Study BHV3000-305, a total of [redacted] participants ([redacted]%) reported at least one AE.[215] AEs related to study treatment were

reported by [redacted] ([redacted]%) of participants. The most frequently reported AEs (AEs occurring in ≥1% of participants) were nausea ([redacted]%), constipation ([redacted]%), alanine aminotransferase increased ([redacted]%), aspartate aminotransferase increased ([redacted]%) and upper respiratory tract infection ([redacted]%).[215] [redacted] participants ([redacted]%) experienced [redacted] SAEs, [redacted]. Only [redacted] SAE, [redacted], occurred in [redacted].[215] AEs leading to discontinuation of treatment occurred in [redacted] patients ([redacted]%). AEs leading to discontinuation of study drug in more than one participant were [redacted] ([redacted]) and [redacted].[215] [redacted].[215]

[redacted].[215]

B.2.11. Ongoing studies

Biohaven Pharmaceuticals and Pfizer are committed to developing a comprehensive clinical evidence base on the efficacy and safety of rimegepant. The clinical development plan includes paediatric, international, and long-term safety studies. The following study is currently ongoing:

- BHV3000-402: Observational Study to Assess Maternal, Foetal and Infant Outcomes Following Exposure to Rimegepant (MONITOR) (NCT05046613)[263]
    - This long-term registry study includes women exposed to rimegepant during pregnancy or within three days of conception, as well as women with migraine who were not exposed to rimegepant
    - The study is expected to be completed in 2024.

One study conducted in China and Korea in the acute treatment of moderate or severe migraine in Asian population, identified in searches of clinical trial registries has recently completed and, as such, is described in Section B.2.2.1 with summary results provided in Appendix L (the study did not support the marketing authorisation application and results are therefore not reported in the main body of the submission.

B.2.12. Innovation

Rimegeant, a novel CGRP antagonist, is the first dual indication treatment approved for both acute and preventive treatment of episodic migraine

Rimegepant is the first and only migraine treatment with a dual indication, effective for both acute and preventive treatment of migraine.[6,13]

Rimegepant has been shown to confer reduction in migraine frequency during repeated acute use, with a lasting reduction in monthly migraine days observed in acute patients taking only PRN dosing.[237]

Rimegepant as the only CGRP antagonist available as ODT form

the ODT formulation, by avoiding the need for water, may improve tolerability for patients who experience nausea with migraines.[224-226]

In prevention treatment of migraine, rimegepant provides an orally administered alternative to anti-CGRP mAbs. more patients preferred rimegepant than injectable treatments.[180,264] As an efficacious oral alternative to injectable preventive options, this innovative feature of rimegepant provides multiple benefits, including: potential for prescribing within primary care, avoiding injection site reactions, a reduction in HCP administration and therefore hospital/clinic visits and healthcare resource utilisation; reduced strain on the NHS, which is still experiencing significant backlog from the COVID-19 pandemic.

Rimegepant's absence of effect on the cardiovascular system

The label does not have contraindicate rimegepant in patients with CV disease, for the first time, patients contra-indicated to triptans, and for whom simple analgesics (e.g. paracetamol and NSAID) have not succeeded, now have an effective treatment option.

No incidence of MOH reported

While certain analgesics and medicines such as triptans are associated with an increase in the risk of **medication overuse headache** (MOH). In our clinical trials, no incidence of MOH was reported. In addition, a recently-published real-world analysis demonstrates that treatment with rimegepant ODT is associated with clinically significant reduction in the burden of MOH.[265]

Rimegepant has demonstrated a favorable safety profile across clinical trials as both an acute and preventive treatment of migraine, with the rate of adverse events (AEs) being similar to placebo

Rimegepant offers clinically important benefits without the tolerability and safety issues associated with alternative acute and preventive treatments; e.g. patients do not have to endure troubling adverse effects such as seen with triptans (brain fog, chest tightness, etc.) in order to obtain benefit.[138,139,141,214,266]

Rimegepant's half-life allows for immediate cessation if needed

As a small molecule rather than monoclonal antibody, rimegepant has an 11-hour half-life, while the injectable mAbs have half-lives ranging from 27 to 30 days. This shorter half-life allows patients to stop treatment as needed without having to wait up to a month for the drug to be eliminated from their system.[6] Given that migraine affects many women of childbearing age, the opportunity to stop therapy quickly provides greater flexibility in planning and managing pregnancy.[256,267]

Potential to utilise rimegepant in a primary care setting by GPs and other allied health professionals

Rimegepant has the potential to avoid inappropriate referrals to secondary care and unnecessarily subjecting migraine patients to long waiting lists to accessing specialists and freeing up specialist capacity for more complex cases.

Societal benefit

Rimegepant has shown societal benefits with reduction in absenteeism and increased productivity at work from significant improvements in presenteeism translating into indirect cost savings for patients and healthcare systems.[187] Given that migraine is about three times more common among women than men,[92] insufficiently managed migraine can have a greater impact on women, particularly in the workplace. Rimegepant is a potential therapy that could help women remain productive through reduced pain/absenteeism/presentism. Moreover, migraine is likely to have a greater impact on hourly workers, who may have fewer opportunities to make up work hours missed due to migraine episodes, relative to salaried professional workers.[186] This issue also has a greater impact on women than men: women comprise the majority of the nearly one million UK workers on a zero-hour contract as of September 2021, with 3.6% of female and 2.5% of male workers on such contracts (564,000 women and 433,000 men).[188]

In addition, 2% of total NHS staff absences in one month were due to migraine or headache, accounting for 51,179 FTE days lost.[98]

B.2.13. Interpretation of clinical effectiveness and safety evidence

B.2.13.1. Acute migraine treatment

Data were available evaluating rimegepant for the **treatment of acute migraine** from three Phase 3 randomised placebo-controlled trials (Study BHV3000-303, Study BHV3000-301, and Study BHV3000-302), and a long-term open-label Phase 2/3 safety study (Study BHV3000-201).

Single attack studies BHV3000-301, -302 and -303 were similar in design, apart from the study drug formulation (Study BHV3000-303 with final ODT formulation, and Studies BHV3000-301/-302 with intermediate tablet formulation). Bioequivalence between the tablet and ODT formulation was established. Evidence was judged to be of good quality using critical appraisal checklists.

Results from pivotal Study BHV3000-303 demonstrate that a single dose of rimegepant 75 mg ODT provides a significant benefit on a number of clinically relevant endpoints, meeting both coprimary endpoints of freedom from pain and MBS at two hours post-dose, in addition to 19/21 hierarchically tested secondary endpoints.[139,212] Furthermore, evidence of significant durability via sustained pain relief, pain freedom, and freedom from functional disability from two to 48 hours post-dose, and early onset via pain relief and freedom from functional disability at 60 minutes post-dose, is further proof of rimegepant's broad spectrum of efficacy.[139,212] A single dose of rimegepant 75 mg ODT also prevented most treated participants in the study from necessitating rescue medication.[139,212] This convenient formulation alongside a strong efficacy profile can provide a novel treatment approach to participants in the acute treatment of migraine.

Study BHV3000-301 and Study BHV3000-302 have proven rimegepant 75 mg tablet to be efficacious, with significant gains for both freedom from pain and MBS at two hours post-dose,[138,211] as well as evidence of sustained benefit (pain relief and pain freedom from two to 24 hours).[138] Secondary endpoints were tested hierarchically, and significant results were achieved on freedom from photophobia, freedom from phonophobia, and pain relief at two hours postdose.[138,211]

Pooled patient data from the above-mentioned studies have shown that a single dose of rimegepant 75 mg was also effective for the acute treatment of migraine in subject with a

history of ≥2 triptan failure, the efficacy of rimegepant was consistent among patients with 1 or >2 triptan failures and those who were triptan naïve. These findings represent a new hope for patients who do not respond to, cannot tolerate, or have contraindications to triptans.

Data from the long-term safety study BHV3000-201, confirmed the safety profile of rimegepant for the acute treatment of migraine for up to 52 weeks. The large study population was representative of the potential patient population treated in the real-world. The population had great diversity with respect to racial, ethnic, sex, and age representation.

In addition, exploratory analyses of this long-term safety study showed that acute treatment with rimegepant 75 mg offers significant improvement in migraine-associated disability, transitioning participants from severe to moderate disability over time.[140,222,230] Observed changes exceeded the minimum clinically important difference (five disability days/three months) by more than two-fold at all time points. These benefits would favourably impact healthcare costs, workplace productivity, and subject well-being. Effective acute treatment with rimegepant 75 mg may be associated with clinically relevant improvements in HRQoL when dosed PRN up to once daily.[233,241,268] These benefits suggest that rimegepant-treated participants might achieve better overall function and reduced impediments to social and work- related activities.

Among patients with a high MMD at baseline, a post-hoc analysis found treatment with rimegepant 75 mg for the acute treatment of migraine was associated with a reductions in MMD frequency over time.[140,222,230] Long-term benefits were most visible with EOD/PRN dosing, which suggests that higher frequency dosing may be linked to greater reductions in attack frequency.[140,222,230] Acute treatment with rimegepant 75 mg offers significant ($p<0.0001$) improvements to absenteeism by 44% (~8 days), presenteeism by 43% (~7 days), and improves lost productivity time by 44% (~11 fewer days per month), reflecting improvements in workplace productivity.[269]

B.2.13.2. Preventive treatment of migraine

Data were available evaluating rimegepant EOD for the **preventive treatment of migraine** from one Phase 2/3 randomised placebo-controlled trial (Study BHV3000-305).[214,216] and a long-term open-label Phase 2/3 safety study (Study BHV3000-201).[140,222,230]

In Study BHV3000-305, participants with 4-18 migraine attacks per month, respectively at least six MD and not more than 18 headache days were eligible for inclusion. Hence, per IHS diagnostic criteria, the inclusion criteria may include both EM and CM patients. An active

control arm was not included. Large and highly variable placebo effects have been observed in past migraine prevention trials.

Throughout the 12-week DBT period, participants had to treat acute attacks (if any occurred) using their usual standard medication, i.e. as needed rimegepant was not allowed. During the subsequent one-year open-label extension (OLE) period rimegepant could be used in case an acute migraine attack occurred. However, a maximum daily dose of 75 mg rimegepant had to be observed, i.e. PRN (as needed) rimegepant could only be taken on days for which every-other-day (EOD) rimegepant for prevention was not scheduled.

Pivotal Study BHV3000-305 demonstrated that rimegepant 75 mg EOD is effective as a **preventive treatment for migraine**. Rimegepant 75 mg EOD demonstrated superiority to placebo on the primary endpoint; the therapeutic gain between treatment groups in MMD reduction was −0.8 days (−4.3 days for rimegepant and −3.5 days for placebo; p=0.0099).[216] Consistent with the primary analysis, rimegepant 75 mg also displayed statistically significant superiority over placebo on the reduction in migraine days per month over the entire 12-week DBT phase (−3.6 days for rimegepant and −2.7 days for placebo; p=0.0017).[216] Nearly half of rimegepant participants demonstrated a ≥50% reduction in the mean number of moderate or severe migraine days per month in the last month of the DBT phase, compared to 41.5% of placebo participants, which was statistically significant (p=0.0438).[216] These results confirm that rimegepant is the first CGRP antagonist to demonstrate benefits for both the acute and preventive treatment of migraine.

Supportive, exploratory efficacy data are obtained from open-label, long-term treatment (LTT) safety study BHV3000-201.

In the absence of a direct comparison of rimegepant with comparators in scope an indirect comparison was conducted. This analysis showed rimegepant to be an efficacious preventive treatment compared to placebo [redacted], in change from baseline in MMD or proportion of patients achieving >50% MMD reduction, when compared to the three mAbs currently reimbursed by NHS. About half the patients treated with rimegepant had at least 50% reduction in MMD which is within the range of 50% responders rate observed for monoclonal antibodies. The proportion of patients achieving >50% reduction in MMD [redacted] in the base case, but not in the sensitivity analysis.

B.2.13.3. Safety

The safety data from the clinical development program for the acute and preventive treatment of migraine, including three Phase 3 single-dose, placebo-controlled studies,[138,139,211,212] a Phase 2/3 multiple-dose, long-term, open-label study,[140] and a Phase 2/3 double-blind, randomised controlled study of rimegepant administered EOD for 12-weeks[222] demonstrate the favourable safety profile of rimegepant. The safety profile of rimegepant was comparable to placebo in the Phase 3 studies.[138,139,211,212] No new safety signals emerged during long-term administration up to 64 weeks in the OLE phase of the pivotal prevention study (BHV3000-305) or up to 52 weeks (PRN) or with scheduled higher frequency dosing (EOD + PRN) up to 12-weeks in the open-label, long-term safety study (BHV3000-201).[140,222] Across the clinical development program, SAEs were infrequent. All of the above safety findings were confirmed in participants who had a higher dosing frequency (e.g. ≥14 tablets per four weeks).[140,222] No pattern suggestive of a safety signal associated with longer duration or higher dosing frequency was observed. Rimegepant 75 mg EOD has a favourable benefit/risk profile. The totality of the safety demonstrated across the broad range of studies supports the use of rimegepant for the acute and preventive treatment of migraine. In addition, as an oral therapy, rimegepant is not associated with injection site reactions which couldn't be included in the NMA.

B.3. Cost effectiveness

Please note that given the appraisal of rimegepant in the acute migraine and episodic migraine prevention indications, this section provides the economic evidence as follows:

Template section	Acute treatment of migraine	Preventive treatment of episodic migraine
Published cost-effectiveness studies	Section B.3.1.A	Section B.3.1.P
Economic analysis	Section B.3.2.A	Section B.3.2.P
Clinical parameters and variables	Section B.3.3.A	Section B.3.3.P
Measurement and valuation of health effects	Section B.3.4.A	Section B.3.4.P
Cost and healthcare resource use identification, measurement and valuation	Section B.3.5.A	Section B.3.5.P
Summary of base-case analysis inputs and assumptions	Section B.3.6.A	Section B.3.6.P
Base case results	Section B.3.7.A	Section B.3.7.P
Sensitivity analyses	Section B.3.8.A	Section B.3.8.P
Subgroup analysis	Section B.3.9.A	Section B.3.9.P
Validation	Section B.3.10.A	Section B.3.10.P
Interpretation and conclusions of economic evidence	Section B.3.11.A	Section B.3.11.P

Acute treatment of migraine

The following sections report the relevant cost-effectiveness evidence for the acute treatment of migraine (heading prefixed with A:)

B.3.1. A: Published cost-effectiveness studies in the acute treatment of migraine

To inform the cost-effectiveness analysis of rimegepant in the acute treatment of migraine, SLRs were conducted on the published economic literature. These SLRs identified literature since database inception on cost-utility analysis, cost-effectiveness analysis, budget impact analysis, cost and resource use, and health state utility studies, for the acute migraine treatment paradigm. A total of 23 publications (18 unique studies) reported economic evidence. These included six unique studies reporting economic evaluations of acute

migraine therapies, nine unique studies on health state utilities, and nine unique studies on cost and resource use.

Full details on the cost-effectiveness studies included in the SLRs are presented in Appendix G: acute. Three of the cost-effectiveness analyses identified in the SLR studied rimegepant for the acute treatment of migraine in the US setting, when compared to other novel acute therapies lasmiditan and ubrogepant (note that these are not currently marketed in the UK; Table 46). These studies were deemed the most applicable to the current economic evaluation, although they were from a US healthcare perspective, as no evaluations were identified that modelled the cost-effectiveness of rimegepant from the UK perspective.

The Institute for Clinical and Economic Review (ICER; Atlas et al. 2020) assessed the cost effectiveness of lasmiditan, rimegepant, and ubrogepant among adults for the acute treatment of migraine (Table 47).[270] Two analyses were conducted: one for a triptan ineligible population and one for patients who did not respond adequately to non-prescription medicines (e.g., triptans were included as comparators).[270] The triptan refractory analysis is further summarised in Table 47, as this was the most relevant to the current decision problem and patient population of interest. The economic evaluation by Touchette et al. (2020) was published as a conference abstract, and therefore limited information on methodology was available.[271] However, this analysis appears to be largely based off of the model by Atlas et al. (2020) (Table 47).[270]

The final cost-effectiveness study of rimegepant by Johnston et al. 2021 evaluated the impact of re-dosing on cost-utility outcomes when rimegepant was compared to lasmiditan and ubrogepant in the US setting.[272] This analysis built off of the ICER model, but accounted for the fact that the rimegepant Phase 3 program only allowed for a single dose of study medication, while ubrogepant and lasmiditan trial programs both allowed for re-dosing, which occurred in 38% and 33% of trial participants respectively.[272] When this re-dosing was taken into account, the ICER per QALY vs BSC for ubrogepant and lasmiditan increased from $40,000 to $163,000 and from $151,800 to $271,500 respectively, while the ICER for rimegepant remained unchanged at $39,800 (Table 47).[272]

All three studies considered a time horizon of two years with cycle lengths of 48 hours, but none of these studies were analysed with the NHS perspective.

Table 47: Summary list of published cost-effectiveness studies of relevance to the acute economic model

Author year, Country	Population summary	Interventions	Perspective	Type of economic evaluation	Time horizon	Cycle length	Health states	ICER per QALY
Atlas et al. 2020, USA (ICER evidence report)	Individuals were from the USA aged ≥18 years experiencing migraines requiring acute treatment Base-case model cohort characteristics: • Mean age, years: 40.8 • Female: 86.0% • Migraine days per month at baseline: 4.8 **Triptan refractory analysis:** patients who had migraine attacks that did not respond to non-prescription medicines and for whom triptans had not been effective, were not tolerated, or were contraindicated	Lasmiditan 100-200 mg (no more than one dose in 24 hours) Rimegepant 75 mg, Ubrogepant 50-100 mg (may repeat after 2 hours) Sumatriptan 50-100 mg (may repeat after 2 hours; maximum dose 200 mg/24 hours), Eletriptan 40 mg (may repeat after 2 hours; maximum dose 80 mg/24 hours), and BSC. BSC was defined as no additional migraine-specific acute treatment and was estimated by the placebo arms of the clinical trials	USA Health sector perspective (direct medical costs only)	Cost-effectiveness analysis Semi-Markov model with time-varying proportions of patients with response to treatment	2-year	48-hours	4 main health states: On treatment with migraine (severe or moderate), on treatment without migraine, off treatment with migraine (severe or moderate) and off treatment without migraine.	In triptan refractory patients rimegepant, ubrogepant, and lasmiditan were compared to each other and to BSC (no additional migraine treatment) ICER per QALY vs BSC: • Rimegepant: $39,800 • Ubrogepant: $40,000 • Lasmiditan: $151,800

Author year, Country	Population summary	Interventions	Perspective	Type of economic evaluation	Time horizon	Cycle length	Health states	ICER per QALY
Johnston et al. 2021, USA	Patients needing acute treatment for migraine. Patients were triptan-refractory or triptan-intolerant	Lasmiditan, and ubrogepant (with and without re-dosing) vs placebo/BSC. Rimegepant vs BSC (rimegepant results are always without re-dosing as re-dosing was not allowed in the clinical trials)	USA; Health sector payer perspective	Cost-effectiveness analysis A semi-Markov decision analytic model was used	2-year	48-hours	NR	ICER per QALY vs placebo/BSC without re-dosing: • Rimegepant: $39,800 • Ubrogepant: $40,000 • Lasmiditan: $151,800 ICER per QALY placebo/BSC with re-dosing: • Rimegepant: $39,800 • Ubrogepant: $163,000 • Lasmiditan: $271,500
Touchette et al. 2020, USA	Patients with acute migraine Patients were further split into the subgroups: patients that could not take triptans and triptan naive patients	Lasmiditan, rimegepant, and ubrogepant compared to BSC (prevalent mix of treatment excluding triptans) and triptans (sumatriptan and eletriptan)	USA; Health care sector perspective	Cost-effectiveness analysis A semi-Markov model was used	2-year	48-hours	NR	ICER per QALY compared to BSC (in patients that cannot take triptans): • Lasmiditan: $327,700 • Rimegepant: $559,500 • Ubrogepant: $569,600

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years; USA, United Stats of America; vs, versus

B.3.2. A: Economic analysis for rimegepant in the acute treatment of migraine

In the acute treatment of migraine, there have been no previous NICE technology appraisals (TAs). Triptans, which were originally developed in the 1990s, and NSAIDs have dominated the acute treatment paradigm and there have been no new therapies approved in Europe or the UK in over 20 years. However, it has been estimated that 15% to 25% of patients currently using migraine-specific acute therapies may have inadequate symptom control and would benefit from access to novel treatments.[108] Rimegepant offers an opportunity for these patients, to achieve symptom relief, with improved productivity and enhanced quality of life.

B.3.2.1. A: Acute patient population

This economic evaluation considers adults with migraine who have had inadequate symptom relief after trials of at least two triptans or in whom triptans are contraindicated or not tolerated.

This population in the economic evaluation is consistent with the proposed place in therapy for rimegepant, and with the acute migraine population described in the decision problem (Section B.1.1).

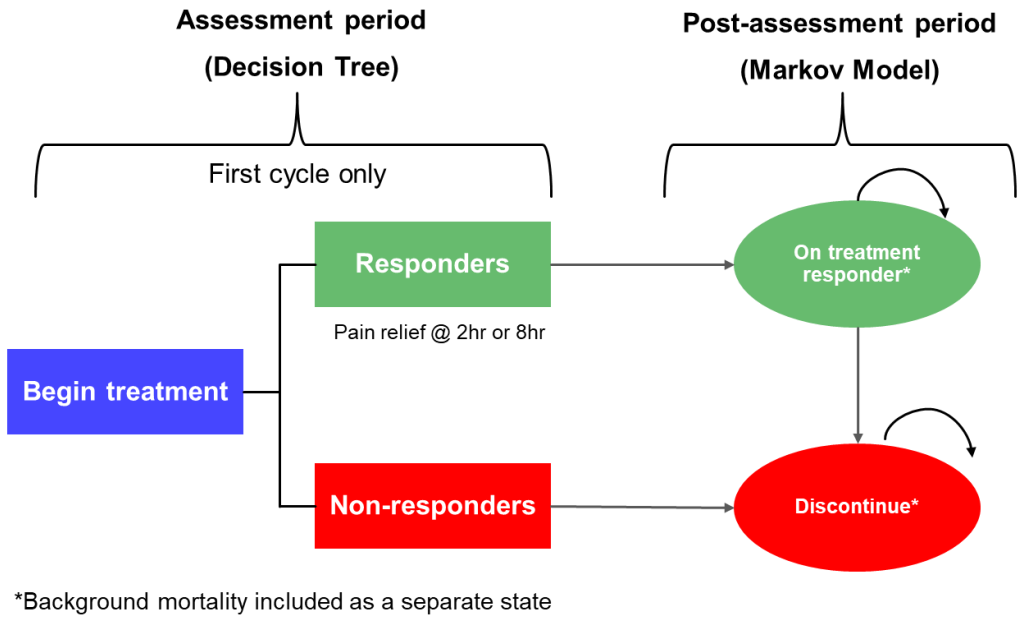
The pivotal acute trials for rimegepant (Study BHV3000-301, -302, and -303) enrolled a mixture of patients with and without prior experience with triptan therapies. Although a triptan non-responder analysis was pre-specified for each trial the patient subgroups were relatively small. Therefore, the pooled analysis of triptan failure patients across the acute phase 3 trials was used in the base case analysis to estimate the treatment effect of rimegepant amongst the intended treatment population; for those in whom triptans are ineffective, not tolerated or inappropriate (see subgroup analysis of pooled Phase 3 acute trials Section B.2.7.1.1.A).[198]

B.3.2.2. A: Acute model overview

A *de novo* Markov model was developed, to assess the cost-effectiveness of rimegepant compared to BSC (placebo), in the acute treatment of adults with migraine, from the perspective of the NHS and Personal Social Services. Given the substantial broader impact of migraine related pain on society and considering that migraine is most prevalent in a younger working-age population,[66,94,95] the wider societal implications, such as sickness absence, were considered in a scenario analysis.

An overview of the model structure is provided in Figure 14. This structure is consistent with the proposed clinical care pathway for rimegepant (Section B.1.3.3.1) and was informed by the recent economic evaluation of novel acute therapies in migraine conducted in the US by ICER, adapted as relevant to reflect a UK setting. [270,271] The US analysis included comparators not yet available in the UK (lasmiditan and ubrogepant).[270,271] In the present UK analysis, only a trial-based comparator of BSC, using the placebo arm of the trials as a proxy, is included, allowing for trial data to be used directly (i.e. full 48-hour pain severity trajectories are available for both rimegepant and BSC). The availability of full patient-level data facilitates a responder-based analysis, assuming that patients who don't achieve a threshold response would discontinue due to lack of efficacy, and these patients can be explicitly identified within the trial data and pain trajectories refined accordingly. Another key difference in the present analysis, compared to the US ICER model, is the incorporation of a potential reduction in MMD frequency of acute treatment with rimegepant (Section B.3.2.3.A), based on evidence from a long-term safety study which demonstrated that repeated acute treatment with rimegepant as needed, can have impact on frequency of migraine in addition to acute pain management.[181]

Figure 14: Overview of the model structure for acute treatment of migraine



Patients enter the model assessment period (decision tree) for which all patients experience their first migraine attack (i.e., in the first model cycle only); 100% of patients experience and treat one attack and patients receive either rimegepant or BSC, depending on treatment arm. The patients are then assessed for response based on pooled efficacy data from the rimegepant acute trials (assessment period; decision tree, Figure 14). Patients who respond,

experience the pain trajectories observed for responders in the relevant treatment arm in the BHV3000-301, BHV3000-302, and BHV3000-303 studies, while those who do not have a response to either rimegepant or BSC are assumed to discontinue their treatment, and subsequently experience pain trajectories of BSC non-responders. In other words, the first migraine event is used to determine whether patients remain on or discontinue treatment in the model.

Pain relief at two hours was selected as the base case definition of response. For acute treatment of migraine, the International Headache Society (IHS) recommends that the proportion of participants achieving pain freedom at two hours, before use of any rescue medications, should be the primary efficacy endpoint, with pain relief at two hours as a secondary endpoint.[99] Although pain relief at two hours is recommended as secondary endpoint in clinical trials, in a real-world practice, a treatment that can decrease pain intensity from moderate or severe to mild or no pain, (i.e. definition of pain relief), would be considered a success. It is unlikely that patients will discontinue their treatment if they achieve an improvement of their pain intensity. Additionally, pain relief is deemed to be both clinically relevant and of importance to patients, and was supported by expert feedback from two advisory boards (Section B.3.10.A).[1] Pain relief at eight hours as the definition of response was considered in a sensitivity analysis.

Modelled individuals then continue to the post-assessment period, where in subsequent model cycles the proportion of the cohort with and without migraine is calculated for each 48-hour model cycle, based on baseline MMD frequency distributions.

Responders are then assumed to continue to respond in following cycles, during subsequent attacks, with a proportion of rimegepant patients discontinuing treatment each cycle (informed by discontinuation patterns observed in long-term safety study BHV3000-201 (Section B.3.3.2.4.A). Patients who discontinue rimegepant will subsequently experience pain trajectories of BSC patients. For parity across treatment arms, the rimegepant discontinuers are also assumed to achieve the benefits of BSC responders for one year, before transitioning to the outcomes of a BSC non-responder (see Section B.3.3.2.4.A for further detail). For BSC patients, no discontinuation data was available, therefore, it was assumed that BSC responders would see the treatment effect dissipate after one year in line with previous NICE migraine appraisals (e.g., erenumab [TA682],[143] galcanezumab [TA659][142] fremanezumab [TA764][4]).

To incorporate the experience of pain trajectories per migraine event, patient-level data from Study BHV3000-301, -302, and -303 were utilised. Pain intensity level (none, mild,

moderate, severe) was characterised over the 48-hour migraine period (Section B.3.3.A), and an area-under-the curve (AUC) approach was used to apply health state utilities by pain category (Section B.3.4.A) and estimate the cumulative quality-adjusted time spent by treatment arm. Regression analyses were conducted to adjust the AUC values for patient covariates related to demographics and clinical disease characteristics of patients in the trials, with resultant quality-adjusted life hours (QALHs) out of a maximum 48 per migraine event, based on pain trajectories and regression analysis, shown in Figure 15.

Figure 15: Quality-adjusted life hours per migraine event by treatment arm and responder status (two hour pain relief)

Abbreviations: BSC, best supportive care; QALH, quality adjusted life hours

In addition, the model also includes the impact of acute (PRN) treatment with rimegepant on the reduction of future migraine episodes, as observed in the long-term safety study 201.[237] In this analysis, the rimegepant arm was associated with reduction in MMDs, leading to reduced cost of treatment and improved HRQoL.

Regression analyses for number of migraine events in the base case of the model were all fit to the acute patient population described in Section B.3.2.1.A, i.e., those who had failed two or more triptans previously, a subset of the overall study populations.

No excess mortality is thought to be associated with migraine, therefore patients in all model states have an equal risk of transitioning to death, which was based on UK life tables. This is consistent with prior NICE TAs in migraine.[4,142,143]

The model was developed in Microsoft Excel and programmed using standard Excel function wherever possible.

B.3.2.2.1. A: Time horizon

The time horizon of the model is 20 years. In addition to capturing the cost-utility implications of taking acute treatment per episode, an extended time horizon also captures treatment discontinuation over time, and potential costs and benefits of repeated acute treatment with rimegepant, which has shown MMD reduction even with acute (PRN) use.[272] Sensitivity analysis explored the impact of differing time horizons.

B.3.2.2.2. A: Cycle length

Cycle length is 48 hours to align with the typical trial length in studies of acute migraine therapies.

No half cycle correction is applied in the base case analysis. Given the short cycle length of 48 hours, the impact of a half-cycle correction is assumed to be negligible.

B.3.2.2.3. A: Model perspective

The model is conducted from the perspective of the UK NHS and Personal Social Services (PSS), in line with the NICE reference case.[273]

A sensitivity analysis was conducted from the societal perspective, in which costs associated with lost productivity were included. As outlined in Section B.1.3.2. migraine-related disability contributes to substantial economic and societal burden. As migraine prevalence is greatest among individuals aged 35-49 years, migraine-related disability has an enormous impact on what are typically the most productive years of life.[66,94,95] About 190,000 migraine attacks are estimated to occur daily in the UK, with 496,293 years lived with disability (YLDs) in 2016 alone.[92] Furthermore, triptan non-responders have been shown to have higher levels of migraine-related disability (measured using the MIDAS), further contributing to lost productivity and societal burden.[186]

B.3.2.2.4. A: Discount rate

An annual discount rate of 3.5% is applied to both costs and benefits, in line with the NICE reference case.[273]

B.3.2.3. A: Acute intervention technology and comparators

The current analysis investigates the cost-effectiveness of rimegepant 75 mg PRN compared with BSC. Rimegepant is positioned as an option for patients who have had inadequate symptom relief after trials of at least two triptans or in whom triptans are contraindicated or not tolerated; and have inadequate pain relief with NSAIDs and paracetamol (e.g., after exhaustion of current pharmacological options for the treatment of acute migraine). Based on its relevance to NHS clinical practice, this is a narrower population than what was included in the technology's marketing authorisation, which does not specify a triptan refractory population. The population modelled in the economic evaluation is aligned with the decision problem (Section B.1.1).

Consistent with the proposed clinical pathway for rimegepant in the acute treatment of migraine (Section B.1.3.3.1), BSC at the end of the treatment paradigm was informed by the placebo arms of the pooled analysis. The availability of relevant comparators in UK clinical practice is discussed in Section B.1.3.3.1.

An overview of model features and parameters is presented in Table 48.

Table 48: Features of the rimegepant migraine acute model

Factor	Current appraisal	
	Chosen values	**Justification**
Model structure	Decision tree plus Markov model	There have been no previous NICE TAs in the acute treatment of migraine, however this model structure was informed by analyses conducted for the US context (ICER; Atlas et al. 2020)[270]
Cycle length	48-hours	Typical duration of clinical trials evaluating acute migraine treatments and clinical duration of migraine events.[139]
Health effects model	QALYs	NICE reference case[273]
Discount rate	3.5% per year	NICE reference case[273]
Perspective	NHS and PSS (with broader societal perspective in scenario analysis)	NICE reference case[273] and broader governmental given that migraine is associated with decreased productivity and absenteeism[66,94,95]

Factor	Current appraisal	
	Chosen values	Justification
Half-cycle correction	No	Given a cycle length of 2 days, it is anticipated that a half-cycle correction would have negligible results.
Time horizon	Lifetime (20 years)	Lifetime horizon as per NICE reference case.[273] Capped at 20 years given that migraine frequency tends to decline with older age.[19]
Comparator	BSC	Please see Section B.1.1 Decision problem for further details on the relevant comparator.
Source of drug costs	BNF[274]	Best practice and aligned with previous NICE technology appraisals[4,142,143,273]
Source of health state utility at baseline and during non-migraine cycles	Patient-level MSQv2 data mapped to EQ-5D-3L utility scores from long term safety Study BHV3000-201	Best practice and aligned with previous NICE TAs.[4,142,143,273] The MSQv2 data has been mapped to EQ-5D-3L using the published algorithm of Gillard et al.[275] This approach has been used in the previous mAbs appraisal[4,142,143]
Source of event utility	Within-migraine utility values, by pain severity (none, mild, moderate, severe), applied to 48-hour pain trajectories from pooled acute trials taken from Stafford et al.[276] Stafford et al. utilities are adjusted (multiplicatively) to ensure that the pain-free utility is equivalent to the non-migraine MSQv2-mapped utility value, and the values for other categories are adjusted accordingly.	Stafford et al. was a cross-sectional observational study conducted in the UK and used the UK population scoring algorithm when calculating utility values.
Source of other costs	NHS reference costs	Best practice and aligned with previous NICE TAs[4,142,143,273]
Resource use	Vo et al.2018[277]	Most relevant data source identified in literature review, linking severity of migraine pain to likelihood of health resource use
Treatment strategy	Responder only (2-hour pain relief)	It was assumed and confirmed with clinical experts that patients would continue therapy only if a response was observed. Given response data availability of single-attack studies only, it was assumed that the first attack would be used to determine response status
Rimegepant discontinuation annual rate (amongst continuing responders)	[redacted]% per year	Informed by discontinuations due to adverse events, lack of efficacy, or withdrawal by subject from BHV3000-201 study.

Factor	Current appraisal	
	Chosen values	Justification
Waning of BSC (placebo) effect	It is assumed that BSC responders will transition to BSC non-responder trajectories after 12 months	The dissipation of the BSC (placebo) effect was included as it is the committees' preferred assumptions for fremanezumab,[143] where the treatment effect for people who responded to BSC (placebo) diminished to baseline over 1 year. Discussion with experts suggests it was the general understanding that placebo always wanes over time. While it was difficult to come to consensus as views were varied and complex. The pragmatic view is that 12 months is a long time for placebo effect in acute but a wide range of time period ranging from 6 months to 12 months was also suggested.
Pain trajectories of non-responders	For both rimegepant and BSC non-responders, the pain trajectories and resultant quality-adjusted life hours of placebo non-responders were applied per migraine	Although the rimegepant non-responders were observed to have more favourable pain trajectories than non-responders from the placebo arm, it is assumed that over time their utilities would be the same in the absence of active treatment
Impact of frequent use of acute treatment on MMD	Regression analysis from the long-term safety study was assumed to be applicable, where frequent use of rimegepant in the acute treatment (MMD greater than approximately 8) is associated with fewer MMD over time	Repeated acute use of rimegepant has been observed to have a preventive impact;[237] clinical data applied within the model
Calculation of quality-adjusted-life-hour trajectories	Regression-based approach, with covariates for treatment arm, responder status, MMD, and proportion with moderate (vs. severe) pain at baseline	Trial-based evidence for pain trajectories; regression approach and variable selection process described in Section B.3.4.A.
Baseline utilities transformation	Multiplicative	Assumption
Include productivity loss	No, scenario only	NICE reference case[273]

B.3.3. A: Clinical parameters and variables <u>acute</u> treatment of migraine

The primary data source for modelling the rimegepant arm in the economic model are the pooled analysis of BHV3000-301, BHV3000-302, and BHV3000-303 acute migraine trials, hereafter referred to as the pooled acute trials (Table 49).[211,213,216]

Table 49: Summary of key parameters and sources

Parameter	Source
Baseline patient characteristics	Rimegepant and BSC – pooled acute trials, 2+ triptan failure group in the base case
Responder rates	Rimegepant and BSC – pooled acute trials, 2+ triptan failure group in the base case
Likelihood of experiencing migraine	Rimegepant and BSC – baseline MMD frequency distribution from long-term safety study BHV3000-201, 2+ triptan failure group
Long-term treatment effects and discontinuation	Rimegepant – long-term safety study BHV3000-201; BSC – assumption
Reduction in MMD frequency of acute treatment	Rimegepant – long-term safety study BHV3000-201

B.3.3.1. A: Baseline patient characteristics

The baseline patient characteristics used in the model are from the pooled acute trials for rimegepant, by triptan failure status (Table 50).[216] The age and sex distribution is used to calculate background mortality based on UK life tables. The long-term safety study BHV3000-201 was assumed in the base case of the model, for a real-world estimate of MMD distribution, noting that the BHV3000-301, -302, and -303 trials restricted inclusion to two to eight migraine attacks per month and thus don't provide a natural distribution of the full range of MMD potentially observed in the UK population for the acute treatment of migraine. [212]

Table 50: Baseline patient characteristics, pooled across acute trials of rimegepant and stratified by triptan failure status

	Study BHV3000-201	Pooled acute trials		
	≥2 triptan failures	mITT	1 triptan failure	≥2 triptan failures
Age (years)	[redacted]	[redacted]	[redacted]	[redacted]
Sex (% female)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline attacks per month (mean)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: mITT, modified intention-to-treat
References: Study BHV3000-303/302/303[211-213] Study BHV3000-201: Data on File Clinical Study Report BHV3000-201;[140] Croop 2020b [222]

To further examine the relationship between repeated PRN use and migraine prevention, and particularly for preventive impact across a range of MMD levels, the base case cost-effectiveness results incorporate both acute treatment and added benefit of the acute treatment to confer reduction in MMD frequency, for the patient distribution as enrolled in BHV3000-201. The distribution of MMD from long-term safety study BHV3000-201 are presented in Table 51.

Model results (including one-way sensitivity analysis [OWSA] and probabilistic sensitivity analysis [PSA]) are generated for each MMD value, and a weighted average is taken according to selected MMD distribution. In the OWSA and the PSA, the weighted MMD distribution for the BHV3000-201 study population (with ≥2 triptan failures) is run for each iteration, such that the results represent this weighted distribution with corresponding potential for migraine reduction from higher-frequency acute use.

Table 51: Baseline MMD distribution from Study BHV3000-201 stratified by triptan failure status

Baseline MMD	Two or more triptan failures		mITT	
	N	%	N	%
1	[redacted]	[redacted]%	[redacted]	[redacted]%
2	[redacted]	[redacted]%	[redacted]	[redacted]%
3	[redacted]	[redacted]%	[redacted]	[redacted]%
4	[redacted]	[redacted]%	[redacted]	[redacted]%
5	[redacted]	[redacted]%	[redacted]	[redacted]%
6	[redacted]	[redacted]%	[redacted]	[redacted]%
7	[redacted]	[redacted]%	[redacted]	[redacted]%
8	[redacted]	[redacted]%	[redacted]	[redacted]%
9	[redacted]	[redacted]%	[redacted]	[redacted]%
10	[redacted]	[redacted]%	[redacted]	[redacted]%
11	[redacted]	[redacted]%	[redacted]	[redacted]%
12	[redacted]	[redacted]%	[redacted]	[redacted]%
13	[redacted]	[redacted]%	[redacted]	[redacted]%
14	[redacted]	[redacted]%	[redacted]	[redacted]%
15	[redacted]	[redacted]%	[redacted]	[redacted]%
16	[redacted]	[redacted]%	[redacted]	[redacted]%
17	[redacted]	[redacted]%	[redacted]	[redacted]%
18	[redacted]	[redacted]%	[redacted]	[redacted]%
19	[redacted]	[redacted]%	[redacted]	[redacted]%
20	[redacted]	[redacted]%	[redacted]	[redacted]%
21	[redacted]	[redacted]%	[redacted]	[redacted]%
22	[redacted]	[redacted]%	[redacted]	[redacted]%
23	[redacted]	[redacted]%	[redacted]	[redacted]%
24	[redacted]	[redacted]%	[redacted]	[redacted]%
25	[redacted]	[redacted]%	[redacted]	[redacted]%
26	[redacted]	[redacted]%	[redacted]	[redacted]%
27	[redacted]	[redacted]%	[redacted]	[redacted]%

Baseline MMD	Two or more triptan failures		mITT	
	N	%	N	%
28	[redacted]	[redacted]%	[redacted]	[redacted]%

Abbreviations: mITT, modified intention-to-treat; MMD, monthly migraine days

B.3.3.2. A: Treatment efficacy

B.3.3.2.1. A: Response definitions

In the base case, pain relief at two-hours was used in the model to define treatment response.

Pain relief at two-hours is deemed to be both clinically relevant and of importance to patients, was supported by expert feedback from two advisory boards (see Section B.3.10.A),[99] and is consistent with how rimegepant will be used in clinical practice. Clinical experts suggested that patients would reasonably expect a therapy to have some pain relief outcome within two hours to be considered effective, and that this can be considered a proxy for binary treatment effect; by eight hours and longer, a greater proportion of patients have experienced pain relief, and treatment effects cannot be fully disentangled from spontaneous improvement that some patients may experience by an eight hour time point (which is less relevant at two hours).

In the UK, there are no clinical stopping rules for patients who have failed ≥2 triptans, or who are intolerant or contraindicated.[107] Clinical guidelines for triptans recommend multiple trials of the same triptan or switching to an alternate triptan before stopping treatment. For example, the European Headache Foundation practice guidelines recommend that three attacks be treated at each step prior to proceeding to the next step to achieve cost-effective care.[82] Based on these existing guidelines for symptomatic and specific migraine therapies, it would be anticipated that in clinical practice, patients would have access to more than one pill after being prescribed rimegepant and would likely repeat attempts to obtain pain relief on subsequent migraines before stopping treatment. However, the single attack study design of the rimegepant acute trials (Study BHV3000-301, -302, and -303) meant that there are no clinical data indicating how many patients would respond after taking rimegepant to treat a second or third migraine, who did not respond during their first episode.

The economic model therefore assumes that patients who do not respond to the first treatment (based on pain relief at two hours) would not respond to a subsequent treatment. As a result, expenditure on rimegepant is estimated to provide greater value overall, as the

cost of treatment is only being incurred in patients with a demonstrable response to an initial event, rather than being repeatedly used in patients who may not respond.

As described further in Section B.3.3.2.4.A, treatment continuation and discontinuation for rimegepant are assumed to be influenced by two factors: initial discontinuation amongst rimegepant non-responders (based on pain relief at two hours) who discontinue treatment immediately, and initial responders who discontinue periodically over the time horizon, based on discontinuation curves observed in the long-term safety study BHV3000-201.

To approximate a scenario where physicians recommend patients trial all doses of rimegepant first dispensed to determine response status (thereby increasing observed response rates in the model), the higher eight hour pain relief response rate was used in a sensitivity analysis. In all scenarios the model accounts for potential wastage of rimegepant, where whole packs are dispensed to patients identified as non-responders.

Responder rates in the pooled acute trials, for two and eight hour definitions are reported in Table 52**.**

Table 52: Responder % by definition (pain relief at 2 vs. 8 hours) and population for pooled acute trials

	Rimegepant	BSC
mITT population	N=[redacted]	N=[redacted]
Responders (2-hour definition)	[redacted]	[redacted]
Responders (8-hour definition)	[redacted]	[redacted]
Exactly one triptan failure	N=[redacted]	N=[redacted]
Responders (2-hour definition)	[redacted]	[redacted]
Responders (8-hour definition)	[redacted]	[redacted]
Two or more triptan failures	N=[redacted]	N=[redacted]
Responders (2-hour definition)	[redacted]	[redacted]
Responders (8-hour definition)	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; mITT, modified intention-to-treat; vs, versus

B.3.3.2.2. A: Probability of experiencing migraine

From the second model cycle onwards, the average probability of experiencing migraine during a 48-hour migraine cycle was calculated based on baseline MMD (e.g., patients with 9.2 MMD at baseline would have a 0.605 probability of experiencing a migraine during each 48-hour cycle, 9.2 MMD ÷ (365 days/12 months) x 2.

B.3.3.2.3. A: Modelling pain hours

As described in Section B.3.3.2.A, the efficacy of rimegepant is primarily characterised by improved pain trajectories per migraine event within treatment responders, resulting in higher utility values on average across a 48-hour migraine cycle, and subsequently additional QALHs. A flow diagram outlining the methods used to calculate QALHs from pain trajectories in the pooled rimegepant acute trials is presented in Appendix O, Section O1.

To evaluate the pain severity trajectories and corresponding QALY regression analyses over 48-hours, patient-level data from the pooled acute trials were analysed, for the base case population with ≥2 triptan failures. The percentage of participants in each pain state at each time point and the average time spent in each state across treatment arms over 48-hours were calculated (see Appendix O, Section O1).

Among [redacted] total participants ([redacted] rimegepant, [redacted] placebo), distributions of pain severity were similar at time 0 across treatment arms (rimegepant: [redacted]% moderate, [redacted]% severe; placebo: [redacted]% moderate, [redacted]% severe). At two-hours only [redacted]% of participants in the rimegepant arm had severe pain ([redacted]% moderate), while [redacted]% of participants in the placebo arm had severe pain ([redacted]% moderate), see Appendix O (Section O1, Figure 11).

By 24- and 48-hours, these values drastically decreased in both arms, although more so in the rimegepant arm. For rimegepant, severe pain was seen in [redacted]% of participants at 24-hours ([redacted]% moderate) and [redacted]% at 48-hours ([redacted]% moderate). For placebo, severe pain was seen in [redacted]% of participants at 24-hours ([redacted]% moderate) and [redacted]% at 48-hours ([redacted]% moderate). Averaging across all participants, the mean [standard deviation] time spent with no pain over 48-hours was higher for rimegepant ([redacted] hours [[redacted] hours]) than it was for placebo ([redacted] [[redacted]]). Likewise, rimegepant participants spent less time in severe pain over 48-hours ([redacted] [[redacted]]) compared to placebo participants ([redacted] [[redacted]]).

Pain hour distributions by responder status are reported in Table 53. Responders were found to spend more time in the no/mild pain categories than non-responders. The mapping of these pain distributions to model inputs of HRQoL is described further in Section B.3.4.A.

Table 53: Pain hours per migraine event for the population with two or more triptan failures in pooled acute trials

	Responders (2-hour)		Non-Responders (2-hour)	
Rimegepant	**N=[redacted]**		**N=[redacted]**	
	Mean	**SE**	**Mean**	**SE**
No pain	[redacted]	[redacted]	[redacted]	[redacted]

Mild pain	[redacted]	[redacted]	[redacted]	[redacted]
Moderate pain	[redacted]	[redacted]	[redacted]	[redacted]
Severe pain	[redacted]	[redacted]	[redacted]	[redacted]
BSC	**N=[redacted]**		**N=[redacted]**	
	Mean	**SE**	**Mean**	**SE**
No pain	[redacted]	[redacted]	[redacted]	[redacted]
Mild pain	[redacted]	[redacted]	[redacted]	[redacted]
Moderate pain	[redacted]	[redacted]	[redacted]	[redacted]
Severe pain	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; SE, standard error

The pain hours described above were combined with utilities from Stafford et al.,[276] (Section B.3.4.5.A) to calculate QALH per event prior to regressing on covariates. A regression analysis was then fitted to describe QALH outcomes (Section B.3.4.5.A), adjusted for treatment arm, two-hour response status, baseline MMD, and baseline migraine severity (% of patients reporting moderate vs severe migraine; Section B.3.3.2.1.A). These QALH regression results are described further in Section B.3.4.5.A and Appendix O.

B.3.3.2.4. A: Long term treatment effects and discontinuation

It was assumed that the acute efficacy observed for the initial migraine attack would continue to be relevant in subsequent attacks. While there is no direct evidence examining specific efficacy outcomes across multiple attacks in the acute setting, as described below there was relatively low discontinuation observed among patients receiving long-term acute treatment in Study BHV3000-201, implying that patients continued to derive acute treatment benefit over time. Treatment discontinuation was incorporated into the model in two ways:

1. For patients who do not respond to rimegpant treatment, it is assumed that they will only treat the first event with rimegepant, and from this point forwards they will follow an untreated trajectory (BSC non-responders). However, they are assumed to incur the cost of one full (eight-tablet) package of rimegepant prior to discontinuing. It is assumed that this non-response to rimegepant is informative, such that they immediately transition to the efficacy trajectory of BSC non-responders. In contrast, patients who initially respond but then discontinue as per the observed treatment discontinuation curve (Figure 16) are assumed to follow the trajectory of BSC responders for 12 months, and then transition to BSC non-responder trajectories after this point. As noted below, this is equivalent to the assumed trajectories for BSC patients, who are assumed to maintain the BSC response status for the first 12

months of the time horizon. Due to the fact that rimegepant patients discontinue at different time points over the time horizon and the memoryless property of a Markov model, this adjustment is achieved by a one-off application of the associated QALYs at the time of discontinuation, adjusted for mortality and any relevant time horizon cap over the subsequent 12 months.

2. Long term discontinuation in the post assessment period was informed by the subset of patients from the pooled acute studies (responders with ≥2 triptan failures from Studies BHV3000-301,302,303) who continued into the long-term safety study (BHV3000-201) and received rimegepant 75 mg PRN for 52-weeks (Figure 16). A discontinuation rate of [redacted]% over one-year was applied based on observed discontinuations due to adverse events, lack of efficacy, or withdrawal by participant (discontinuations due to loss-to-follow-up, pregnancy, protocol deviation, or screen failure were considered to be non-relevant and treated as censored; Figure 16).

Figure 16: Kaplan Meier curve for patients discontinuing rimegepant treatment due to adverse event, lack of efficacy, failed two or more triptans, or withdrawal by subject

Regarding the BSC arm, it is assumed that BSC patients would lose response status after one year and experience the pain-trajectories of BSC non-responders from this point forwards. The dissipation of the BSC effect was included as it is the committees' preferred assumptions for fremanezumab for migraine prevention in TA631/TA764, where the treatment effect for people who responded to BSC diminished to baseline over one year.[4] However, there are no data available to inform the duration of the placebo effect in the acute treatment. Discussion with experts suggests it was a general understanding that BSC (placebo) always wanes over time. It was difficult to come to consensus as views were varied and complex, the pragmatic view is that 12 months is a long time for BSC in acute, but a wide range of time period ranging from six to 12 months, and the more conservative 12-month period was assumed (Section B.3.10.2.A).

B.3.3.2.5. A: Reduction in MMD frequency of acute treatment

As observed in the long-term safety study (BHV3000-201), there is evidence of migraine reduction with PRN rimegepant (Section B.2.6.3.4.A).[181,237] As such, this is included in the model, in which the rimegepant arm is associated with a decrease in MMDs in addition to acute pain relief. This assumption was supported by a panel of clinical experts (Section B.3.10.2.A). The reduction in MMD associated with PRN treatment of rimegepant is hypothesised to be due the extended CGRP inhibition effect of rimegepant; this reduction was not added to BSC in the model.

In order to predict MMD reductions for given cohort characteristics, a regression analysis for change from baseline in MMD was conducted using patient-level data from the long-term safety Study BHV3000-201, PRN dosing groups (Table 54;Section B.2.6.3.4.A). The following were taken into consideration when selecting regression covariates:

1. Clinical significance of a covariate.
2. Statistical significance of a covariate in both univariate and multivariate regression analyses.
3. Alignment with the population of interest (≥2 triptan failures).
4. Alignment with adjustments made in the primary outcome of Study BHV3000-305 ("*Analysed using a generalised linear mixed-effects model with treatment group, preventive migraine medication use at randomisation, study month, and month-by-treatment group interaction as fixed effects and participant as random effect.*").[216]

Decisions on the inclusion/exclusion of specific covariates were as follows:

- Considerations **1.** and **4.** led to the inclusion of the **prophylactic migraine covariate**, even though this covariate with not statistically significant in regression analyses.
- Considerations **2.** and **3.** led to the justification of including the **triptan lines covariate**.
- Since the BHV3000-201 trial treated participants with rimegepant PRN, we sought to explore the relationship between actual pills taken and MMD (Consideration **2.**). This led to the justification of including the **pills/migraine covariate**.
- Baseline MMD were included under Considerations **1.** and **2.**
- A random effects was also included to account for repeated measures in participants.
- Other covariates that were considered but did not meet any of the considerations for inclusion were: linear time, non-linear time, presence of the subject in a previous rimegepant single-event acute trial (BHV3000-301, BHV3000-302, or BHV3000-303), age, and sex.
    - After an initial drop in MMD, CFB in MMD were relatively stable throughout the 52-week period. This led to the justification on not including a time covariate in the final model, but still accounting for repeated measurements.

The final chosen regression covariates were defined as follows:

- BL_MMD: Baseline monthly migraine days.
- trip_lines [0 (reference), 1, 2+]: Number of prior refractory triptan lines of therapy.
- pills_per_migraine: The total number of rimegepant pills taken per migraine within each given 4-week time interval.
- Proph_mig_meds [Yes, No (reference)]: Whether the patient used prophylactic migraine medication throughout the trial period while on rimegepant.

Results from the regression indicate that higher frequencies of MMD (and so rimegepant administration) are associated with greater MMD reduction. Applying base case patient characteristics this reduction in MMD applies at a frequency of greater than eight. At MMD below this level the frequency in rimegepant and BSC patients is equal.

Table 54: Regression analysis for the change from baseline in MMD associated with acute PRN rimegepant treatment over time

Term	Estimate	Standard error	Lower bound of 95% CI	Upper bound of 95% CI	p-value
(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BL_MMD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
trip_lines1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
trip_lines2+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
pills_per_migraine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proph_mig_medsYes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BL, baseline; CI, confidence interval; MMD, monthly migraine days; trip_lines [0 (reference), 1, 2+]: Number of prior refractory triptan lines of therapy proph_mig_meds, prophylactic migraine medications;

B.3.3.3. A: Mortality

Only all-cause mortality is considered in the model, which aligns with prior NICE TAs in migraine prevention,[4,142,143] and is supported by a published meta-analysis, which found no association between migraine and all-cause mortality.[278] Age- and sex-specific UK life tables for the years 2018-2020 were applied.[279]

B.3.4. A: Measurement and valuation of health effects <u>acute</u> treatment of migraine

B.3.4.1. A: Health-related quality-of-life data from clinical trials

Given the short duration of single-attack trials for acute treatment of migraine, HRQoL measures are not typically collected. As these data were not available from the pooled acute trials to assess the impact of pain trajectories on health state utilities, estimates of utility values by pain severity were taken from the published literature, sourced in the SLR (Appendix H: acute), to describe HRQoL associated with migraine pain severity levels (described below and in Table 57), and applied to the pain distributions described in Section B.3.4.5.A.

Although these acute pain utilities were not available from within the trials, Study BHV3000-201 did include MSQv2 responses which were mapped to EQ-5D utilities.[275] These mapped utilities inform the baseline values and the values for patients who do not experience migraine in each 48-hour cycle, based on MMDs. When the option to incorporate MMD reduction benefits of acute treatment with rimegepant is incorporated, this leads to improved

HRQoL for rimegepant patients due to fewer migraine events and improved utility during non-migraine model cycles.

B.3.4.2. A: Mapping

To generate baseline utility values, pooled patients from the 2-8 PRN and 9-14 PRN arms of Study BHV3000-201 were used to map MSQv2 data at baseline and throughout the trial to EQ-5D using a validated algorithm.[275] As the trial population consisted fully of participants with a history of episodic migraine, the episodic migraine regression coefficients from Gillard et al were used. [275] Regression models of EQ-5D using similar covariate considerations as the MMD CFB regression were explored. In this case, preference was given to a simple model, where it was preferable to not have baseline EQ-5D and baseline MMD as model covariates because the cost-utility model was designed to explore populations with varying baseline MMD levels, which would in turn impact expected baseline EQ-5D, resulting in a circular model structure.

Models were considered using baseline only data (using baseline MMD), post-baseline only data (using either absolute MMD or CFB in MMD as a covariate), and baseline + post-baseline data (using absolute MMD as a covariate). Each of the post-baseline only and baseline + post-baseline models were fit with and without a covariate for time. Where applicable, a random effect was included to account for repeated measures in participants. The post-baseline only and baseline + post-baseline models all performed similarly well, so a version that was best suited for incorporating into the CUA was selected. This model was a baseline + post-baseline model that incorporated the following covariates: age, sex, triptan lines, and absolute MMD (Table 55).

The resulting utilities are relevant to interictal burden and are applied at baseline and during model cycles for which a migraine event does not occur. A coefficient of -0.0054 was estimated per MMD; i.e. each MMD averted is associated with an increment of 0.0054 to utility.

Table 55: EQ-5D regression coefficients and standard errors, acute model

Term	Coefficient	Standard error
(Intercept)	[redacted]	[redacted]
age	[redacted]	[redacted]
Sex = Male	[redacted]	[redacted]
trip_lines1	[redacted]	[redacted]
trip_lines2+	[redacted]	[redacted]

Term	Coefficient	Standard error
MMD	[redacted]	[redacted]

Abbreviations: MMD, monthly migraine days; trip_lines [0 (reference), 1, 2+]: Number of prior refractory triptan lines of therapy

B.3.4.3. A: Acute health-related quality-of-life studies

An SLR to identify HRQoL studies was performed as part of the SLR described in Section B.3.1.A using the inclusion and exclusion criteria and search strategy defined in Appendix H: acute.

A total of nine unique studies were identified that met eligibility criteria for the review and are described in detail in Appendix H: acute. The three most relevant publications for the current decision problem are summarised in Table 56.

Table 56: Summary of utility studies identified in the SLR relevant to the acute economic model

Author year, Country	Study design	Population and sample size	Health states and adverse events	Methods of elicitation and valuation	Utility values and uncertainty, Mean (SD) or (95% CI)
Johnston et al. 2021, USA[280]	Utility mapping study (MSQv2 to EQ-5D) for patients receiving rimegepant	Patients were part of Study BHV3000-201, a long-term, open-label safety study of rimegepant 75 mg. Patients with 2–8 MMD (n=1,033) and 9–14 MMD (n=286) at baseline were given PRN regimen and patients with 4–14 MMD were given EOD + PRN (n=481)	MSQv2 was assessed at baseline and Week 12 for the EOD + PRN group, and at baseline and at weeks 12, 24, 36, and 52 for the two PRN groups. The MSQv2 measures the effect of migraine on three HRQoL dimensions: role function restrictive, role function preventive and emotional function.[281]	MSQv2 was mapped to EQ-5D-3L utilities using a validated algorithm developed by Gillard et al. 2012, which uses a UK valuation set[275]	Mapped EQ-5D-3L utility scores were as follows: **2-8 MMD PRN** Baseline: 0.66 (0.12) CFB (52-weeks): 0.09 (0.08, 0.10) **9-14 MMD PRN** Baseline: 0.63 (0.12) CFB (52 weeks): 0.10 (0.09, 0.11) **4-14 MMD EOD** Baseline: 0.65 (0.11) CFB (12-weeks): 0.12 (0.11, 0.14)
Stafford et al., 2012, UK[276]	Cross-sectional, observational study	Patients who had recently experience a migraine were included, of which 52.9% were prescribed medication to treat migraine (n=106)	The health states considered included patient's current health outside of a migraine attack and different levels of migraine pain severity (mild, moderate and severe) during their most recent migraine attack within 7 days of assessment.	Patients completed the EQ-5D (version 3L); utility values were calculated using the York preference tariff	See Table 57
Xu et al. 2011, USA[282]	Multicentre, double-blind, placebo- and active-controlled, parallel-group-randomised clinical trial to evaluate the safety, tolerability, and efficacy of MK-0974 (Telcagepant)	330 patients treated a migraine attack during the time period and are included in this analysis. The focus of this utility analysis was on headache severity and is not treatment specific, so data were pooled across treatment groups.	Utility health states were migraine patients with mild, moderate and severe pain, as measured during the on-trial migraine attack. Only patients who were pain free at 24 hours were included in the calculations for disutility for moderate and severe pain.	Self-administered EQ-5D questionnaire data were collected at baseline (while with moderate/severe migraine headache prior to dosing) and 24 hours post-treatment within the acute migraine attack if the patients were pain free.	See Table 57

Author year, Country	Study design	Population and sample size	Health states and adverse events	Methods of elicitation and valuation	Utility values and uncertainty, Mean (SD) or (95% CI)
	in the treatment of acute migraine	Patients were only allowed to take the study drug when they had a migraine with moderate or severe pain.	The disutility for mild pain was calculated indirectly by using the patients with moderate /severe pain at baseline and mild pain at 24 hours. The disutility from these patients were then subtracted from the disutility from the moderate/severe to no pain group.	The D1 time-trade-off scoring algorithm for the US population was applied (Shaw 2005).[283]	

Abbreviations: CFB, change from baseline; EOD, every other day; EQ-5D (3L), EuroQol five dimension (three level); HRQoL, health-related quality of life; MMD, monthly migraine days; MSQv2, Migraine-Specific Quality-of-Life Questionnaire version 2; PRN, *pro re nata* (as needed); SLR, systematic literature review; UK, United Kingdom; US, United States

For baseline utility values and cycles where patients do not experience a migraine, the same utility mapping methodology was used as in Johnston et al. 2021,[280] however, the pooled PRN subgroups from BHV3000-201, were adjusted for age, sex, triptan lines, and absolute MMD (Table 56).

For migraine-event utilities, data from the studies by Stafford et al. and Xu et al. were deemed to be most relevant to this submission, and are described in more detail below.[276,282] These studies, which examined within-attack and post-attack health utility values for migraine patients, were selected as both measured EQ-5D health state utilities by migraine pain severity (Table 56).[276,282] Pain severity is thought to be the primary driver of within-attack HRQoL, and allowed us to apply utility values to the pain severity trajectories (described further in Section B.3.4.5.A).

Table 57: Health state utility values by migraine pain severity

	Stafford et al. 2012[276] (EQ-5D)		Xu et al. 2011[282] (EQ-5D)	
	Mean	**SE**	**Mean**	**SE**
Severe pain	-0.20	0.1372	0.44	0.12544
Moderate pain	0.53	0.1176	0.773	0.03332
Mild pain	0.66	0.3528	0.835	0.09114
Pain free	0.87	0.0588	0.959	0.03408

Abbreviations: EQ-5D, EuroQol five dimension; SD, standard deviation

Of these two sources, Stafford et al. was selected for the base case for a number of reasons related to its relevance to the UK population and the current decision problem. Briefly, Stafford et al. was a cross-sectional observational study in which a sample of 106 patients with migraine from the UK completed the EQ-5D to evaluate utilities for mild, moderate, and severe levels of migraine pain, and for health status within seven days post-migraine attack.[276] In this study, a UK population scoring algorithm was applied.[276]

Xu et al. calculated within-attack health utilities, using the US scoring algorithm, among 330 patients with migraine from the US who were enrolled in a trial for an acute migraine therapy.[282] Patients completed the EQ-5D at baseline (when they had moderate or severe pain) and 24 hrs post-treatment (only if they reported pain freedom), and rated their pain level using a four-point Likert scale.[282] The disutility for mild pain in Xu et al was indirectly estimated from the results of other pain states.[282]

Upon review of these studies, there were concerns regarding the face validity of the findings by Xu et al.[282] for modeling the UK population. Using the UK EQ-5D value set, setting the

pain dimension to the highest level, and assuming perfect health on all other dimensions would result in a hypothetical utility value of 0.264 for severe pain, indicating that the 0.4 in Xu et al. 2011 is implausibly high. Furthermore, based on the responses provided by clinical experts when asked to completet the EQ-5D for a patient experiencing a severe migrainei, the highest utility that could be derived for the severe health state was 0.05, which again suggests that the values in Xu et al. lack face validity in the UK. The baseline utilities without pain from Xu are reported as 0.933 to 0.959, whereas the weighted mean population for the UK population (using the mean population from Stafford et al.[276] of 47.5 years) is closer to 0.85.[284]

The value for the "pain free" health state of 0.87 reported by Stafford et al.[276] is more closely aligned with the age- and sex-adjusted UK population norms and closer to the baseline value from BHV3000-201 (0.72), which provides additional justification for its use in the base case.[284] Finally, UK community-based EQ-5D scores for individuals with migraine have been reported to be 0.750 (mean, unadjusted value) and 0.796 (median, adjusted value),[285] which challenges the validity of the values reported in Xu et al.,[282] and makes the case for use of the Stafford et al. in the current economic analysis.

In Stafford et al., the utility value for severe migraine pain was estimated at -0.20, a negative number indicating a state worse than death. The impact of this was explored in a scenario analysis, where the severe pain level was set to 0. Further it should be noted that over the 48-hour observation period in the rimegepant pooled acute trials, the time spent on the highest pain intensity "severe pain" is relatively short compared to the three other categories (Table 53).

B.3.4.4. A: Adverse reactions

Disutilities and costs associated with AEs were not incorporated in the model, given that when all AE severities were considered, all events occurred in <2% of the trial population, in both treatment arms of pooled single dose Phase 3 studies (Section B.2.10; Table 44).

B.3.4.5. A: Health-related quality-of-life data used in the cost-effectiveness analysis

Baseline utility values for patients not experiencing an attack every 48-hour cycle were based on clinical trial data from BHV3000-201 and are related to MMD frequency (Section B.3.4.1.A).

For migraine attacks, the approach used in the economic analysis is to extrapolate utility based on pain severity trajectories experienced in rimegepant and BSC study arms (aka. “event utility”). During a migraine attack, pain severity is thought to be the driving factor of HRQoL, an assumption that was validated by UK clinical experts (Section B.3.10.2.A). A flow diagram outlining the methods used to calculate QALHs from pain trajectories in the pooled rimegepant acute trials is presented in Appendix O (Section O1). Briefly, the time per pain category (none, mild, moderate, severe) was multiplied by health state utilities derived from Stafford et al., and then summed over the 48-hour study period to generate QALH over 48 hours. A regression analysis was then fitted to describe QALH outcomes adjusted for treatment arm, two-hour response status, baseline MMD, and baseline migraine severity.

The predicted QALH from regressions described above were adjusted to reflect the baseline utility value (Table 58). Of note, the utility values associated with a “pain free” state in Stafford et al. (2012) are relatively high (0.87; Appendix O, Section O2). Conversely, depending on baseline parameter settings, the interictal utility value predicted from Study BHV3000-201 (to be referred to here as U_0) is estimated to be approximately 0.72 (which is also lower than the value estimated by Stafford et al. for “mild pain”). Thus, the utility values from Stafford et al. (2012) were adjusted in order to retain the differences across pain categories, while reflecting the expectation that time periods without a migraine will have better HRQoL than time periods with a migraine. The model includes options to do so additively or multiplicatively. The multiplicative model was used in the base case as, due to smaller disutilities, it is more conservative (Appendix O, Section O2).

QALH regression analyses fit to pain-hour trajectories for Stafford et al. (2012),[276] and a two-hour response definition are provided below (Table 58).

Table 58: QALH regression analyses fit to pain-hour trajectories for base case parameters

Term	Stafford et al. 2012[276]	
	Coefficient	Standard error
Intercept	[redacted]	[redacted]
Treatment	[redacted]	[redacted]
Responder	[redacted]	[redacted]
MMD	[redacted]	[redacted]
BL_severity	[redacted]	[redacted]

Abbreviations: BL, baseline; MMD, monthly migraine days

Utility values are assumed to remain constant over time, including both the migraine-specific pain utilities from Stafford et al. (2012),[276] and the background utilities applied at baseline, with variation coming only by treatment for rimegepant patients for instances in which based on baseline characteristics there is a predicted decline in future MMD resulting in increased level of background utility. However, in such cases this rimegepant reduction in MMD frequency effect is also modelled as constant in time and applied from the first cycle onwards.

The limitation of not modelling age-adjustment to utilities is acknowledged; this approach was taken given the complexities of the linkage between the pain-free utility and the assumed utility of migraine pain categories. In addition, given that migraine severity may decrease with age,[19] it is unclear whether the standard population-based decrease in utility would be relevant vs. offset by improvements in migraine-specific utility. In the absence of direct data to support these complex relationships over time, a constant age-based utility was retained.

B.3.5. A: Cost and healthcare resource use identification, measurement and valuation acute treatment of migraine

The SLR used to identify costs and healthcare resource use (HCRU) related to acute migraine treatment is described in Appendix I: acute.

The primary direct medical cost in migraine is the price of treatment. Other background costs that were incorporated included general practitioner (GP) visits, emergency department (ED) visits, and hospitalisations. For each acute migraine episode, a probability of incurring costs for each of the HCRU categories was applied.

B.3.5.1. A: Acute intervention and comparators' costs and resource use

The drug acquisition cost for rimegepant is £20 for both initial and ongoing treatment. No cost for BSC was considered, given the proposed placement of rimegepant among triptan-failure patients, and no other active comparators available (Section B.1.3.3.1).

Treatment	Dosing schedule	Dose strength		Cost	
		Initial dose strength	Ongoing dose strength	Initial cost	Ongoing cost
Rimegepant	PRN	75 mg	75 mg	£20	£20

B.3.5.2. A: Modelling of treatment duration in acute migraine treatment

Non-responders who discontinue in the first model cycle incur the cost of a whole pack of rimegepant (eight tablets).

Responders incur cost until they discontinue treatment informed by the observed 1-year discontinuation rate estimated by the Kaplan-Meier curve from Study BHV3000-201 (Section B.3.3.2.4.A).

B.3.5.3. A: Health-state unit costs and resource use

Four unique studies of HCRU related to migraine were identified in the SLR to identify costs and healthcare resource use (HCRU) related to acute migraine treatment and are described in detail in Appendix I: acute. All four studies were from the UK perspective, however none were considered to be useful inputs into the current economic evaluation, for various reasons described in Appendix I: acute

The SLR was designed to exclude studies that did not report UK-specific HCRU results. As no relevant studies were identified with this criteria, we supplemented the SLR with a review of prior migraine submissions, which identified a study by Vo et al.,[277] from the fremanezumab appraisal (TA631/TA764).[4] Of note, we are aware of a more recent publication by Doane et al. 2020,[134] which is similar in study design and has similar findings to Vo et al.[277] However, to remain consistent with the prior migraine submissions, Vo et al. was selected for use in the base-case analysis.

In summary, Vo et al. was a retrospective cross-sectional study that used data from the 2016 National Health and Wellness Survey (n=80,600).[277] Patients were from France, Germany, Italy, Spain, and the UK. HCRU was assessed by the number of hospitalisations, ED visits, and GP visits reported in the six-months prior to the survey.[277] Result were reported overall, and for a low frequency (four to seven MMD) and high frequency (eight to 14 MMD) episodic migraine subgroup (Table 61).

The six-month values were converted to a per-migraine probability of HCRU by dividing by the midpoint of each migraine frequency group. For example, for the low frequency episodic migraine group, 5.5 MMD, and for the high frequency episodic migraine group, 11 MMD. Then, we took a weighted average of the two values, (using baseline data for 4-7 vs 8-14 MMD from the BHV3000-201 2+ triptan failure subgroup), to estimate the HCRU probability per-migraine event (Table 61).

Table 59: Probability of health care resource use per migraine event

	Utilisation per 6 months				Utilisation per event (assuming mid-point)				Weighted average (2012+ triptan failure distribution for 4-7 vs. 8-14 MMD)	
	4-7 MMD		8-14 MMD		4-7 MMD		8-14 MMD			
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Hospitalization	0.12	0.035	0.16	0.061	0.004	0.001	0.002	0.001	0.003	0.001
ED visit	0.37	0.103	0.61	0.177	0.011	0.003	0.009	0.003	0.010	0.003
GP visit	3.05	0.328	2.94	0.489	0.092	0.010	0.045	0.007	0.066	0.009

Abbreviations: ED, emergency department; GP, general practitioner; MMD, monthly migraine days; SE, standard error; vs, versus

In the model, the HCRU per-event probabilities were applied to patients who experienced severe migraine events only, consistent with the prior economic analysis by ICER (Atlas et al. 2020).[270] A severe event was assumed to be one at which pain was still moderate or severe at 24 hours. Based on the pooled trial data, this was the case for [redacted]% for rimegepant vs [redacted]% for BSC when considering only patients with two or more triptan failures. The proportion of patients with moderate or severe pain at 24 hours, by two- and eight-hour responder status is presented in Table 60.

Table 60: Proportion of patients with moderate or severe pain at 24 hours, overall, by response status, and for subgroup who had previously failed ≥2 triptans

	2 hr responder		8 hr responder	
	Y	N	Y	N
Rimegepant	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: hr, hour(s)

The unit costs were derived from PSSRU and NHS references costs, as presented in Table 61.[286,287]

Table 61: List of resource use and associated costs

Resource	Unit costs (£)	Description	Source
General practitioner visit	39.23	Based on cost per patient contact lasting 9.22 minutes	PSSRU[286]
Emergency department visit	188.07	HRG code VB09Z, as per onabotulinumtoxinA submission (TA260)[5]	NHS reference costs[287]

Resource	Unit costs (£)	Description	Source
Hospitalisation	643.29	Weighted average of HRG codes AA31C, AA31D, and AA31E	NHS reference costs[287]

Abbreviations: HRG, healthcare resource group; PSSRU, Personal Social Services Research Unit

B.3.5.4. A: Adverse reaction unit costs and resource use acute

As described in Section B.3.4.A, AEs are not included in the model given the low (<2%) incidence observed in clinical trials.

B.3.5.5. A: Miscellaneous unit costs and resource use acute

The model includes an option to incorporate lost productivity costs, in sensitivity analysis. This option is based on the variable included in the pooled acute trials, indicating ability to return to normal function (binary). This model was linked to treatment response, such that the proportion of patients returning to normal function is predicted by response to treatment. Patients who do not return to normal function are assumed to miss 7.5 hours of work, costed at the UK national average wage of £16.29/hour (Table 62).

Table 62: Lost productivity unit costs, UK employment and labour market statistics

Parameter	Value	Source
Median hourly wage	£16.29	Office for National Statistics, 2021[288]
Cost of missed workday*	£122.20	Office for National Statistics, 2021[288]
Employment rate	75.6%	Office for National Statistics, 2022[289]

Abbreviations: UK, United Kingdom
Notes:
*Assuming 7.5 hour working day

B.3.6. A: Summary of base-case analysis inputs and assumptions acute treatment of migraine

B.3.6.1. A: Summary of base-case analysis inputs for acute treatment of migraine

Table 63 presents a summary of the key variables applied in the economic model for acute treatment of migraine.

Table 63: Summary of variables applied in the economic model for acute treatment of migraine

Area	Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty: values used in sensitivity analyses	Reference to section in submission
General	Time horizon	20 years	OWSA 10-40 years	B.3.2.2.1.A
	Comparators	BSC	NA	B.3.2.3.A
	Discount rate	3.5%	1.5% (scenario analysis)	B.3.2.2.4.A
	Cycle length	48 hours	Typical migraine length and trial duration	B.3.2.2.2.A
	Population characteristics	Study BHV3000-201 (≥2 triptan failure subgroup)	Population more closely aligned to real-world migraine population than restricted Study BHV3000-301, -302, and -303 populations – allows for observing potential reduction in MMD frequency with high-frequency acute use	B.3.3.1.A
Efficacy	Response rate definition	2-hour pain relief	8 hour pain relief (scenario analysis)	B.3.3.2.1.A
	Response rate (from pooled acute trials)	[redacted]% rimegepant [redacted]% usual care	OWSA: 2.5th & 97.5th confidence bounds (beta distribution) PSA: Beta distribution	B.3.3.2.1.A
	"Placebo effect" diminishing	12 months (followed by treatment effects consistent with BSC non-responders)	OWSA 6 months -24 months	B.3.3.2.4.A
	Discontinuation rate of rimegepant	[redacted]%	OWSA: 2.5th & 97.5th confidence bounds (beta distribution) PSA: Beta distribution	B.3.3.2.4.A
	Response following rimegepant discontinuation	Assumed to revert to BSC non-responders after one year at BSC responder rate	Revert immediately to BSC non responder at discontinuation (scenario analysis)	B.3.3.2.4.A
	Frequent use of acute treatment confer reduction	Included	Scenario (Excluded)	B.3.3.2.5.A

Area	Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty: values used in sensitivity analyses	Reference to section in submission
	in MMD frequency			
Utilities	Per migraine event	Area-under-the-curve regression analysis on QALH (pre-fit to Stafford at 2-hour and 8-hour responder definitions)	OWSA: 2.5th & 97.5th confidence bounds for regression parameters (Normal distribution) PSA: Cholesky distribution	B.3.4.1.A B.3.4.2.A
	Interictal period	Mapped MSQv2 to EQ-5D data from BHV3000-201, with regression analysis fit to incorporate MMD and other covariates	OWSA: 2.5th & 97.5th confidence bounds for regression parameters (Normal distribution) PSA: Cholesky distribution	B.3.4.1.A B.3.4.2.A
	MMD parameter in QALH regression	Regression point estimate (-0.4918) used in base case	OWSA: 2.5th & 97.5th confidence bounds for regression parameters (Normal distribution) PSA: Cholesky distribution	B.3.4.1.A B.3.4.2.A
HCRU	Probability of hospitalisation, ED, GP visit	Vo et al.[277]	OWSA: 2.5th & 97.5th confidence bounds (beta distribution)	B.3.5.3.A
Costs	Drug acquisition cost	£20 per attack	No	B.3.5.1A
	Resource unit costs	NHS unit costs	No	B.3.5.3.A

Abbreviations: BSC, best supportive care; ED, emergency department; GP, general practitioner; NA, not applicable; NICE, National Institute for Health and Care Excellence; OWSA, one-way sensitivity analysis; PSA, probabilistic sensitivity analysis;

B.3.6.2. A: Assumptions in acute treatment of migraine model

Table 64 presents a list of the main parameters and assumptions used in the acute economic analysis.

Table 64: Key assumptions in the acute economic model

Parameter	Base-case assumption	Justification
MMD distribution	Weighted results across the MMD distribution from the BHV3000-201 trial	Base case model analysis assumes MMD consistent with core modelled population of the BHV3000-201 trial.
Efficacy of rimegepant over time	Constant over time for patients continuing therapy	Limited data available for pain trajectories (single-attack study only), but relatively high retention of acute patients in long-term safety study BHV3000-201[140] implies ongoing effectiveness. Responder-based analysis assumes that only patients retaining benefit will remain on treatment, further justifying assumption of retained benefit for those patients remaining on therapy. In real-world practice, patients losing response are expected to discontinue therapy and no longer incur costs, accounted for with the annual discontinuation rate estimated from BHV3000-201.
Waning of placebo effect	It is assumed that placebo responders will transition to placebo non-responder trajectories after 12 months	The dissipation of the placebo effect was included as it was the committees' preferred assumptions for fremanezumab,[4] where the treatment effect for people who responded to BSC diminished to baseline over 1 year. Discussion with experts suggests it was the general understanding that placebo always wanes over time. While it was difficult to come to consensus as views were varied and complex, the pragmatic view is that 12 months is a long time for placebo effect in acute, but a wide range of time period ranging from 6 months to 12 months was also suggested.
Rimegepant discontinuation	[redacted]% per year	Informed by 1-year point estimate from Study BHV3000-201[140] Kaplan-Meier analysis of discontinuation data.
Response following rimegepant discontinuation	Assumed to revert to placebo non-responders after one year at placebo responder rate	Assumption of parity for BSC responders, who experience 12 months of response prior to reversion to non-response
Mortality	Assumed to follow general population mortality	Aligns with prior NICE TAs in migraine prevention,[4,142,143] and is supported by a published meta-analysis, which found no association between migraine and all-cause mortality.[278]
Effect of rimegepant treatment on monthly migraine frequency	Potential for reduction in MMD frequency based on patient characteristics (including baseline MMD)	As observed in the long-term safety study 201, there is evidence of migraine reduction with as-needed acute treatment of rimegepant;[181,237] further supported by clinical expert panel.
Time horizon	20 years	Lifetime horizon as per NICE reference case.[273] Capped at 20 years given that migraine frequency tends to decline with older age.[19] and a negligible proportion of patients would be modelled to continue on any treatment beyond 20 years.
Adverse drug events	Not included	All events/severity levels occurred in <2% of the trial population, in both treatment arms

Parameter	Base-case assumption	Justification
Productivity	Included in scenario analysis only	Not included in base case as per NICE reference case. However, migraine prevalence is greatest among individuals aged 35-49 years, and as such migraine-related disability has an enormous impact on what are typically the most productive years of life.[66,94,95]

Abbreviations: BSC, best supportive care; MMD, monthly migraine days; NICE, National Institute of Health and Care Excellence

B.3.7. A: Base-case results acute treatment of migraine

These results of the model are presented for rimegepant versus BSC in the acute treatment of migraine, in patients who have had inadequate symptom relief after trials of at least two triptans or in whom triptans are contraindicated or not tolerated.

B.3.7.1. A: Base-case incremental cost-effectiveness analysis results acute treatment of migraine

In Table 65 the total costs, QALYs, and incremental cost per QALY for rimegepant vs BSC are presented. Compared with BSC in the base case analysis rimegepant generated 0.49 incremental QALYs, and the rimegepant treatment cohort had higher total lifetime costs. The ICER was £18,221 per QALY gained.

Table 65: Base-case results acute treatment of migraine

Technologies	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
Weighted across MMD distribution observed in Study BHV3000-201 (≥2 triptan failure group)					
Rimegepant	11,464	8.14	8,872	0.49	18,221
BSC	2,592	7.65			

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

B.3.8. A: Sensitivity analyses acute treatment of migraine

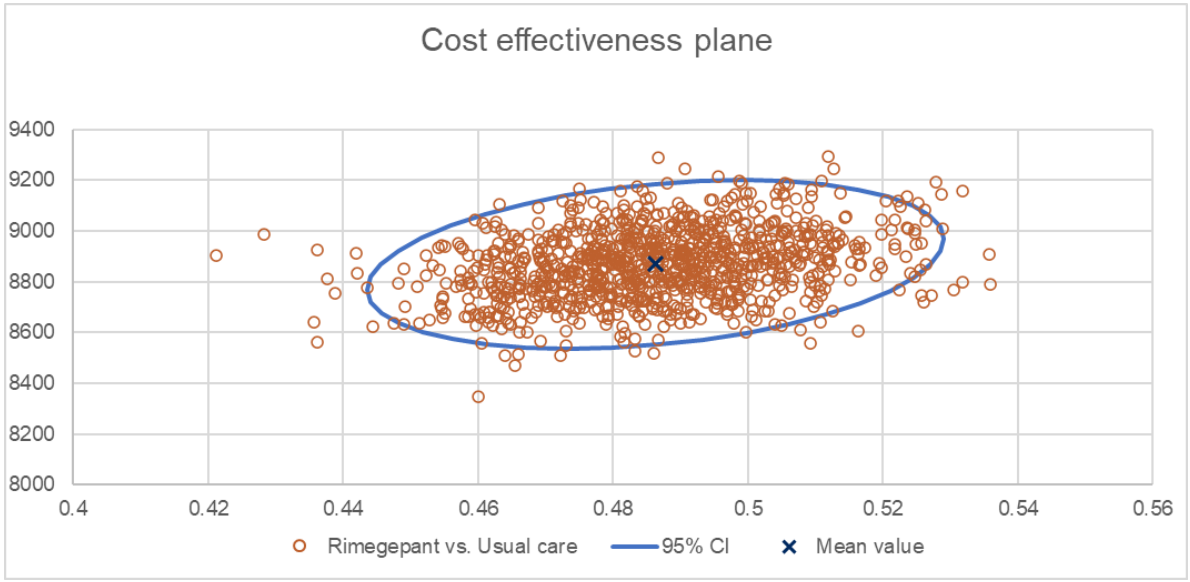
B.3.8.1. A: Probabilistic sensitivity analysis acute treatment of migraine

A probabilistic sensitivity analysis (PSA) was undertaken to examine the uncertainty surrounding model parameters. The PSA was conducted using 1,000 iterations.

The scatter plot of incremental cost versus incremental QALYs for rimegepant versus BSC from 1,000 iterations is presented in Figure 17. The 95% credible ellipse is also presented in the figure. All iterations were in the north-east quadrant indicating that under all estimates rimegepant provided a clinical benefit versus BSC and was associated with an incremental cost. The mean probabilistic ICER was £18,257, aligned with deterministic results.

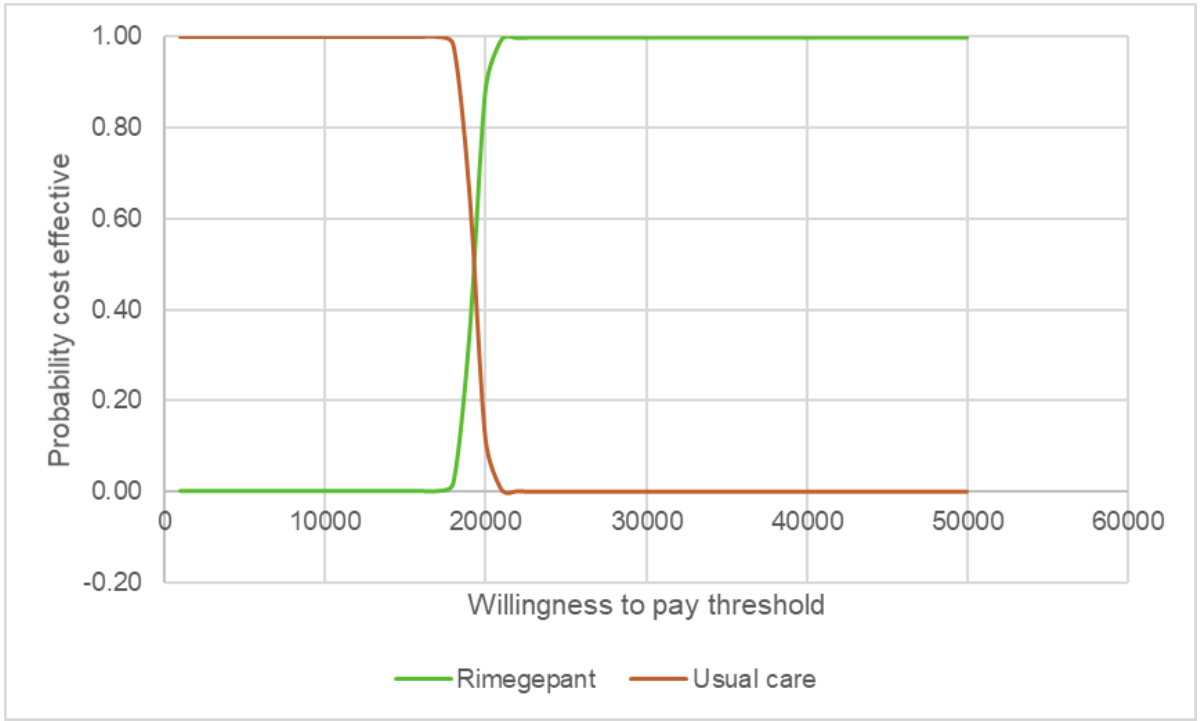
The cost-effectiveness acceptability curve (CEAC), demonstrated that there is an 88% chance that rimegepant is cost-effective at a WTP of £20,000 per QALY and 100% chance at a WTP of £23,000 per QALY or higher. (Figure 18)

Figure 17: Cost-effectiveness plane vs BSC acute treatment of migraine



Abbreviations: BSC, best supportive care; CI, confidence interval; vs, versus

Figure 18: Cost-effectiveness acceptability frontier vs BSC acute treatment of migraine



Abbreviations: BSC, best supportive care; vs, versus

Table 66: Results of the probabilistic sensitivity analysis for rimegepant vs BSC acute treatment of migraine

Technologies	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
Rimegepant	11,464	8.14	8,869	0.49	18,257

Technologies	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	2,592	7.65			

Abbreviations: BSC, best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs, versus

B.3.8.2. A: Deterministic sensitivity analysis

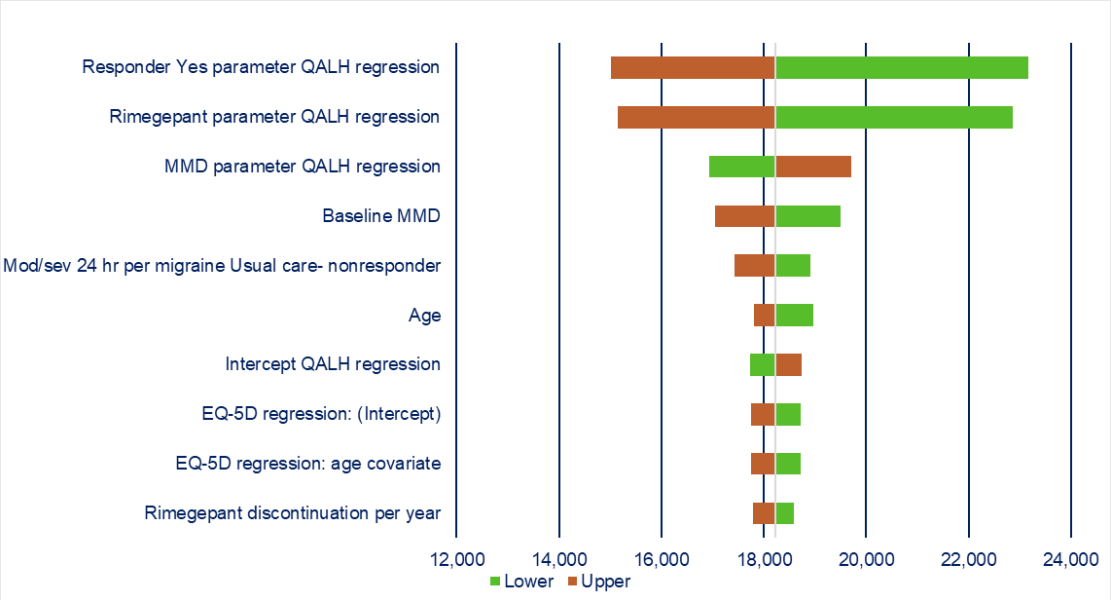
Overall, the OWSA for key inputs yielded very similar results as the base case. Results of the OWSA are shown in Table 67 and Figure 19. Results were most sensitive to the parameter values in the QALH regression, with a higher ICER associated with a lower parameter value for responder rates or rimegepant. Results were also relatively sensitive to baseline MMD, probability of moderate/severe pain at 24 hours for usual care patients, and age.

Table 67: Results of the deterministic sensitivity analysis for rimegepant versus BSC <u>acute</u> treatment of migraine

Parameters (Base case, lower value, upper value)	Low value ICER	High value ICER	Max difference from base case
Responder Yes parameter QALH regression (6.46, 4.1, 8.82)	23,157	15,020	4,936
Rimegepant parameter QALH regression (2.74, 0.46, 5.03)	22,864	15,146	4,643
MMD parameter QALH regression (-0.68, -1.27, -0.1)	16,941	19,711	1,490
Baseline MMD (9.2, 7.36, 11.04)	19,495	17,056	1,274
Mod/sev 24 hr per migraine, Usual care- nonresponder (0.28, 0.16, 0.41)	18,911	17,433	788
Age (45.7, 18, 65)	18,974	17,805	753
Intercept QALH regression (34.05, 30.55, 37.54)	17,728	18,743	521
EQ-5D regression: (Intercept) (0.71, 0.7, 0.73)	18,720	17,748	499
EQ-5D regression: age covariate (0.001, 0.0006, 0.0014)	18,712	17,756	490
Rimegepant discontinuation per year (0.1, 0.02, 0.22)	18,594	17,863	431

Abbreviations: BL, baseline; BSC, best supportive care; hr, hour; ICER, incremental cost-effectiveness ratio; Max, maximum; MMD, monthly migraine days; NA, not applicable; vs, versus

Figure 19: Tornado diagram for the deterministic sensitivity analysis of rimegepant vs BSC showing impact on the ICER acute treatment of migraine



Abbreviations: BL, baseline; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; MMD, monthly migraine days; vs, versus

B.3.8.3. A: Scenario analysis

In Table 68 the scenario analyses undertaken to investigate the effect of certain model inputs on costs and outcomes are presented. The largest increase in ICER were observed for a two-year time horizon (as per the OWSA), resulting in an ICER of £22,116 and an assumption of no reduction in MMD frequency among frequent PRN user , which resulted in an ICER of £22,199. The largest decreases in ICER were observed for a responder definition of pain relief at eight hours, which resulted in an ICER of £10,656, and an additive vs. multiplicative adjustment to utilities, which resulted in an ICER of £14,299. The additive adjustment was particularly impactful given the negative utility associated with severe pain, reported by Stafford et al. (2012);[276] a multiplicative adjustment in bringing the pain-free utility to the background regression-predicted utility for non-migraine states results in the negative utility being adjusted to a value closer to 0, while the additive adjustment results in a smaller negative value (and hence greater HRQoL impact of a more severe migraine event offset by rimegepant treatment). However, for the scenario analysis in which that negative utility was capped at 0 (for a multiplicative adjustment), the ICER was relatively close to base case, at £19,159. Thus, for the base case setting of multiplicative utility adjustment, the incorporation of a negative utility did not have a notable impact on the ICER. All remaining scenario analyses were also within approximately +/- £2,000 of the base case value.

Table 68: Scenario analysis: rimegepant vs BSC (using Study BHV3000-201 MMD distribution option) acute treatment of migraine

Scenario	Description	Base case	Parameter value in scenario	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
1	Base case	--	--	8,872	0.49	18,221
2	Adopt societal perspective	NHS and PSS	--	-33,905	0.49	Rimegepant dominant
3	Discount rate	3.5%	1.5%	10,987	0.55	18,113
4	Time horizon	20 years	2 years	2,313	0.10	22,116
		20 years	5 years	4,705	0.24	19,281
		20 years	10 years	7,065	0.38	18,515
5	Responder definition	Pain relief at 2-hours	Pain relief at 8-hours	8,305	0.78	10,656
6	Reduction of MMD frequency among frequent PRN rimegepant users	Include	Exclude	9,782	0.44	22,199
7	QALH utility	From regression	Raw data: Pain intensity x hour	8,872	0.51	17,311
8	Event utility regression	Multiplicative adjustment	Additive adjustment	8,872	0.62	14,299
9	Migraine event utility values Pain intensity x hour	Stafford et al.[276] as published	Set severe utility to 0 instead of negative value	8,872	0.46	19,159
10	Patient population from pooled rimegepant acute trials	≥2 triptan failure	mITT	6,888	0.43	16,058
11	Rimegepant discontinuation annual rate	Use discontinuation due to adverse events, lack of efficacy, or withdrawal by participant from Study BHV3000-201[140] ([redacted]% annually)	Use "all cause" discontinuation to inform the model (20% annually) from Study BHV3000-201[140]	5,378	0.30	17,844
12	Response following rimegepant discontinuation	Assumed to revert to placebo non-responders after one year at placebo responder rate	Immediately revert to BSC non-responders at discontinuation	8.872	0.46	19,287
13	BSC waning effect (time period before BSC responders transition to BSC non-responder trajectories)	12 months	6 months	8,848	0.48	18,250
		12 months	18 months	8,895	0.49	18,181

Abbreviations: BSC, best supportive care; mITT, modified intention to treat; PRN, *pro re nata* (as needed); QALYs, quality adjusted life years

B.3.8.4. A: Summary of sensitivity analyses results acute treatment of migraine

As shown in Section B.3.8.3.A, the results of the scenario analyses are generally robust, but results are sensitive to some key parameters, including time horizon, response definition, discounting, and relationship between response and QALH. Across scenario analyses, OWSA, and PSA, rimegepant for acute treatment of migraine is a cost-effective use of NHS resources.

B.3.9. A: Subgroup analysis acute treatment of migraine

No subgroup analyses were performed.

B.3.10. A: Validation acute treatment of migraine

B.3.10.1. A: Validation of cost-effectiveness analysis acute treatment of migraine

Extensive technical validation was undertaken by a third-party. This involved a detailed review of programming and extreme value testing. The cost-effectiveness model was quality-assured using the internal processes of the health economists who built the model. Additionally, the model was also quality checked and validated by an external health economist not involved with the original programming of the models. This was primarily done to ensure accuracy in calculations and programming logic. The technical validation of the model included review of implementation and typing errors, validation of the logical structure of the model, expressions, and sequences of calculations. Further, extreme value testing has been performed to investigate and ensure robustness of model behaviors for wide range of input parameter values.

B.3.10.2. A: External expert validation acute treatment of migraine

Two virtual consultation meetings were held in March 2022 with 19 UK experts consisting of a broad range of consultants from primary, secondary and tertiary care, including general practitioners (GPs), GPs with special interest (GPwSI), neurologists, pharmacists, nurse specialists, pain specialists, and health economists to validate the model structure and assumptions.[1]

Regarding the model methods, the following items were discussed and validated during the meeting:

- Although migraine is a spectrum disorder, with patients in clinical practice distributed from those who need acute treatment only to people on prevention for EM and CM, the

experts suggested to keep separate the decision problem from acute and prevention. Hence two separate economic models were built for this submission.

- In the treatment of acute migraine, it is generally recommended to try a particular treatment on two or three episodes before abandoning it. In the context of a single attack design, the response rate after the first attempt is unknown, but it is conceivable that some of the initial non-responders would respond on the second attack. To simulate the potential increase in responders, pain relief at 8 hours as responder was considered in a scenario analysis.

- Similarly, there is currently no long-term data to inform how response to a single attack may predict response on future migraine episodes. Experts suggested to examine the persistence data from Study BHV3000-201, as low discontinuation rates may imply that patients continue to derive acute treatment benefit over time.

- Clinical experts confirmed that pain relief at two hours is a reasonable and pragmatic choice to determine treatment response in the acute setting and is the most appropriate for clinical practice. Furthermore, it is correlated with patient ability to function, another key marker of patient benefit.

- The absence of medication overuse is a unique benefit of rimegepant and presents a novelty in that increased use as an acute medication has the potential to start working as a preventive treatment. This hypothesis is supported by a post-hoc analysis showing patients taking medication as needed for acute treatment was associated with significant reduction in MMD, and clinical experts agreed this is clinically plausible.

- The two sources of utility (Stafford [2012][276] and Xu [2011][282]) were discussed. Experts were asked to answer the EQ-5D corresponding to severe pain intensity. Based on the responses provided by the experts to the EQ-5D instant polls, the highest utility that could be derived was 0.05, indicating that the 0.4 in Xu (2011)[282] is relatively high and not applicable for the UK population.

B.3.11. A: Interpretation and conclusions of economic evidence acute treatment of migraine

For the acute treatment of adults with migraine in whom triptans are inappropriate due to inadequate symptom relief (after trying ≥2 triptans) or in whom triptans are contraindicated or not tolerated, rimegepant can be considered cost-effective in comparison to BSC. The base case ICER was £18,221 per QALY gained.

There are no prior NICE TAs in the acute treatment of migraine to compare the results of the current economic evaluation to, as no novel therapies have been developed for the acute treatment of migraine in the last 20-years.

B.3.11.1. A: Generalisability of the results to clinical practice in England and relevance to all patients as identified in the decision problem acute treatment of migraine

The analysis is likely to be directly applicable to clinical practice in the UK. The patient population in the acute economic model is consistent with the proposed place in therapy for rimegepant in the acute setting as described in the decision problem. Although narrower than the marketing authorisation for rimegepant, this ensures generalisability to the UK clinical practice setting as the unmet need is the greatest in patients with inadequate response to or safety or tolerability issues with triptans. In the rimegepant pooled acute trials, the subgroup of patients with ≥2 triptan failures were selected for the base case which is consistent with the population who would be eligible to receive this therapy in real world practice.

B.3.11.2. A: Strength and weaknesses of the evaluation acute treatment of migraine

The economic evaluation accurately reflected the decision problem, clinical practice, and targeted population. The efficacy of rimegepant versus BSC was informed by three high quality RCTs and used a patient and clinically relevant efficacy endpoints (pain relief, pain intensity level). Patient-level data were available for the comparators of interest, allowing for comprehensive analyses of pain trajectories per migraine and subgroup analysis (particularly for the key subgroup of interest, triptan-refractory patients).

A limitation of the model was its inability to capture any change over time in the efficacy of rimegepant to treat acute attacks, or to capture patients who tried rimegepant several times before achieving adequate response. However, the impact of this uncertainty has been explored through the eight hours response analysis and discontinuation of rimegepant over time has also been included. Furthermore, low rates of discontinuation in the long-term safety study (BHV3000-201) and the open label extension of prevention trial BHV3000-305 support continued efficacy of rimegepant over time. The trial did not include EQ-5D elicitation during a migraine event, however, utilisation of published mapping algorithm and published UK data were utilised to connect clinical pain data to utilities. An assumption was required regarding the nature of the placebo effect, although this followed a previous committee preferred assumption and was explored in sensitivity analysis.

B.3.11.3. A: Conclusions acute treatment of migraine

A pooled analysis from three Phase 3 trials showed that rimegepant 75 mg was effective for the acute treatment among patients with a history of ≥2 triptan failures.

This analysis assesses the cost-effectiveness of rimegepant versus BSC in the treatment of acute migraine among patients who have had inadequate symptom relief after taking at least two triptans or in whom triptans are contraindicated or not tolerated. The effectiveness data was derived using head-to-head data from a pooled analysis of three randomised phase III studies. Significant clinically meaningful results were observed in rimegepant compared to placebo across primary and key secondary endpoints which translated into incremental QALYs of 0.49 in the base-case analysis.

The base-case analysis demonstrated rimegepant to be cost-effective with an estimated ICER of £18,221 per QALY, a finding robust to one-way and probabilistic sensitivity and scenario analyses.

This analysis indicates the potential for rimegepant to represent a cost-effective use of NHS resources for the acute treatment of migraine, in patients with lack of response or contraindication to triptans.

Preventive treatment of migraine

The following sections report the relevant cost effectiveness evidence for the preventive treatment of migraine (heading prefixed with P:)

B.3.1. P: Published cost-effectiveness studies in migraine prevention

SLRs were conducted on the published economic literature to inform the economic evaluation of rimegepant in the preventive treatment of refractory migraine. The prevention economic SLRs identified all literature since database inception on cost-utility analysis, cost-effectiveness analysis, budget impact analysis, cost and resource use, and health state utilities. A total of 41 publications (24 unique studies) reported economic evidence, these included 27 publications (17 unique studies) reporting economic evaluations of prevention therapies, 19 publications (11 unique studies) on health state utilities, and eight publications (three primary publications) on cost and resource use.

Full details on the studies included in the SLRs are presented in Appendix G: prevention. No economic evaluations were identified that reviewed rimegepant from the UK perspective, in the prevention treatment paradigm. Published literature that examined relevant comparators to rimegepant (erenumab, galcanezumab, and fremanezumab) informed the current economic evaluation and are summarised in Table 69.

In the studies identified in the SLR, modelled patient populations included adults with migraine who had responded inadequately to 1 – 4 prior preventive therapies (Table 69). The most common time horizon used was 10-years, with 1- to 3-month cycles. Model perspectives and specific comparators differed across studies (Table 69). The hybrid decision-tree plus Markov model structure described by Mahon et al (2021)[290] was designed based on expert consultation and systematic review of clinical practice guidelines, and has been adopted in prior TAs in migraine prevention (Table 71). This structure was deemed to be the most relevant to the current decision problem and informed the economic model of rimegepant in migraine prevention.

Table 69: Summary of published cost-effectiveness studies informing the rimegepant prevention economic model

Author Year, Country	Population summary	Interventions	Perspective	Type EE	Time horizon	Cycle length	Health states	ICER per QALY or key finding
Lipton et al. 2018[291], USA	EM and CM patients that have failed ≥1 preventive therapy In the base-case analysis, the migraine population was modelled as 33% with EM and 67% with CM	Erenumab 140 mg, self-administered every 28 days by subcutaneous injection and standard care (acute treatments only)	Societal perspective, USA	CEA Markov model	10-year	28-day	The model comprises "on preventive treatment", "off preventive treatment", and "death" health states	**Societal value-based price for erenumab:** *WTP threshold $100,000:* $14,238 *WTP threshold $200,000:* $23,998
Mahon et al. 2021[290], Sweden	Patients had severe migraine experiencing ≥4 MMD per month and had ≥2 prior preventive treatments failures (defined as insufficient treatment response or AE-related discontinuation) and had been seen by a specialist (i.e., neurologist or headache expert)	Erenumab 140 mg was administered at 4-week intervals in prefilled syringes. BSC included only acute treatment (triptans, analgesics, etc.), as this best reflected clinical practice	Societal perspective (healthcare system perspective as a scenario analysis), Sweden	CEA Hybrid decision-tree plus Markov model was designed based on expert consultation, systematic review of clinical practice guidelines and previous modelling approaches for preventive treatments of migraine.	10-year	12-week	The decision tree created 2 health states: responders and non-responders. In the Markov model non-responders moved to the negative discontinuation state (no preventive treatment). Responders moved into the on-treatment state and could then subsequently move to the negative discontinuation state, the re-evaluation period or the positive discontinuation state (paused preventive treatment on the	**ICER per QALY, erenumab vs PBO:** *All migraine patients:* 34,696 kr *CM:* Erenumab dominant *EM:* 301,565 kr

Author Year, Country	Population summary	Interventions	Perspective	Type EE	Time horizon	Cycle length	Health states	ICER per QALY or key finding
							basis of well controlled migraine)	
Silva et al. 2020[292], Portugal	Adult migraine patients with ≥3 preventive treatment failures	Erenumab 140 mg and PBO	Societal and NHS perspectives, Portugal	CEA Hybrid decision-tree and Markov model	Lifetime (60 years)	12-week	NR	**ICER per QALY (erenumab vs PBO):** *Societal perspective:* Erenumab is dominant *NHS perspective:* <€20,000 (reported as considerably below 20,000)
Smolen et al. 2019[293], USA	Patients had CM (67%) or EM (33%) and were being treated with either fremanezumab or no treatment	Fremanezumab vs no treatment. Model accounted for the cessation of fremanezumab in non-responders (CM/EM patients not achieving 30%/50% reductions, respectively, in MDs per 28days at 12-weeks [non-responders] stopped treatment)	Societal and payer perspectives, USA	CEA Semi-Markov model	10-year	4-week	Not explicitly reported; patient cohorts were distributed among MD categories (0–28 MDs per 28 days) based on mean MD levels	**ICER for fremanezumab vs no treatment:** *Including indirect costs:* Fremanezumab dominates no treatment (less costly, more effective) *Excluding indirect costs:* $13,606
Smolen et la. 2020,[294] USA	Patients with EM (4–14 MDs per 28 days at the start of the study) that have responded inadequately to 2 to 4 classes of prior preventive treatments	Fremanezumab vs erenumab 140 mg	Societal and payer perspectives, USA	CEA Semi-Markov model	10-year	4-week	Not explicitly reported, however, patient cohorts were distributed among MD categories (0–28 MDs per 28 days) based on mean MD levels	**ICER for fremanezumab vs erenumab:** *Direct and indirect costs:* Fremanezumab dominates erenumab

Author Year, Country	Population summary	Interventions	Perspective	Type EE	Time horizon	Cycle length	Health states	ICER per QALY or key finding
								Excluding indirect costs: Fremanezumab dominates erenumab
Sussman et al. 2018[295], USA	Adult (≥18 years) patients with EM and CM who failed ≥1 prior preventive therapy Patients in the EM cohort must have had 4–14 MMD at baseline; patients in the CM cohort must have had ≥15 MMD at baseline	Erenumab 140 mg, no preventive treatment and onabotulinumtoxin A	Societal and payer perspectives, USA	CEA Hybrid Monte Carlo patient simulation and Markov cohort model	2-year	1-month	Patients were assigned a post-treatment MMD category based on baseline MMD and treatment effect: 0–3 MMD, 4–9 MMD, and 10–14 MMD (for EM); 15–19 MMD, 20–23 MMD, and 24–30 MMD (for CM patients). Patient could also discontinue treatment or move to the death state	**Societal perspective** *ICER per QALY for EM patient:* Erenumab vs no preventive treatment: $122,167 **Payer perspective** *ICER per QALY for EM patients:* Erenumab vs no preventive treatment: $180,012

Abbreviations: AE, adverse event; BSC, best supportive care; CEA, cost-effectiveness analysis; CM, chronic migraine; EE, economic evaluation; EM, episodic migraine; ICER, incremental cost-effectiveness ratio; kr, Swedish krona; MDs, migraine days; MMD, monthly migraine days; NHS, National Health Service; NR, not reported; PBO, placebo; QALYs, quality adjusted life years; USA, United States of America; vs, versus

B.3.2. P: Economic analysis for rimegepant in migraine prevention

A *de novo* economic model was developed to assess the cost-effectiveness of rimegepant versus relevant comparators for the preventive treatment of migraine, from the perspective of the NHS and PSS.

The general structure and inputs of previous economic analyses of erenumab, fremanezumab, and galcanezumab were considered in developing the prevention model (TA682, TA631/TA764, TA659; see Table 47).[4,142,143] The focus of the model is on the distribution of MMDs, with these modelled according to response to treatment using count models for the frequency of MMD in each 28-day period. Data is taken from Study BHV3000-305 clinical study.[216] Response is predicted at 12 weeks post treatment initiation based on a 50% reduction (or greater) in MMD based on analysis of BHV3000-305 and an NMA incorporating erenumab, fremanezumab, and galcanezumab (Section B.2.9.P). No excess mortality is thought to be associated with migraine, therefore patients in all model states face standard rates of mortality over lifetime based on UK life tables. The model was developed in Microsoft Excel.

B.3.2.1. P: Prevention patient population

This economic evaluation considers adults with EM who have at least four migraine days per month but fewer than 15 headache days per month, and have failed three or more conventional preventive therapies (e.g., beta-blockers, antidepressants, antiepileptics; Table 70).

The patient population in the prevention economic evaluation is narrower than the marketing authorisation for rimegepant which specifies “preventive treatment of episodic migraine in adults who have at least four migraine attacks per month.” This is due to its relevance to NHS clinical practice, based on expert clinical opinion (Section B.3.10.P), and greater unmet need for patients who fail to respond to conventional preventive therapies (Section B.1.3.3.2). This population in the economic evaluation is consistent with the proposed place in therapy for rimegepant in the prevention setting described in the decision problem and at a position in the treatment pathway where the three mAbs are currently used in the NHS clinical practice (Section B.1.1 and Section B.1.3.3.2).

In the pivotal prevention trial for rimegepant (BHV3000-305), which acts as a key data source for the economic evaluation, 22% of patients were receiving concurrent conventional preventive therapies at randomisation. Data regarding response to current and prior

conventional prevention therapy is not available. Given the similarity to the mITT treatment effect, the data from Study BHV3000-305 is considered generalisable to the decision problem and used to estimate relative treatment efficacy versus placebo among patients who have failed three or more conventional preventive therapies for utilisation within the NMA.[216]

There is a difference between the BHV3000-305 trial population (which included both episodic [77%] and chronic migraine [23%] patients) and the marketing authorisation and proposed place in UK clinical practice, which specify that rimegepant should be used in patients with episodic migraine only. However, it was not possible to restrict the analysis to the EM-only subgroup without breaking randomisation, as this was not a pre-specified stratification factor for randomisation in Study BHV3000-305. The perceived bias of using the mixed population was deemed less than the bias of using a subgroup that broke randomisation. This is discussed further in Section B.2.9.1.4.P.

Table 70: Patient population considered in the economic model for migraine prevention

Treatment experience	Episodic migraine
Patients with a history of at least 3 failed preventive treatments	> 4 migraine days per month but fewer than 15 headache days per month

B.3.2.2. P: Prevention model overview

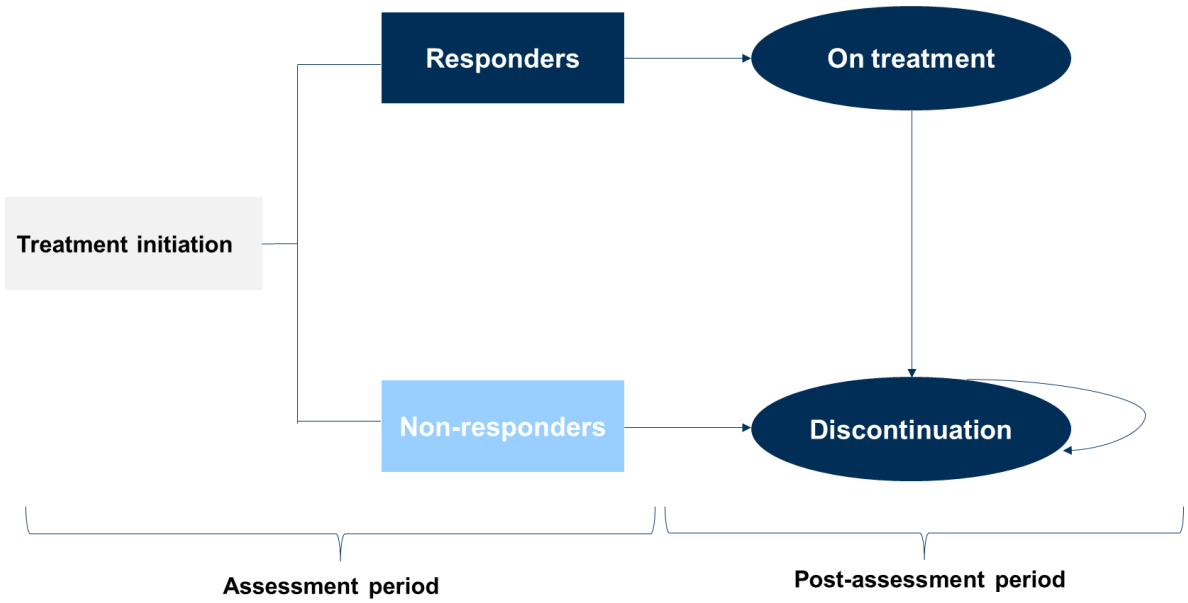
B.3.2.2.1. P: Model structure

P: Assessment period

A decision tree plus Markov model was developed to evaluate the incremental cost-utility of rimegepant versus erenumab, fremanezumab, and galcanezumab, in adult patients with episodic migraine (Figure 20). At the start of the model, patients initiate treatment on rimegepant or comparators for a period of 12 weeks. The decision tree represents the "assessment period" of 12 weeks; which is aligned with the UK clinical care pathway described in Section B.1.3.3.2, and stipulates that the mAbs are to be assessed after a 12-week trial period (using criteria of ≥50% reduction from baseline in MMD) to justify continued use.[4,142,143] The response criteria of 50% is consistent with the IHS guidelines which considers a ≥50% MMD reduction from baseline to be a clinically meaningful reduction in episodic migraine, and recommends the use of this endpoint in prevention clinical trials.[256] Recent NICE TAs of erenumab, fremanezumab, and galcanezumab have also used ≥50% MMD reduction from baseline to define response in their economic modelling of episodic migraine.[4,142,143]

For each 28-day cycle within the assessment period, the distribution of MMD is determined based on the selected statistical distribution (count model). For weeks 1 to 4 (cycle 1) and weeks 5 to 8 (cycle 2) this distribution is conditional only on treatment arm. In weeks 9 to 12 (cycle 3), the probability of treatment response is estimated based on at least a 50% reduction from baseline in MMD (taken as the frequency of MMD in the 28-day period prior to baseline date), and the distribution of MMD is conditional on treatment arm and response. Non-responders immediately discontinue treatment at 12 weeks, consistent with previous NICE appraisals in migraine prevention.[4,142,143] The Markov model is then used to represent the post-assessment period, during which the responders and non-responders follow different pathways. The model structure is presented in Figure 20. The model also includes a health state for background mortality; however, this did not differ across treatment arms.

Figure 20: Overview of the decision tree plus Markov model for migraine prevention

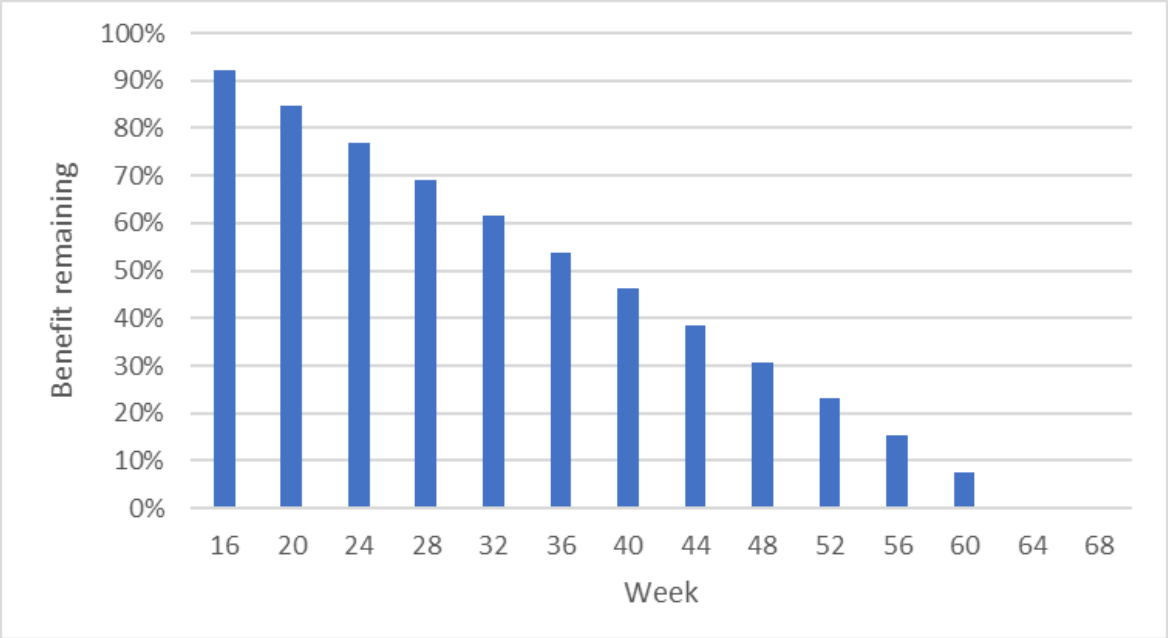


P: Post assessment period

At 12 weeks, response is determined and MMD predicted accordingly. In all future cycles patients who remain on treatment maintain this predicted distribution of MMD, which is aligned with prior NICE appraisals.[4,142,143] Non-responders discontinue treatment at 12 weeks but retain a proportion of their predicted MMD distribution for a specified duration. In previous NICE appraisals non-/ at 15 months (12 months after the initial assessment), so that any improvement in MMD among non-responders who immediately discontinue treatment persists for a period. We assume a gradual loss of benefit over a similar period. This attenuation is termed 'reversion to baseline' in the current model. In Figure 21 the proportion of change from baseline retained at each cycle up to month 16 assuming a full linear attenuation of effect after model week 12 is presented, as applied in the base case.

Note, an immediate reversion to baseline instantaneously after week 12 can be implemented (by specifying the per cycle reversion rate as 100%).

Figure 21: Reversion to baseline (off-treatment at 12 weeks)



Treatment responders remain on treatment beyond 12 weeks but may discontinue. The model does not specifically account for discontinuation due to adverse events (AEs) as these were infrequent and generally non-serious in BHV3000-305. Discontinuation estimates are applied based on KM analysis of all-cause discontinuation in the open-label extension of BHV3000-305.[214,215] Patients who discontinue over the longer term (i.e. after initially being assessed as responders), are assumed to immediately return to the baseline distribution of MMD.

B.3.2.2.2. P: Time horizon

Patients enter the model in the base case at approximately 40 years of age. The model supports time horizons of up to 40 years. In the base case the time horizon adopted is 20 years, given that migraine frequency tends to decline with older age.[19] In previous appraisals, ERGs have noted that a time horizon less than lifetime may not be sufficient to capture all relevant costs and outcomes associated with the intervention.[4,142,143] However, as noted in the submission for galcanezumab (where the manufacturer adopted a time horizon of 25 years) "migraine affects predominately women and the natural course of disease suggests that prevalence of migraine reduces significantly after menopause".[142] Given anticipated rates of discontinuation from treatment, and as there is no mortality or other prognostic implication of migraine prevention, this suggests a time horizon shorter than

lifetime may be appropriate, though as noted above a time horizon of up to 40 years is accommodated in the model.

B.3.2.2.3. P: Cycle length

A 28-day cycle length is maintained throughout the model. This reflects the schedule of MMD reporting in BHV3000-305.[216] Though longer cycle lengths could have been adopted over the longer term there appeared to be no material computational advantage in doing so. Given the short cycle length, half-cycle adjustment has not been applied.

B.3.2.2.4. P: Model perspective

The model adopts the perspective of the UK NHS and PSS, in line with the NICE reference case.[2]

B.3.2.2.5. P: Discount rate

Discount rates of 3.5% per year are applied to both costs and benefits, consistent with the NICE reference case.[273]

Features of the current model are compared with previous NICE appraisals of relevance in Table 71.

Table 71: Features of the rimegepant migraine prevention model

Factor	Previous appraisals			Current appraisal	
	Erenumab (TA682)	**Fremanezumab (TA631 [and TA764])**	**Galcanezumab (TA659)**	**Chosen values**	**Justification**
Model perspective	NHS/PSS	NHS/PSS	NHS/PSS	NHS/PSS	NICE reference case[273]
Model structure	Decision tree plus Markov model	Semi-Markov model	Semi-Markov model	Decision tree plus Markov model	This structure permits modelling of both responder status and MMD distribution, in line with published recommendations for the UK (Mahon et al.[296]) and prior NICE submissions in migraine prevention.[4,142,143]
Cycle length	12 weeks	4 weeks	Monthly (30 days)	4 weeks	Consistent with MMD assessment in Study BHV3000-305.[216]
Time horizon	10 years	Lifetime	Lifetime (25 years)	20 years	Based on ERG feedback to previous NICE appraisals.[4,142,143] Negligible proportion expected to remain on treatment beyond 20 years given the discontinuation rate (and no longer term effect of treatment).[19]
Long-term treatment effect	Maintained over time	Maintained over time	Maintained over time	Maintained over time	Consistent with prior NICE appraisals in migraine prevention.[4,142,143]
Discontinuation rate long term (beyond the assessment period)	2.38% per cycle risk based on open label data – all cause discontinuation	Based on data from open label long term study, discontinuation rate for all causes	[redacted]% per cycle for galcanezumab. Discontinuation rate for BSC is assumed to be zero – base: discontinuation due to AEs (Beta) – all cause discontinuation included in sensitivity analysis.	Annual probability of [redacted]% discontinuation ([redacted]% per cycle), based on Kaplan-Meier analysis of discontinuation data in the BHV3000-305 open label extension trial, all causes	Consistent with prior NICE appraisals in migraine prevention.[4,142,143]
Discontinuation rate over the assessment	Patients could discontinue due to	Not implemented	One off discontinuation probability. Patients	Not implemented	AE rates in the rimegepant prevention trial were low and

Factor	Previous appraisals			Current appraisal	
	Erenumab (TA682)	Fremanezumab (TA631 [and TA764])	Galcanezumab (TA659)	Chosen values	Justification
period due to AEs	treatment-specific AEs over the assessment period. Rates based on trial data.		who discontinue due to AE go to the off treatment.		were not considered in the model, consistent with prior TAs.[216] Furthermore, the AE rate is already embedded in the 20% long-term discontinuation rate
Stopping rule	Negative stopping rule at 3 months if there was no response at 3 months	Negative stopping rule at 3 months if there was no response at 3 months	Negative stopping rule at 3 months if there was no response at 3 months	Negative stopping rule at 3 months if there was no response at 3 months	Consistent with prior NICE appraisals in migraine prevention.[4,142,143]
Source of drug costs	BNF	BNF	BNF and database of prescription and generic drugs, clinical guidelines (MIMS)	BNF. No administration costs for mAbs or rimegepant.	Established source of drug costs within the NHS. Consistent with prior NICE appraisals in migraine prevention.[4,142,143]
Source of utilities	Patient-level MSQ mapped onto EQ-5D-3L utility scores	Patient-level MSQ mapped onto EQ-5D-3L utility scores	Patient-level MSQ mapped onto EQ-5D-3L utility scores	Patient-level MSQ mapped to EQ-5D-3L utility scores	Consistent with prior NICE appraisals in migraine prevention.[4,142,143]
Source of other costs	National Tariff, PSSRU 2016, NHWS, BNF	BNF, PSSRU, NHS reference costs	BNF, NHS Tariff and PSSRU	BNF, PSSRU, NHS schedule of costs	Source of HCRU costs align with most recent mAb TAs;[4,142,143] standard UK unit cost sources.
Resource use	NHWS	NHWS	Trial-specific data and Lipton et al 2018[291]	NHWS from erenumab appraisal	Consistent with prior NICE appraisals for erenumab (TA682)[143]
Health effects model	QALYs	QALYs	QALYs	QALYs	NICE reference case.[2]
Discount rate	3.5% per year	3.5% per year	3.5% per year	3.5% per year	NICE reference case.[2]
Half-cycle correction	Yes, for disease management and indirect costs, no for treatment costs	Not specified	No	No	Short cycle length, and consistent with prior NICE appraisals in migraine prevention.[4,142]

Abbreviations: AEs, adverse events; BNF, British national Formulary; BSC, best supportive care; EQ-5D (3L), EuorQol Five Dimension (three level); HCRU, healthcare resource use; mAb, monoclonal antibody; MIMS, Monthly Index of Medical Specialties; MMD, monthly migraine days; MSQ, Migraine Specific Questionnaire; NHS, National Health Service; NHWS, National Health and Wellness Survey; NICE, National Institute of Health and Care Excellence; PSSRU, Personal Social Services Research Unit; QALY(s), quality adjusted life year(s); TA, technology appraisal
References: Erenumab (TA682);[143] Fremanezumab (TA631 [and TA764]);[4] Galcanezumab (TA659)[142]

B.3.2.3. P: Prevention intervention technology and comparators

The intervention of interest in the economic analysis is rimegepant 75 mg EOD, a small molecule, orally administered CGRP antagonist. Rimegepant is positioned as an option for patients who have failed ≥3 conventional preventive therapies, consistent with where the three mAbs are currently used in the NHS clinical practice. Based on its relevance to NHS clinical practice, this is a narrower population than is indicated in the technology's marketing authorization, which does not specify a population refractory to ≥3 conventional therapies. The population modelled in the economic evaluation is aligned with the decision problem (Section B.1.1).

Currently, in NHS clinical practice, patients with migraine who fail ≥3 conventional therapies are eligible to receive one of three injectable mAb CGRP antagonists: erenumab, fremanezumab, or galcanezumab. The current analysis investigates the cost-effectiveness of rimegepant 75 mg EOD compared to each of these therapies. As noted in section B.1.3.3.2.P, BSC is not considered an appropriate comparator given that the three injectable mAbs are recommended by NICE for patients refractory to ≥3 conventional therapies.

To note, injectable onabotulinumtoxinA is not a relevant comparator in this economic evaluation, since this therapy is only indicated for patients with chronic migraine, and the regulatory label for rimegepant restricts its use to patients with episodic migraine. Therefore, onabotulinumtoxinA was not considered in the model. The availability of relevant comparators in UK clinical practice is discussed further in Section B.1.3.3.2.

B.3.3. P: Clinical parameters and variables in migraine prevention

The primary data source in the economic model is Study BHV3000-305 (prevention trial).[216] Efficacy of rimegepant relative to the mAb comparators was determined via NMA (Section B.2.9.P and Appendix D.8.P). The relevant NMA endpoint for the model is the odds ratio for ≥50% reduction from baseline in MMD at 12-weeks. Baseline data, response, and MMD distributions are modelled based on the following data, presented in Table 72.

Table 72: Summary of key parameters and sources informing the prevention model

Parameter	Source
Baseline patient characteristics and MMD distributions	Placebo and rimegepant arms of BHV3000-305
Treatment response, proportion achieving 50% reduction from baseline in MMD at 12 weeks	Rimegepant from BHV3000-305; erenumab, galcanezumab, fremanezumab – network meta-analysis described in Section B.2.9.P.

Parameter	Source
MMD distribution	Placebo and rimegepant arms of BHV3000-305
Treatment discontinuation	Study BHV3000-305 open label extension study. [214,215]
Mortality	UK lifetables, Office for National Statistics[279]

Abbreviations: MMD, monthly migraine day; UK, United Kingdom

B.3.3.1. P: Baseline patient characteristics

The baseline patient characteristics used in the model are from BHV3000-305 and are shown in Table 73.[216] The age and sex distribution is used to calculate background mortality based on UK life tables. Baseline MMD is taken from the efficacy evaluable population in BHV3000-305.[216] The MMD distribution is presented in Figure 22

Table 73: Baseline patient characteristics, migraine prevention

Characteristic	Mean
Age (years)	41
Sex (% female)	82.5
Baseline MMD (SD)	10.05 (3.08)

Abbreviations: MMD, monthly migraine days; SD, standard deviation
References: Croop 2021[216]

B.3.3.2. P: Treatment efficacy

In the model, treatment efficacy is assessed based on change from baseline MMD at 12 weeks. The model captured the distribution of patients across the frequency of MMD based on patient-level MMD data from study BHV3000-305 for rimegepant. MMD is assumed conditionally independent of treatment (i.e., is common across each of the four treatments given a common response status). MMD is modelled for each four-week period in the 12-week assessment period, with the week 8-12 period also accounting for response.

B.3.3.2.1. P: Response assessment at 12-weeks

Full details describing the conduct of the NMA have been reported in Section B.2.9.P and Appendix D: prevention (Section D.8.P). In summary, studies included in the NMA evidence synthesis were restricted to Phase 2/3 or Phase 3 RCTs on the interventions of interest (erenumab, fremanezumab, galcanezumab, and rimegepant), among episodic or mixed episodic and chronic study populations, with doses restricted to those recommended by NICE.

Probability of 12-week response was defined as the proportion of patients achieving a ≥50% reduction in baseline MMD. Efforts were made to align efficacy endpoint definitions across included trials as described in Section B.2.9.1.4.P.

Fixed- and random-effects models were conducted (with and without adjustments for baseline risk) and compared based on deviance information criterion (DIC). A Bayesian framework was used to fit all NMA models in accordance with The NICE Decision Support Unit (DSU) guidelines.[245] R (V3.6.1) and JAGS (V4.3.0) were used to conduct all analyses. A binomial likelihood model incorporating a logit link was used for the ≥50% reduction in baseline MMD outcome. The fixed-effects baseline risk adjusted model was selected as the best fitting model for this endpoint.

The probability of 50% MMD reduction at 12-week response in Study BHV3000-305 for placebo and rimegepant was 0.415 and 0.491 respectively (Table 74). The probability of response for comparator mAbs is estimated by application of odds ratios taken from the NMA (Table 75). The NMA estimated effects separately for fremanezumab 225 mg and 675 mg. These were similar, and the model adopts the 225 mg estimate (which is slightly more advantageous for fremanezumab).

Table 74: Probability of response at 12 weeks in BHV3000-305

	Response	Probability (95% CI)
Rimegepant	171 / 348	0.491 (0.439, 0.544)

Abbreviations: CI, confidence interval

Table 75: Odds ratios for response at 12 weeks and corresponding probabilities

	Fixed effects		Random effects	
	OR (95% CrI)	Probability response	OR (95% CrI)	Probability response
Rimegepant	[redacted]	[redacted]	[redacted]	[redacted]
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 225 mg	[redacted]	[redacted]	[redacted]	[redacted]
Galcanezumab 120 mg	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CrI, credible interval; OR, odds ratio

B.3.3.2.2. P: Distribution of MMD

P: Baseline MMD distribution:

The distribution of MMD at baseline can be based on either the observed (non-parametric) data or as a normal distribution fitted to the observed data (both arms) in Study BHV3000-305(mean 10.05, SD 3.08) (Figure 22).

Figure 22: Baseline MMD distribution

Abbreviations: MMD, monthly migraine days

P: MMD distribution over the assessment period

To estimate the distribution of MMD, count models were fit to the individual patient-level data from Study BHV3000-305 allowing to estimate the impact of key covariates. Analysis of the patient-level data allowed the proportion of patients experiencing a given MMD frequency to be captured by treatment group in BHV3000-305 and at different timepoints in the study, and according to response at 12-weeks. A number of statistical distributions including the zero-inflated negative binomial, beta-binomial, negative binomial, and Poisson were assessed. Full details of the statistical distribution selection are provided in Appendix N.

MMD is predicted by treatment for each 28-day cycle during the assessment period for cycle 1 (period week 0-4) and cycle 2 (period week 4-8) and according to response status for cycle 3 (week 9-12). The MMD models adjust for mean MMD at baseline.

Patient-level data were not available to fit equivalent distributions for the three comparators, and it was not feasible to run the NMA on the mean change from baseline on MMD by response status. Therefore, similar to previous NICE appraisals (erenumab [TA682][143] and fremanezumab [TA764][4]), it was assumed that the three mAbs were associated with the

same MMD distribution as rimegepant based on their responder status only, i.e. the difference in effectiveness between rimegepant and the comparators was modelled solely as difference in the proportion of patients achieving 50% MMD reduction.

Table 76: Predicted mean MMD

	Rim	Galcanezumab	erenumab	fremanezumab
Baseline	[redacted]*			
Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]
Week 12 non-response	[redacted]	[redacted]	[redacted]	[redacted]
Week 12 response	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: MMD, monthly migraine days; RIM, Rimegepant
Notes:
*Observed baseline MMD in Study BHV3000-305 prevention trial

P: MMD distribution after the assessment period

It was assumed that those on treatment maintain the improved number of MMD achieved when response is established at week 12, i.e. the distribution of MMD by responder status estimated at week 12 will be maintained over the full post-assessment period for rimegepant, erenumab, fremanezumab, and galcanezumab; this is aligned with the previous mAbs appraisals. This assumption is also supported by the results from the OLE of study BHV3000-305, where the efficacy was maintained over the long-term. (Figure 7)

Non-responders (at 12 weeks) revert to baseline MMD over 12 months after assessment.[4].

B.3.3.2.3. P: Discontinuation

Patients who remain on treatment following 12-week response assessment are subject to discontinuation of treatment over time. Consistent with prior NICE appraisals, reduction in MMD from baseline is conditional upon continuation of treatment.[4,142,143]

Patients may discontinue treatment either:

1. Due to lack of response at the end of the assessment period (response being defined as a reduction in MMD compared to baseline of at least 50%).
2. Due to a treatment discontinuation over the long-term.

Treatment discontinuation over the long-term is based on the OLE study for Study BHV3000-305.[214,215] Of the 185 rimegepant treated participants who achieved ≥50% response at 12 weeks (end of DBT period) and continued into the OLE study period, almost [redacted]% remained on treatment after one-year (Figure 23). On this basis, an annual rate of

[redacted]% discontinuation was estimated and applied to all treatment arms, in the absence of evidence for differing rates of discontinuation.

Figure 23: Kaplan Meier discontinuation curve for patients receiving rimegepant in Study BHV3000-305 OLE

Abbreviations: OLE, open-label extension

B.3.3.2.4. P: Adverse events

AEs have not been modelled. Given the small proportion of patients experiencing serious events (<2% regardless of treatment arm),[216] and their transient nature, it is expected that AEs have a limited impact on resource use, costs, and health related quality of life. This is a conservative assumption given the potential for injection site reactions, constipation and hypersensitivity reactions with mAbs.[165-168]

B.3.3.2.5. P: Mortality

Only all-cause mortality is considered in the model, which aligns with prior NICE TAs in migraine,[4,142,143] and is supported by a published meta-analysis, which found no association between migraine and all-cause mortality.[278] Age- and sex-specific UK life tables (2018-20) were applied.[279]

B.3.4. P: Measurement and valuation of health effects in migraine prevention

B.3.4.1. P: Health-related quality-of-life data from clinical trials

Health-related quality of life data were collected in Study BHV3000-305 using the disease-specific MSQv2.1. In both study arms, participants were assessed at baseline, and at completion of the DBT phase (week 12). Individual patient-level MSQv2.1 data were mapped to EQ-5D following the approach adopted in prior NICE appraisals.

B.3.4.2. P: Mapping

Patient-level MSQv2.1 domain values (role function restrictive [RFR], role function preventive [RFP], emotional function [EF]) from BHV3000-305 were mapped to EQ-5D-3L utilities using the mapping by statistical association algorithms by Gillard et al.[275] These algorithms have been validated and utilised in prior NICE TAs.[4,142,143] There were negligible missing MSQv2.1 data in BHV3000-305 therefore no adjustments were made in this regard.

B.3.4.3. P: Prevention health-related quality-of-life studies

An SLR to identify HRQoL studies was performed as part of the SLR described in Section B.3.1.P using the inclusion and exclusion criteria and search strategy defined in Appendix H: prevention. A total of 11 unique studies were identified that met eligibility criteria for the review and are described in detail in Appendix H: prevention. One study by Johnston et al. 2021,[280] mapped MSQv2 values to EQ-5D health state utilities, using data from an open-label safety study of rimegepant. This included a subgroup of patients with 9-14 MMD at baseline, who took rimegepant 75 mg EOD (prevention regimen) plus PRN, for 52-weeks.[280] The same mapping methodology used by Johnston et al. was employed using data from BHV3000-305 prevention trial, as described in Section B.3.4.2.P. Two studies reported EQ-5D derived directly from patients.[297,298] One is based on CM patients only and not relevant for this decision problem. The BECOME study included 2,419 patients with > 4 MMD, 41.6% suffered from CM, and had ≥1 prior preventive treatment failure, the reported mean EQ-5D was 0.76 (95% CI 0.75 – 0.77) as compared to the mapped raw average EQ-5D score of 0.61 (95% CI 0.59 – 0.62) from the BHV3000-305 at baseline.

B.3.4.4. P: Adverse reactions

Adverse reactions were not considered in the cost-effectiveness model of rimegepant. The clinical evidence for rimegepant showed SAE rates were very low and comparable to those of placebo.

B.3.4.5. P: Health-related quality-of-life data used in the cost-effectiveness analysis

Mapped utility values (MSQv2.1 to the EQ-5D-3L) from Study BHV3000-305 were applied in the base case, as this was the most aligned with the NICE reference case,[273] and is consistent with methods used in prior NICE TAs of migraine preventive therapies.[4,142,143] The MSQv2 (mapped to EQ-5D) captures the aspects of migraine that most impact patients' quality of life. It was developed to assess the long-term impact of migraine on patients, with respect to three key domains: limitations of usual activities, prevention of usual activities, and emotional impact.[281] .

The regression model for utility based on the mapped data at the end of Week 12 is shown in Table 77. This is based on MMD and treatment arm. The utility increment for treatment applies at all time points while patients remain on treatment.

Table 77 Regression models for mapped EQ-5D-3L utility

	Coef.	SE	p-value	95% confidence interval	
				lower	upper
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Coef., coefficient; EQ-5D (3L), EuroQol five dimension (three level); MMD, monthly migraine days; SE, standard error

A summary of utility values by MMD used in the economic model is presented in Table 78. Baseline estimates are reported for reference based on a separate regression but do not inform the model. Note these represent predicted utilities at the start of the model based on age at entry. These MMD specific utilities are then adjusted (multiplicatively) for age over the course of the model based on predicted UK norms per Ara and Brazier (2010):[299]

$$Ara\ \&\ Brazier: 0.950857 + 0.02121\ male - 0.000259\ age\ - 0.000033\ age\ squared$$

Table 78: Summary of utilities by monthly migraine day at model entry

MMD	Baseline	Best supportive care	Rimegepant
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]

MMD	Baseline	Best supportive care	Rimegepant
7	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]
23	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]

Abbreviations: MMD, monthly migraine days

The utility regression provides a [redacted]. This is comparable with committee preferences from previous mAb submissions' utility gains independent of MMD. We apply the estimate based on Study BHV3000-305 across all active therapies. Though there will be numerical differences between this estimate and those in previous submissions there is no robust basis for applying distinct utility advantages for individual therapies.

B.3.5. P: Cost and healthcare resource use identification, measurement and valuation in migraine prevention

For migraine, the primary direct medical cost is the price of treatment. Other background costs that were incorporated included GP visits, ED visits, and hospitalisations. Lipton et al. (2018)[291], NHWS (analysed by Vo et al. [2018])[277] have informed HCRU and cost inputs for prior mAb submissions to NICE (erenumab [TA682][143]). This submission adopts data from

the NHWS (analysed by Vo et al. [2018]), which includes data from Europe including the UK. Lipton et al. (2018) is not considered as the study does not contain data from the UK.

B.3.5.1. P: Prevention intervention and comparators' costs and resource use

The unit costs for comparators were sourced from the British National Formulary (BNF; Table 79).[274] These monthly costs are adjusted to 28-day cycles in the model (ratio 28: 365.25/12).

In addition, for the three mAb treatments, a single cost for training in self-administration is applied based on one hour of a practice nurse's time (as per prior mAb TAs [erenumab TA682; galcanezumab TA659; and fremanezumab [TA764][4,142,143]). As per the committee's preferred assumption in the fremanezumab appraisal (TA631/TA764),100% self-administration was thought to be unlikely, and subsequently 10% of patients require half an hour of nurse time, per cycle.

B.3.5.2. P: Modelling of treatment duration in prevention

Treatment duration is governed by 12-week response and subsequent discontinuation rates in responders as outlined above (Section B.3.3.2.3.P).

Table 79: Drug unit costs for prevention

Treatment	Dosing schedule	Dose strength		Cost per 28 day cycle			Source
		Initial dose	Ongoing dose	Initial cost	Ongoing cost	Administration cost	
Rimegepant	EOD	75 mg	75 mg	£280.00	£280.00		
Erenumab	Monthly	140 mg	140 mg	£386.50	£355.50	£2.10	BNF[274]
Fremanezumab	Monthly	225 mg	225 mg	£900.00	£414.00	£2.10	BNF[274]
Galcanezumab	Monthly	240 mg	120 mg	£450.00	£414.00	£2.10	BNF[274]

Abbreviations: BNF, British national Formulary; EOD, every other day; PAS, patient access scheme

B.3.5.3. P: Health-state unit costs and resource use

Three unique studies of health resource use related to migraine were identified in the prevention economic SLR, and are described in detail in Appendix I: prevention. None were considered to be practical inputs for the current economic evaluation. Instead, recent NICE TAs for the CGRP mAbs were reviewed to identify relevant sources for cost and HCRU inputs into the model (Table 71).[4,142,143]

HCRU conditional on MMD is informed by the National Health and Wellness Survey (NHWS). This data has been reported for a number of updates by Vo and others.[277] The study provides estimates of resource use from the major EU5 (France, Germany, Italy, Spain and the UK). The data relates to headache frequency rather than migraine, but has been adopted in previous submissions as an approximation for resource use by migraine frequency. In the base case analysis the estimates reported in the submission for erenumab (TA682)[143] were adopted, which appeared to be based on separate data from those reported in Vo et al (2018). Aspects of resource use covered include primary care usage, accident and emergency, hospitalisation, and specialist (neurological) consultations. Data provided in the submission for fremanezumab are similar (there are slight differences for hospitalisations over the range MMD 8-14), and is available as an alternative option within the model. A more recent publication by Doane also reported this cross-sectional data;[134] this is not contained as a separate option in the model, as it does not contain complete information needed for the economic model (e.g. no value reported for MMD=0).

In the current evaluation, unit costs are taken from the PSSRU Unit Costs of Health and Social Care (2021), NHS Schedule of Costs (2019/20) and the BNF (Table 80). Resource use and aggregate costs by MMD for the base case are presented in Table 81.[286,287].

Table 80: List of resource use and associated costs used in the prevention economic model

Resource	Unit costs (£)	Description	Source
GP visit	39.23	Based on cost per patient contact lasting 9.22 minutes	PSSRU[286]
Neurologist visit	192.24	Consultant led neurology visit (service code 400) unit cost	NHS schedule costs[287]
ED visit	188.07	HRG code VB08Z	NHS schedule costs[287]
Hospitalisation	643.28	Weighted average of HRG codes AA31C, AA31D, and AA31E	NHS schedule costs[287]
Nurse practitioner	42.00	One hour of working time for Band 5 nurse--	PSSRU[286]
Triptan use	0.19	1.3 sumatriptan tablet	BNF[274]

Abbreviations: BNF, British National Formulary; ED, emergency department; GP, general practitioner; HRG, healthcare resource group; NHS, National Health Service; PSSRU, Personal Social Services Research Unit

Table 81: Mean HCRU by MMD (National Health and Wellbeing Survey)

Migraine days	Mean resource use						Total HCRU cost (£)
	Physician visits	ED visits	Hospital stays	Nurse practitioner visits	Specialist consultation	Acute medication	
0	0.61	0.09	0.07	0.01	0.19	0.00	95.79
1	0.87	0.2	0.13	0.05	0.31	0.30	178.00
2	0.87	0.2	0.13	0.05	0.31	0.79	178.00
3	0.87	0.2	0.13	0.05	0.31	1.28	178.00
4	1.24	0.18	0.12	0.04	0.53	1.78	189.64
5	1.24	0.18	0.12	0.04	0.53	2.27	189.64
6	1.24	0.18	0.12	0.04	0.53	2.77	189.64
7	1.24	0.18	0.12	0.04	0.53	3.26	189.64
8	1.66	0.28	0.12	0.12	0.15	3.75	224g.34
9	1.66	0.28	0.12	0.12	0.15	4.25	224.34
10	1.66	0.28	0.12	0.12	0.15	4.74	224.34
11	1.66	0.28	0.12	0.12	0.15	5.24	224.34

Migraine days		Mean resource use					Total HCRU cost (£)
	Physician visits	ED visits	Hospital stays	Nurse practitioner visits	Specialist consultation	Acute medication	
12	1.66	0.28	0.12	0.12	0.15	5.73	224.34
13	1.66	0.28	0.12	0.12	0.15	6.22	224.34
14	1.66	0.28	0.12	0.12	0.15	6.72	224.34
15	1.76	0.35	0.16	0.22	0.38	7.21	296.05
16	1.76	0.35	0.16	0.22	0.38	7.71	296.05
17	1.76	0.35	0.16	0.22	0.38	8.20	296.05
18	1.76	0.35	0.16	0.22	0.38	8.69	296.05
19	1.76	0.35	0.16	0.22	0.38	9.19	296.05
20	1.76	0.35	0.16	0.22	0.38	9.68	296.05
21	1.76	0.35	0.16	0.22	0.38	10.18	296.05
22	1.76	0.35	0.16	0.22	0.38	10.67	296.05
23	1.76	0.35	0.16	0.22	0.38	11.61	296.05
24	1.76	0.35	0.16	0.22	0.38	11.66	296.05
25	1.76	0.35	0.16	0.22	0.38	12.15	296.05
26	1.76	0.35	0.16	0.22	0.38	12.65	296.05
27	1.76	0.35	0.16	0.22	0.38	13.14	296.05
28	1.76	0.35	0.16	0.22	0.38	16.33	296.05

Abbreviations: ED, emergency department; HCRU, healthcare resource use; MMD, monthly migraine days; NHWS, National Health and Wellbeing Survey;

B.3.5.4. P: Adverse reaction unit costs and resource use prevention

As noted above AEs are not considered in the model.

B.3.5.5. P: Miscellaneous unit costs and resource use prevention

There are no miscellaneous costs included in the model.

B.3.6. P: Summary of base-case analysis inputs and assumptions in migraine prevention

B.3.6.1. P: Summary of base-case analysis inputs for prevention in migraine prevention

Table 82 presents a summary of the key variables applied in the economic model in migraine prevention.

Table 82 Summary of variables applied in the economic model in migraine prevention

Area	Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty: values used in sensitivity analyses	Reference to section in submission
General	Patient population	Adults with episodic migraine who have failed three oral preventive treatments (e.g. topiramate, propranolol, amitriptyline). Age 41 Female 82.5%	Age OWSA: 18-65 Female OWSA: 60% - 100%	B.3.2.1.P
	Comparators	Erenumab Fremanezumab Galcanezumab	n/a	B.3.2.3.P
	Time horizon	20 years	Scenario: 5 , 40	B.3.2.2.2.P
	Model cycle length	4 weeks (28 days) throughout model	n/a	B.3.2.2.3.P
	Discount rate	3.5% per year	OWSA: 1.5%	B.3.2.2.5.P
Clinical	Baseline MMD	Normal distribution applied to Study BHV3000-305 baseline	Scenario: non-parametric BHV3000-305 baseline	B.3.3.1.P
	12-week response	Odds ratios from NMA (Table 75) applied to observed probability (0.51) for rimegepant in Study BHV3000-305 (Table 74)	OWSA: 0.44 – 0.54 PSA: Sampled from regression for response in BHV3000-305 Odds ratios for mAbs response. OWSA: 95% credible intervals for individual mAbs.	B.3.3.2.P

Area	Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty: values used in sensitivity analyses	Reference to section in submission
			Erenumab 1.177 (0.872, 1.618) Galcanezumab 1.401 (1.043, 1.894) Fremanezumab 1.293 (0.931, 1.845) PSA: Individually sampled from distributions for log odds ratios.	
	Post baseline MMD distribution	Zero-inflated negative binomial	OWSA/PSA; Uncertainty as characterised by regression estimates. Scenario: Beta-binomial, Negative binomial, and Poisson distributions	B.3.3.2.P
	Post-assessment reversion to baseline in non-responders	12 months (i.e. 15 months from baseline)	n/a	B.3.3.2.P
	Discontinuation	23% per annum (1.99% per cycle)	OWSA: 17.2% - 29.3% p.a. PSA: Beta (42.55, 142.45)	B.3.3.2.3.P
Utilities	EQ-5D utility based on MMD (0-28)	See Table 77 and Table 78.	OWSA/PSA: Uncertainty as characterised by regression estimates. intercept 0.766 (0.747, 0.785) mmd -0.13 (-0.015, -0.11) treatment 0.022 (0.003, 0.041)	B.3.4.P
Drug acquisition costs	List prices	See Table 79	n/a	B.3.5.1.P
HCRU	Resource use based on MMD	NHWS See Table 80	OWSA: 95% confidence interval for gamma distribution – s.e. 20% of mean. PSA: gamma distribution with shared random point on distribution across MMD.	B.3.5.3.P
Unit Costs	Unit costs applied to HCRU	See Table 80	Assumed standard error (10% of mean)	B.3.5.3.P

Abbreviations: EQ-5D (3L), EuroQoL five dimension (three level); HCRU, healthcare resource use; MMD, monthly migraine days; NA, not applicable; NHWS, National health and Wellbeing Survey

B.3.6.2. P: Assumptions in migraine prevention

Table 83 presents a list of the main parameters and assumptions used in the economic analysis in migraine prevention.

Table 83: Key assumptions in the economic model in migraine prevention

Parameter	Base-case assumption	Justification
MMD at baseline	Distributed as a normal distribution based on the observed mean and standard deviation in BHV3000-305	This reflects the MMD at baseline for the key clinical study for rimegepant.
Model cycle length	4-week cycle lengths are adopted throughout the model.	This is consistent with evaluation periods in BHV3000-305, and aligns with 12-week assessment while allowing for differences during this period to be reflected in the MMD count model.
Model time horizon	20 years	Given 12-week non-responders and discontinuation rate only a negligible proportion of patients would be modelled to continue on any treatment beyond 20 years. Moreover, migraine frequency may naturally decline with age, and no impact of treatment is modelled to give rise to subsequent effects on costs, survival, or health related quality of life that would require a lifetime horizon.
MMD distributions	The MMD distributions of responders and non-responders for rimegepant are derived from the study BHV3000-305. It is assumed that responder and non-responders to other comparators have the same MMD distribution. The relative treatment effectiveness of rimegepant compared to the mAbs is accounted for through responder rate.	As patient-level data from the mAbs are not available to produce their individual MMD distribution of responders and non-responders. Similar assumptions were adopted for the previous mAbs TAs.
12-week response	Modelled as achievement of ≥50% improvement in MMD compared to baseline for rimegepant (efficacy evaluable population in BHV3000-305). Odds ratios derived from a NMA are applied to generate response rate for the mAbs comparators. For fremanezumab the odds ratio for the 225mg monthly dose was adopted, though an alternative quarterly estimate is provided by the NMA.	The probabilities for achieving response were derived from an NMA, which was conducted in accordance with the NICE DSU guidelines.[245] The odds ratio for fremanezumab 225mg monthly and 675mg quarterly were very similar. The former dose is more frequently prescribed and its estimate numerically favours fremanezumab. Monthly dosing also allows consistency of dosing across the mAbs in the model.

Parameter	Base-case assumption	Justification
Response assessment / stopping rule	Patients on treatment who are assessed as having responded to treatment at 12 weeks continue on treatment. 12-week non-responders cease treatment immediately.	This is consistent with UK clinical practice and assessment based stopping rule applied in previous NICE TAs[4,142,143].
MMD non-responders	It is assumed that non-responders at the assessment period will discontinue, with a reversion to baseline MMD over a period up to one year from assessment.	Some retention of MMD improvement in non-responders is consistent with prior NICE TAs.[4,142,143] The gradual reversion to baseline strikes a balance between assuming immediate full loss of benefit
MMD on treatment	It is assumed that patients who achieved ≥ 50% MMD reduction and continue on treatment maintain the reduction in MMDs achieved in the assessment period.	Maintenance of MMD reduction over the long-term is supported by open label extension studies for rimegepant and mAbs, and has been the assumption adopted in previous NICE appraisalsIndividual patient-level data from mAb comparators were not available with which to model treatment specific MMD distributions accounting for 12-week response. Similar assumptions have been adopted in previous mAb appraisals.
Discontinuation	A common [redacted]% annual probability of discontinuation is applied for all treatments.	This assumption is based on the Kaplan-Meier estimate of maintenance of treatment in 12-week responders at 12 months post assessment in the open label extension study of BHV3000-305. In the absence of comparative evidence for rates for different treatments this assumption is applied across all arms of the model.
MMD after therapy discontinuation	In the longer term there is a reversion to baseline MMD distribution immediately after discontinuation.	This is consistent with prior NICE TAs.[4,142,143]
Mortality	Hazards for mortality are based solely on ONS UK life table mortality rates; no additional migraine specific mortality is applied and there is no effect of treatment on mortality.	This aligns with prior NICE TAs in migraine prevention,[4,142,143] and is supported by a published meta-analysis, which found no association between migraine and all-cause mortality.[278]
Costs & resource use	Acquisition costs for treatments are based on list prices taken from the British National Formulary. Estimated based on MMD frequency. Initial training and ongoing administration costs assumed (for a proportion of patients) treated with mAbs. No training or administration cost is assumed to be required for treatment with rimegepant Resource use conditional on MMD is based on the NHWS data. No additional resource use for patients managed with best supportive care following non-response or discontinuation is assumed beyond that	Training and administration costs assigned to mAbs are consistent with previous NICE appraisal assumptions and reflect requirements for administration of these therapies, which oral rimegepant does not require. The approach to MMD related resource use is in line with previous literature and NICE appraisals. Mahon et al. 2020,[296] Prior NICE TAs[4,142,143] NHWS includes EU5 data including from the UK.

Parameter	Base-case assumption	Justification
	owing to higher rates of MMD. The NHWS based data adopted in the base case are as reported in the erenumab NICE submission (there are minor differences depending upon source), with migraine specific medication use based on the data reported for the fremanezumab submission.	
Health related quality of life (utilities)	Utility estimates are based on Estimated based on BHV3000-305 MVQ2.1 mapped to EQ-5D using Gillard et al's mapping algorithm. Regression analysis accounted the effect of increasing MMD and an independent effect of rimegepant treatment. The resulting utility estimates for MMD and being on-treatment were applied across all treatment arms in the model.	As in prior NICE TAs[4,142,143] health related quality of life is assumed to improve with declining MMD. Previous appraisals have also recognised an independent favourable effect of mAbs in regression analyses of EQ-5D data. Analysis of the mapped MVQ2.1 to EQ-5D found a similar relationship between MMD and utility and also identified an effect of rimegepant on utility independent of that due to MMD reduction. This effect was comparable to that estimated for previous appraisals of mAbs and in the absence of comparative evidence on these independent effects of treatments the estimated rimegepant utility effects is applied for all treatments arms while people remain on treatment, irrespective of MMD. The algorithm employed in the analysis is a validated approach to mapping MVQ2.1 and has been employed in previous NICE appraisals.

Abbreviations: AIC, Akaike Information Criterion; mAb, monocloncal antibodies; MMD, monthly migraine days; NICE, National Institute for Health and Care Excellence; ONS, Office for National Statistics; TA, technology appraisal; UK, United Kingdom

B.3.7. P: Base-case results in preventive treatment of episodic migraine

The results of the model are presented for rimegepant versus erenumab, fremanezumab, and galcanezumab based on list price, there are confidential PAS discounts for mAbs, so the results may be different based on the magnitude of the discount. These results reflect the positioning of rimegepant as an option for patients who have failed ≥3 conventional preventive therapies, and eligible for the three mAbs currently used in the NHS clinical practice.

B.3.7.1. P: Base-case incremental cost-effectiveness analysis results in preventive treatment of episodic migraine

The results of the base case analysis based on list price of rimegepant, and all the comparators are presented in Table 84. The results of this analysis show that rimegepant had the lowest cost at £ 47,860 compared to other mAbs, but also resulted in slightly lower QALYs (0,018 – 0.036). With a cost-effectiveness threshold of £30,000, these results indicate rimegepant is cost-effective versus all comparators.

Table 84: Base-case results prevention

	Total		Incremental		ICER (£/QALY)	ICER incremental (£/QALY)	NHB rimgepant vs mABs (QALY)[a]
Technologies	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**			
Galcanezumab	53,090	9.073	5,230	0.036	144,182	144,295	0.138
Fremanezumab	52,331	9.065	4,471	0.028	161,132	Dominated	0.121
Erenumab	50,397	9.055	2,538	0.018	144,062	144,062	0.067
Rimegepant	47,860	9.037					

Abbreviations: Dominated, strictly or extendedly dominated; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years
Notes:
[a]NHB at £30,000 per QALY (Rimegepant vs mAbs)

Table 85: Cost breakdown

Technologies	Treatment cost (£)	Health care cost (£)	Total cost (£)
Galcanezumab	12,443	40,647	53,090
Fremanezumab	11,628	40,703	52,331
Erenumab	9,628	40,769	50,397
Rimegepant	6,975	40,885	47,860

B.3.8. P: Sensitivity analyses in migraine prevention

B.3.8.1. P: Probabilistic sensitivity analysis in migraine prevention

The impact of the joint uncertainty around the key parameters of the model was assessed through a probabilistic analysis with 1,000 iterations. The values of the inputs were determined by random variation with statistical distributions described in Appendix O.

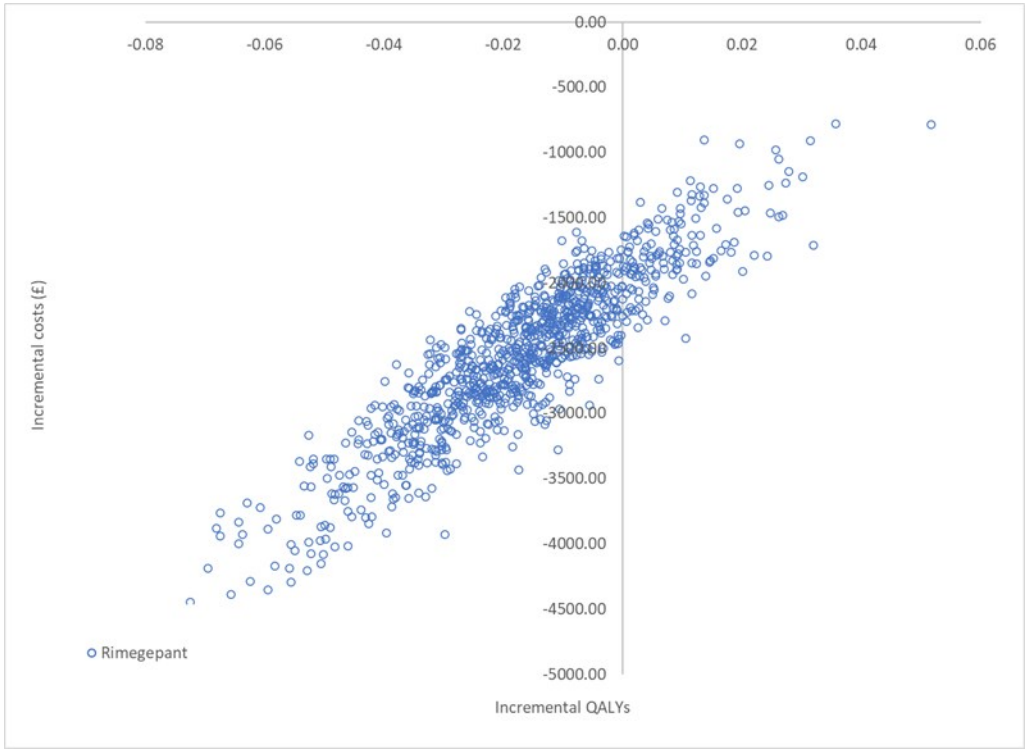
Results from probabilistic analysis in migraine prevention are provided in Table 86. The probabilistic results are similar to those obtained in the deterministic base case analysis. The scatter plots (cost-utility planes) of incremental cost versus incremental QALYs comparing rimegepant versus each of the comparators are presented in Figure 24, Figure 25, and Figure 26.

Table 86: Probabilistic base-case results (migraine prevention)

	Total		Incremental		ICER (£/QALY)	ICER incremental (£/QALY)	NHB rimegepant vs mABs (QALY)[a]
Technologies	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**			
Galcanezumab	53,145	9.076	5,270	0.036	146,088	146,088	0.140
Fremanezumab	52,384	9.068	4,508	0.027	164,614	Dominated	0.123
Erenumab	50,426	9.057	2,550	0.017	149,456	Dominated	0.068
Rimegepant	47,876	9.040					

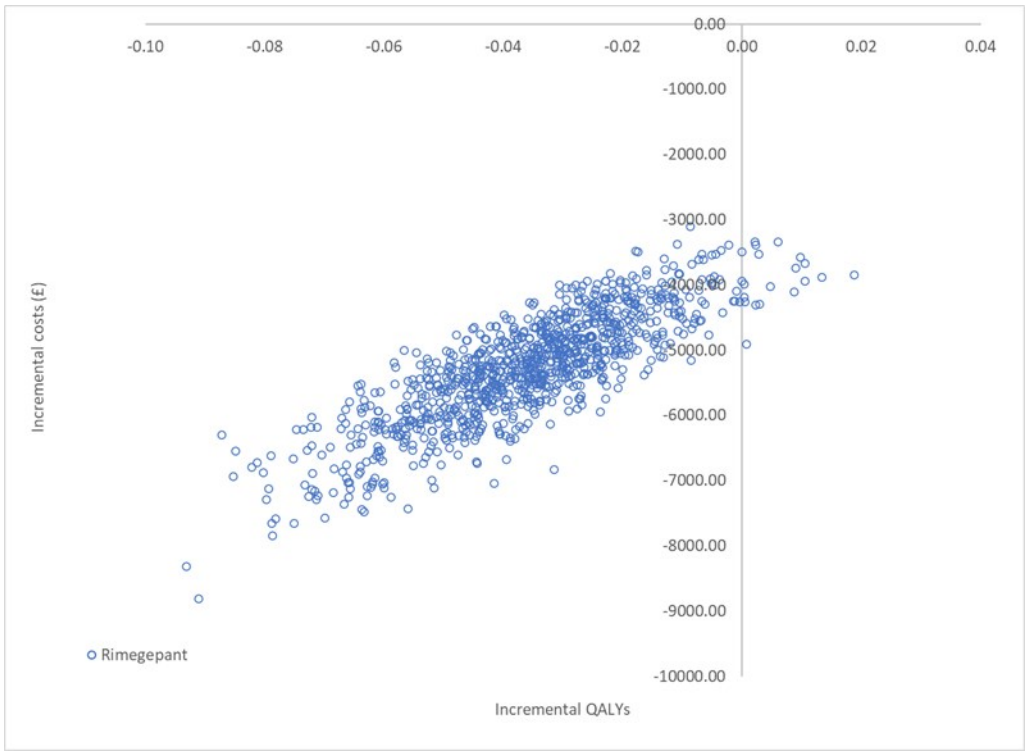
Abbreviations: Dominated, strictly or extendedly dominated; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years
Notes:
[a]NHB at £30,000 per QALY (Rimegepant vs mAbs)

Figure 24: Probabilistic cost-utility plane rimegepant vs erenumab



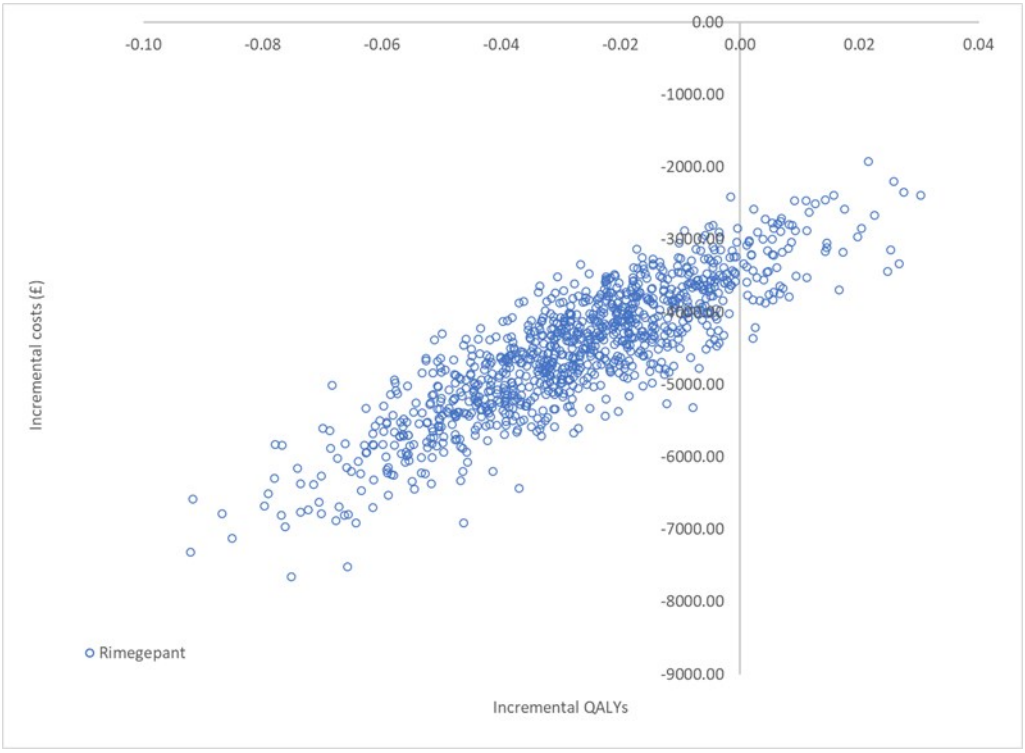
Abbreviations: QALYs, quality-adjusted life years

Figure 25: Probabilistic cost-utility plane rimegepant vs galcanezumab



Abbreviations: QALYs, quality-adjusted life years

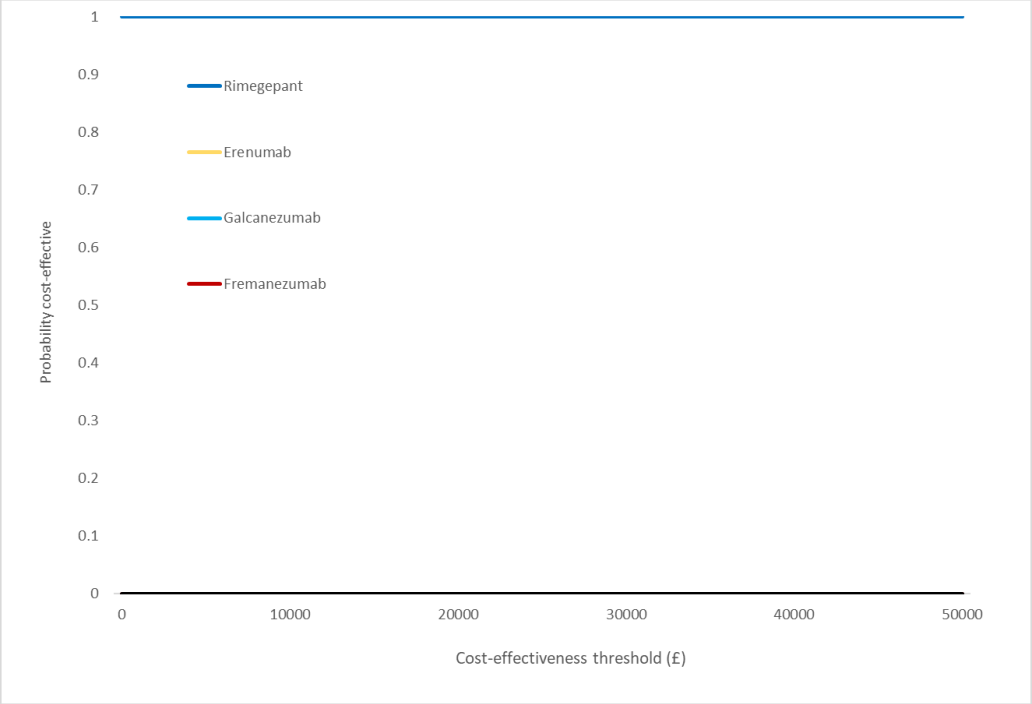
Figure 26: Probabilistic cost-utility plane rimegepant vs fremanezumab



Abbreviations: QALYs, quality-adjusted life years

The CEAC, showing the probability of being cost-effective at different cost-effectiveness thresholds is presented in Figure 27. At list price, rimegepant has a 100% probability of cost-effectiveness versus the three mAbs.

Figure 27: Cost-effectiveness acceptability curves (migraine prevention)



B.3.8.2. P: Deterministic sensitivity analysis in migraine prevention

Sensitivity analysis replaced the base case value with lower and upper bounds for relevant parameters and the ten most influential are shown below in the pairwise analysis comparing rimegepant with galcanezumab. Galcanezumab was selected as the comparator on the basis of it having the highest QALY gain among the three mAbs; similar patterns are expected across the two other comparators**.** Parameters entered in the analysis included those related to patient age and sex, discounting, rate of reversion to baseline MMD, EQ-5D utility, probability of response, treatment effects in MMD distribution, resource use by MMD, and unit costs of healthcare (Table 87). Resource use by MMD adopted the lower and upper bounds across the spectrum of MMD (Table 87 indicates the values only for MMD of zero), based on a 20% of mean standard error, and unit costs were assigned a nominal 10% standard error. Time horizon is not included in the analysis but is included as a separate scenario analysis (Section B.3.8.3.P).

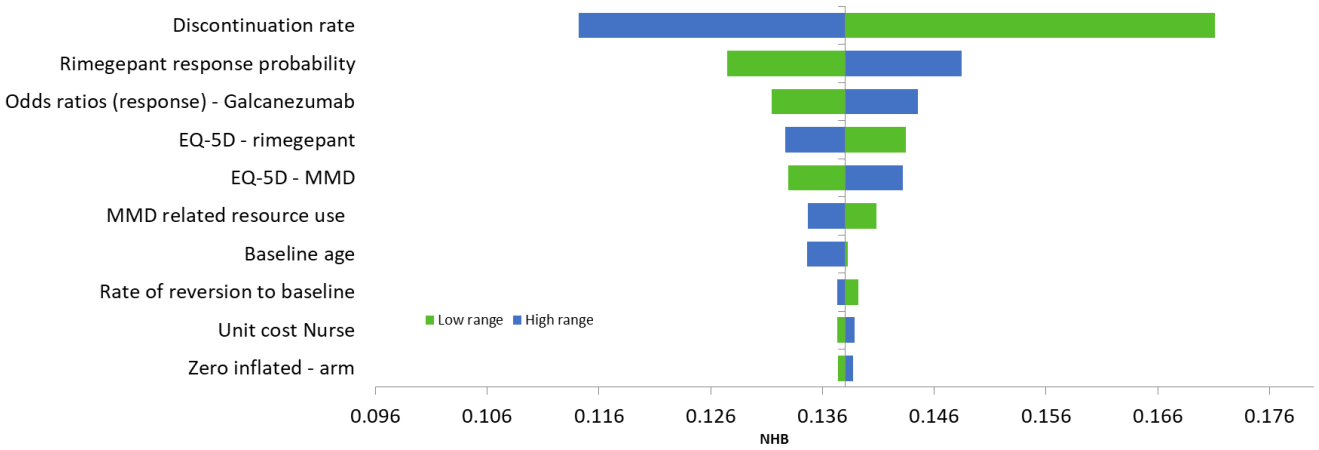
Table 87: Ranges for most influential parameters for rimegepant versus galcanezumab (migraine prevention)

Parameter (basecase, lower, upper)	NHB (QALY)[a]		
	Lower parameter value	Upper parameter value	Difference
Discontinuation rate (0.23, 0.17, 0.29)	0.171	0.114	0.057
Rimegepant response probability (0.491, 0.439, 0.544)	0.127	0.148	0.021
Odds ratios (response) – galcanezumab (1.401, 1.043, 1.894)	0.131	0.145	0.013
EQ-5D - rimegepant (0.022, 0.003, 0.041)	0.143	0.133	0.011
EQ-5D - MMD (-0.013, -0.015, -0.011)	0.133	0.143	0.010
MMD related resource use (95.79, 61.99, 136.82)	0.141	0.135	0.006
Baseline age (41, 18, 65)	0.138	0.135	0.004
Rate of reversion to baseline (0.077, 0.011, 0.2)	0.139	0.137	0.002
Unit cost – nurse, per hour (£42, £34, £51)	0.137	0.139	0.001
Zero inflated - arm (-0.104, -0.168, -0.04)	0.137	0.139	0.001

Abbreviations: EQ-5D , EuroQol five dimension; MMD, monthly migraine day(s);
Notes: [a]NHB at £30,000 per QALY (Rimegepant vs mAbs)

As shown in Figure 28 the most influential parameters for this pairwise comparison included discontinuation, response, and utility estimates. Overall, however, the analysis was relatively insensitive to the bounds of these parameters.

Figure 28: Tornado plot for rimegepant versus galcanezumab (migraine prevention)



Abbreviations: EQ-5D , EuroQol five dimension; MMD, monthly migraine day(s)

B.3.8.3. P: Scenario analysis in migraine prevention

Several alternative scenario analyses assess the impact of certain assumptions or model settings on the analyses of rimegepant versus each comparator. The assumptions and settings considered and the resulting pairwise ICERs and NHB are provided in Table 88.

Table 88: Pairwise ICERs and NHB (rimegepant vs mAbs) for scenario analyses

Scenario number	Scenario description	Erenumab		Galcanezumab		Fremanezumab	
		ICER	NHB[1]	ICER	NHB[1]	ICER	NHB[1]
	Base Case	144,062	0.067	144,182	0.138	161,132	0.121
1	Time horizon set to 5 years	147,577	0.053	150,357	0.112	164,494	0.096
2	Time horizon set to 40 years	144,058	0.067	144,155	0.138	161,132	0.122
3	Discounting - 1.5% for costs & outcomes	143,328	0.071	142,941	0.145	160,420	0.128
4	MMD baseline – normal distribution for 305 baseline MMD	150,868	0.068	150,994	0.140	168,717	0.123
5	MMD distribution - Beta-binomial	149,780	0.068	149,904	0.140	167,426	0.123
6	MMD distribution - Negative binomial	143,881	0.067	144,001	0.139	160,859	0.122
7	MMD distribution - Poisson	144,769	0.067	144,889	0.139	161,812	0.122
8	MMD distribution - Non-parametric	144,853	0.067	144,974	0.138	162,025	0.121
9	OR response – random effects NMA	133,443	0.067	140,515	0.138	133,240	0.123
10	OR response - All equal to rimegepant	Rimegepant dominant	0.067	Rimegepant dominant	0.131	Rimegepant dominant	0.116
11	Reversion rate (per cycle) – 100% (i.e. immediate full reversion to baseline)	140,357	0.066	140,474	0.137	157,008	0.120

Abbreviations: BSC, best supportive care; HCRU, healthcare resource use; ICER, incremental cost-effectiveness ratio; MMD, monthly migraine day(s); NHWS, national health and Wellbeing Survey; NMA, network meta-analysis; NMB, net monetary benefit; OR, odds ratio

[1]:NHB at £30,000 per QALY (Rimegepant vs mAbs)

B.3.8.4. P: Summary of sensitivity analyses results in migraine prevention

Probabilistic analyses resulted in scatter plots on the cost-utility plane that suggested broadly similar distributions of QALY gains for each active treatment option though with discernible differences in terms of total costs driven by differences in list price acquisition costs. As in the deterministic analysis, mean QALY gains for mAbs are modelled to be associated with substantial additional costs, with ICERs exceeding £140,000 per QALY versus rimegepant. Rimegepant had the higher probability of being cost-effective, and no other therapy featured on the CEAC.

As shown in Table 88 the comparison of rimegepant with galcanezumab the analysis was relatively insensitive to alternative parameter values. Note that the positive net benefit for rimegepant versus active comparators is due to rimegepant lying in the south-west quadrant of the cost-effectiveness plane versus each of these comparators (i.e. the ICERs are the cost per QALY for the relevant comparator versus rimegepant). At list prices rimegepant therefore iscost-effective under a range of scenarios versus active comparators.

B.3.9. P: Subgroup analysis in migraine prevention

No subgroup analyses were performed.

B.3.10. P: Validation in migraine prevention

B.3.10.1. P: Validation of cost-effectiveness analysis in migraine prevention

The design of the economic model is comparable with a number of previous evaluations for the prevention of episodic migraine. The fit of key model regression equations was assessed by comparison of predicted outputs with those observed in Study BHV3000-305.

Extensive technical validation was undertaken by a third party. This involved a detailed review of programming and extreme value testing. This was primarily done to ensure accuracy in calculations and programming logic. The technical validation of the model included review of implementation and typing errors, validation of the logical structure of the model, expressions, and sequences of calculations. Further, extreme value testing has been performed to investigate and ensure robustness of model behaviours for wide range of input parameter values.

B.3.10.2. P: External expert validation in migraine prevention

Discussing with external experts supported following precedent set in prior mAbs appraisals. Unless the information is redacted, the current model structure and assumptions are aligned with the NICE committee's preferred assumptions from the previous NICE technology appraisal for erenumab, galcanezumab, and fremanezumab.

B.3.11. P: Interpretation and conclusions of economic evidence in migraine prevention

B.3.11.1. P: Generalisability of the results to clinical practice in England and relevance to all patients as identified in the decision problem in migraine prevention

The patient population in the prevention economic evaluation may be considered narrower than the marketing authorisation for rimegepant, however the population in the economic evaluation is consistent with the proposed place in therapy for rimegepant in the prevention setting described in the decision problem and at a position in the treatment pathway where the three mAbs are currently used in the NHS clinical practice.

The approach taken in this submission of using NMA to inform the relative treatment effects between rimegepant and the three mAbs in the preventive treatment of episodic migraine, is associated with acknowledged limitations due to inclusion of mixed EM/CM study populations, whilst there were limitations to this methodology it was considered the best available approach for estimating the comparative effectiveness between these treatment options based on the available data. [redacted].

B.3.11.2. P: Strength and weaknesses of the evaluation in migraine prevention

The strengths of this economic evaluation include that the model structure and assumptions are largely based on three recent NICE appraisals assessing the same patient population. Similar to those appraisals, key clinically meaningful efficacy measures such as the proportion of patient achieving ≥ 50% was used to inform the current model and therefore gives confidence that the key clinically relevant parameters have been modelled in this analysis.

This analysis is based on Study BHV3000-305 a high-quality RCT. Estimates of health-related quality of life based on analysis of mapped MSQv2.1 to EQ-5D provided evidence of utility gains with lower MMD and a benefit associated with treatment independent of MMD reduction. This is consistent with previous analyses of EQ-5D in migraine prevention. Utility gains ultimately accrue from modelled reductions in MMD.

MMD gains for on-treatment responders are applied until patients discontinuation. However, this assumption is supported by open label extension studies for rimegepant and mAbs, and has been adopted in previous NICE appraisals. An annual rate was estimated based on open label follow up of BHV3000-305, and sensitivity analysis suggests the model is relatively insensitive to uncertainty around this estimate.

B.3.11.3. P: Conclusions in migraine prevention

This analysis assesses the cost-effectiveness of rimegepant versus erenumab, fremanezumab, and galcanezumab in the preventive treatment of episodic migraine. As shown from the NMA results, rimegepant is not substantially different in key efficacy outcomes compared to the three mAbs. The results of this analysis show that while rimegepant resulted in slightly less QALYs, it had the lowest cost compared to other mAbs leading to a positive NHB, demonstrating the potential for rimegepant to represent a cost-effective use of NHS resources for the prevention of episodic migraine.

B.4. References

1. Pfizer. Data on File: Advisory Board Meeting on Rimegepant. 2022.

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

3. Leroux E, Buchanan A, Lombard L, Loo LS, Bridge D, Rousseau B, et al. Evaluation of Patients with Insufficient Efficacy and/or Tolerability to Triptans for the Acute Treatment of Migraine: A Systematic Literature Review. Adv Ther. 2020;37(12):4765-96.

4. National Institute for Health and Clinical Excellence. Fremanezumab for preventing migraine Technology appraisal guidance (TA764) Manchester: NICE; 2022 [updated 3 June 2020. Available from: https://www.nice.org.uk/guidance/ta764 (last accessed April 2022)

5. National Institute for Health and Clinical Excellence. Botulinum toxin type A for the prevention of headaches in adults with chronic migraine (TA260) Manchester: NICE; 2012 [updated January 2016. Available from: https://www.nice.org.uk/guidance/ta260 (last accessed April 2022)

6. Pfizer. Vydura (rimegepant oro-dispersible tablets [ODT]): Summary of Product Characteristics. 2022.

7. Goadsby PJ. Pathophysiology of migraine. Neurol Clin. 2009;27(2):335-60.

8. Doods H, Arndt K, Rudolf K, Just S. CGRP antagonists: unravelling the role of CGRP in migraine. Trends in pharmacological sciences. 2007;28(11):580-7.

9. Cutrer F. Pathophysiology, clinical manifestations, and diagnosis of migraine in adults 2019 [Available from: https://www.uptodate.com/contents/pathophysiology-clinical-manifestations-and-diagnosis-of-migraine-in-adults (last accessed July 27)

10. Monteith TS. Chronic Migraine: Epidemiology, Mechanisms, and Treatment. Chronic Headache: Springer; 2019. p. 37-62.

11. American Headache Society. Pathophysiology of Migraine. 2018.

12. Edvinsson L, Haanes KA, Warfvinge K, Krause DN. CGRP as the target of new migraine therapies - successful translation from bench to clinic. Nature reviews Neurology. 2018;14(6):338-50.

13. European Medicines Agency (EMA). Assessment Report: Vydeura (International Non-proprietary name: rimegepant) Procedure No. EMEA/H/C/005725/0000 Amsterdam (The Netherlands): EMA; 2022 [Available from: https://www.ema.europa.eu/en/documents/assessment-report/vydura-epar-public-assessment-report_en.pdf (last accessed May 2022)

14. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1-211.

15. Mayans L, Walling A. Acute Migraine Headache: Treatment Strategies. Am Fam Physician. 2018;97(4):243-51.

16. Ailani J, Burch RC, Robbins MS, Board of Directors of the American Headache S. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. Headache. 2021;61(7):1021-39.

17. Goadsby P, Holland P, Martins-Oliveira M, et al. Pathophysiology of Migraine: A Disorder of Sensory Processing. Physiol Rev. 2017;97(2):553-622.

18. Krause DN, Warfvinge K, Haanes KA, Edvinsson L. Hormonal influences in migraine—interactions of oestrogen, oxytocin and CGRP. Nature Reviews Neurology. 2021;17(10):621-33.

19. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology. 2007;68(5):343-9.

20. Arnold M. Headache classification committee of the international headache society (IHS) the international classification of headache disorders. Cephalalgia. 2018;38(1):1-211.

21. Stanford Health Care. Diagnosing Headaches 2016 [Available from: https://stanfordhealthcare.org/medical-conditions/brain-and-nerves/headache/diagnosis.html (last accessed May 2022)

22. Demarquay G, Mawet J, Guégan-Massardier E, de Gaalon S, Donnet A, Giraud P, et al. Revised guidelines of the French headache society for the diagnosis and management of migraine in adults. Part 3: Non-pharmacological treatment. Rev Neurol (Paris). 2021;177(7):753-9.

23. Lipton R. Chronic Migraine, Classification, Differential Diagnosis, and Epidemiology. Headache. 2011;51:77-83.

24. Goadsby PJ, Evers S. International Classification of Headache Disorders - ICHD-4 alpha. Cephalalgia. 2020;40(9):887-8.

25. Lucchesi C, Baldacci F, Cafalli M, et al. Fatigue, sleep-wake pattern, depressive and anxiety symptoms and body-mass index: analysis in a sample of episodic and chronic migraine patients. Neurol Sci. 2016;37:987-9.

26. Ruscheweyh R, Muller M, Blum B, et al. Correlation of Headache Frequency and Psychosocial Impairment in Migraine: A Cross-Sectional Study. Headache. 2013;54(5):861-71.

27. Serrano D, Lipton R, Scher A, et al. Fluctuations in episodic and chronic migraine status over the course of 1 year: implications for diagnosis, treatment and clinical trial design. The Journal of Headache and Pain. 2017;18:101.

28. Dahlöf CG, Johansson M, Casserstedt S, Motallebzadeh T. The course of frequent episodic migraine in a large headache clinic population: A 12-year retrospective follow-up study. Headache: The Journal of Head and Face Pain. 2009;49(8):1144-52.

29. Lipton R. Tracing transformation: Chronic migraine classification, progression, and epidemiology. Neurology. 2009;72:S3-S7.

30. WebMD. Timeline of a Migraine 2020 [Available from: https://www.webmd.com/migraines-headaches/timeline-

migraine#:~:text=The%20last%20phase%20is%20the,hours%20after%20your%20migraine%20ends. (last accessed Aug 10)

31. American Migraine Foundation. Understanding Migraine Progression Can Help You Anticipate & Manage Your Symptoms 2018 [Available from: https://americanmigrainefoundation.org/resource-library/timeline-migraine-attack/ (last accessed Aug 10)

32. Reuter U. GBD 2016: still no improvement in the burden of migraine. The Lancet Neurology. 2018;17(11):929-30.

33. 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(7):519-27.

34. National Health Service. Migraine: a comprehensive guide [Available from: https://www.thewaltoncentre.nhs.uk/patient-leaflets/migraine-a-comprehensive-guide/479279 (last accessed May 2022)

35. Deuschl G, Beghi E, Fazekas F, Varga T, Christoforidi KA, Sipido E, et al. The burden of neurological diseases in Europe: an analysis for the Global Burden of Disease Study 2017. Lancet Public Health. 2020;5(10):e551-e67.

36. Agosti R. Migraine Burden of Disease: From the Patient's Experience to a Socio-Economic View. Headache. 2018;58:17-32.

37. Silberstein S, Lipton R. Chronic daily headache, including transformed migraine, chronic tensiontype headache, and medication overuse. In: Silberstein S, Lipton R, Dalessio D, editors. Wolff's Headache and Other Head Pain. New York: Oxford University Press; 2001. p. 247-82.

38. Bigal M, Lipton R. The differential diagnosis of chronic daily headaches: an algorithm-based approach. J Headache Pain. 2007;8:263-72.

39. Peters G. Migraine overview and summary of current and merging treatment options. Am J Manag Care. 2019;25:S23-S34.

40. Xu J, Kong F, Buse DC. Predictors of episodic migraine transformation to chronic migraine: A systematic review and meta-analysis of observational cohort studies. Cephalalgia. 2020;40(5):503-16.

41. Lipton RB, Fanning KM, Serrano D, Reed ML, Cady R, Buse DC. Ineffective acute treatment of episodic migraine is associated with new-onset chronic migraine. Neurology. 2015;84(7):688-95.

42. Noseda R, Burstein R. Migraine pathophysiology: anatomy of the trigeminovascular pathway and associated neurological symptoms, cortical spreading depression, sensitization, and modulation of pain. PAIN®. 2013;154:S44-S53.

43. Buse DC, Greisman JD, Baigi K, Lipton RB. Migraine progression: a systematic review. Headache: The Journal of Head and Face Pain. 2019;59(3):306-38.

44. Lipton RBS, D.; Nicholson, R. A.; Buse, D. C.; Runken, M. C.; Reed, M. L. Impact of NSAID and Triptan use on developing chronic migraine: results from the American Migraine Prevalence and Prevention (AMPP) study. Headache. 2013;53(10):1548-63.

45. Ghiotto N, Sances G, Galli F, Tassorelli C, Guaschino E, Sandrini G, et al. Medication overuse headache and applicability of the ICHD-II diagnostic criteria: 1-year follow-up study (CARE I protocol). Cephalalgia. 2009;29(2):233-43.

46. Wilson M, Jimenez-Sanders R. Medication Overuse Headache: American Migraine Foundation; 2016 [Available from: https://americanmigrainefoundation.org/resource-library/medication-overuse/ (last accessed Aug 26)

47. Kristoffersen E, Lundqvist C. Medication-overuse headache: epidemiology, diagnosis and treatment. Ther Adv Drug Saf. 2014;5(2):87-99.

48. Fenton C, Lee A. Educate patients with medication overuse headache, and intervene, when necessary. Drugs & Therapy Perspectives. 2021;37(12):573-8.

49. Thorlund K, Sun-Edelstein C, Druyts E, Kanters S, Ebrahim S, Bhambri R, et al. Risk of medication overuse headache across classes of treatments for acute migraine. J Headache Pain. 2016;17(1):107.

50. Limmroth V, Katzarava Z, Fritsche G, Pryzwara S, Diener H-C. Features of medication overuse headache following overuse of different acute headache drugs. Neurology. 2002;59(7):1011-4.

51. Schwedt T, Alam A, Reed M, et al. Factors associated with acute medication overuse in people with migraine: results from the 2017 migraine in America symptoms and treatment (MAST) study. The Journal of Headache and Pain. 2018;19:38.

52. Bigal ME, Lipton RB. Overuse of acute migraine medications and migraine chronification. Curr Pain Headache Rep. 2009;13(4):301-7.

53. GBD 2016 Headache Collaborators. Global, regional, and national burden of migraine and tension-type headache, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet neurol. 2018;17(11):954-76.

54. Steiner TJ, Stovner LJ, Vos T, Jensen R, Katsarava Z. Migraine is first cause of disability in under 50s: will health politicians now take notice? J Headache Pain. 2018;19(1):17.

55. Holroyd KA, Drew JB, Cottrell CK, Romanek KM, Heh V. Impaired functioning and quality of life in severe migraine: the role of catastrophizing and associated symptoms. Cephalalgia. 2007;27(10):1156-65.

56. Bussone G, Usai S, Grazzi L, et al. Disability and quality of life in different primary headaches: results from Italian studies. Neurological Sciences. 2004;25(Suppl 3):s105-s7.

57. Buse DC, Yugrakh MS, Lee LK, Bell J, Cohen JM, Lipton RB. Burden of Illness Among People with Migraine and ≥ 4 Monthly Headache Days While Using Acute and/or Preventive Prescription Medications for Migraine. J Manag Care Spec Pharm. 2020;26(10):1334-43.

58. Irimia P, Garrido-Cumbrera M, Santos-Lasaosa S, Aguirre-Vazquez M, Correa-Fernández J, Colomina I, et al. Impact of monthly headache days on anxiety, depression and disability in migraine patients: results from the Spanish Atlas. Sci Rep. 2021;11(1):8286.

59. Suzuki K, Suzuki S, Shiina T, Okamura M, Haruyama Y, Tatsumoto M, et al. Investigating the relationships between the burden of multiple sensory hypersensitivity

symptoms and headache-related disability in patents with migraine. J Headache Pain. 2021;22(1):77.

60. Ruiz de Velasco I, González N, Etxeberria Y, Garcia-Monco J. Quality of Life in Migraine Patients: A Qualitative Study. Cephalalgia. 2003;23(9):892-900.

61. Walters AB, Hamer JD, Smitherman TA. Sleep disturbance and affective comorbidity among episodic migraineurs. Headache. 2014;54(1):116-24.

62. Lombard L, Farrar M, Ye W, Kim Y, Cotton S, Buchanan AS, et al. A global real-world assessment of the impact on health-related quality of life and work productivity of migraine in patients with insufficient versus good response to triptan medication. J Headache Pain. 2020;21(1):41.

63. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. Headache: The Journal of Head and Face Pain. 2001;41(7):646-57.

64. Gibbs SN, Shah S, Deshpande CG, Bensink ME, Broder MS, Dumas PK, et al. United States Patients' Perspective of Living With Migraine: Country-Specific Results From the Global "My Migraine Voice" Survey. Headache: The Journal of Head and Face Pain. 2020;60(7):1351-64.

65. Kikui S, Chen Y, Todaka H, Asao K, Adachi K, Takeshima T. Burden of migraine among Japanese patients: a cross-sectional National Health and Wellness Survey. J Headache Pain. 2020;21(1):110.

66. Stewart WF, Shechter A, Lipton R. Migraine heterogeneity: Disability, pain intensity, attack frequency and duration. Neurology. 1994;44(6 Suppl 4):S24-39.

67. Brandes J. The Migraine Cycle: Patient Burden of Migraine During and Between Migraine Attacks. Headache. 2008;48(3):430-41.

68. Lo SHG, Katy; Smith, Timothy; Powell, Lauren; Hubig, Lena; Williams, Emma; Coric, Vladimir; Harris, Linda; L'Italien, Gilbert; Lloyd, Andrew. Real-world experience of interictal burden and treatment in migraine: a qualitative interview study [Data on File]. 2022.

69. Vos T, Abajobir AA, Abate KH, Abbafati C, Abbas KM, Abd-Allah F, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet. 2017;390(10100):1211-59.

70. Buse D, Manack A, Fanning K, et al. Chronic Migraine Prevalence, Disability, and Sociodemographic Factors: Results From the American Migraine Prevalence and Prevention Study. Headache. 2012;52(10):1456-70.

71. Lipton R, Manack Adams A, Buse D, et al. A Comparison of the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study and American Migraine Prevalence and Prevention (AMPP) Study: Demographics and Headache-Related Disability. Headache. 2016;56:1280-9.

72. Wang S, Wang P, Fuh J, et al. Comparisons of disability, quality of life, and resource use between chronic and episodic migraineurs: A clinic-based study in Taiwan. Cephalalgia. 2012;33(3):171-81.

73. Blumenfeld A, Varon S, Wilcox T, et al. Disability, HRQoL and resource use among chronic and episodic migraineurs: Results from the International Burden of Migraine Study (IBMS). Cephalalgia. 2011;31(3):301-15.

74. Burch R, Rizzoli P, Loder E. The Prevalence and Impact of Migraine and Severe Headache in the United States: Figures and Trends From Government Health Studies. Headache. 2018;58(4):496-505.

75. Buse D, Fanning K, Reed M, et al. Life With Migraine: Effects on Relationships, Career, and Finances From the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study. Headache. 2019;59:1286-99.

76. Hirata K, Ueda K, Ye W, Kim Y, Komori M, Jackson J, et al. Factors associated with insufficient response to acute treatment of migraine in Japan: analysis of real-world data from the Adelphi Migraine Disease Specific Programme. BMC Neurology. 2020;20(1):274.

77. Ford JH, Jackson J, Milligan G, Cotton S, Ahl J, Aurora SK. A Real-World Analysis of Migraine: A Cross-Sectional Study of Disease Burden and Treatment Patterns. Headache. 2017;57(10):1532-44.

78. Lipton R, Hutchinson S, Ailani J, et al. Discontinuation of Acute Prescription Medication for Migraine: Results From the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study. Headache: The Journal of Head and Face Pain. 2019;59(10):1762-72.

79. Peng KP, Wang SJ. Migraine diagnosis: screening items, instruments, and scales. Acta anaesthesiologica Taiwanica : official journal of the Taiwan Society of Anesthesiologists. 2012;50(2):69-73.

80. Horsman J, Furlong W, Feeny D, Torrance G. The Health Utilities Index (HUI®): concepts, measurement properties and applications. Health and quality of life outcomes. 2003;1(1):54.

81. Kawata AK, Hareendran A, Shaffer S, Mannix S, Thach A, Desai P, et al. Evaluating the Psychometric Properties of the Migraine Functional Impact Questionnaire (MFIQ). Headache: The Journal of Head and Face Pain. 2019;59(8):1253-69.

82. Steiner TJ, Jensen R, Katsarava Z, Linde M, MacGregor EA, Osipova V, et al. Aids to management of headache disorders in primary care (2nd edition): on behalf of the European Headache Federation and Lifting The Burden: the Global Campaign against Headache. Journal of Headache and Pain. 2019;20(1):57.

83. National Health Service. Improved NHS migraine care to save thousands of hospital stays London: NHS; 2020 [Available from: https://www.england.nhs.uk/2020/01/improved-nhs-migraine-care/ (last accessed April 2022)

84. Silberstein S, Lee L, Gandhi K, et al. Health care Resource Utilization and Migraine Disability Along the Migraine Continuum Among Patients Treated for Migraine. Headache. 2018;58(10):1579-92.

85. NHS RightCare. RightCare: Headache & Migraine Toolkit optimising a headache and migraine system 2019 [Available from: https://www.england.nhs.uk/rightcare/wp-content/uploads/sites/40/2020/01/rightcare-headache-and-migraine-toolkit-v1.pdf (last accessed June 2022)

86. Saylor D, Steiner TJ. The Global Burden of Headache. Semin Neurol. 2018;38(2):182-90.

87. Hazard E, Munakata J, Bigal M, et al. The Burden of Migraine in the United States: Current and Emerging Perspectives on Disease Management and Economic Analysis. Value in Health. 2009;12(1):55-64.

88. Martelletti P, Schwedt T, Lanteri-Minet M, et al. My Migraine Voice survey: a global study of disease burden among individuals with migraine for whom preventive treatments have failed. The Journal of Headache and Pain. 2018;19:115.

89. Paris N, Vo P, De Reydet de Vulpillieres F, Fang J, Naujoks C, Bilitou A, et al. A descriptive analysis of the burden of migraine based on self-reported migraine diary data using the Migraine Buddy application in Europe. European Journal of Neurology. 2017;24 (Supplement 1):392-3.

90. Tepper S, Silberstein S, Rosen N, et al. The Influence of Migraine on Driving: Current Understanding, Future Directions, and Potential Implications of Findings. Headache: The Journal of Head and Face Pain. 2020;60(1):178-289.

91. D'Amico D, Grazzi L, Grignani E, Leonardi M, Sansone E, Raggi A. HEADWORK Questionnaire: Why Do We Need a New Tool to Assess Work-Related Disability in Patients With Migraine? Headache: The Journal of Head and Face Pain. 2020;60(2):497-504.

92. Migraine Trust. What we currently know about migraine 2021 [Available from: https://migrainetrust.org/understand-migraine/what-do-we-currently-know-about-migraine/ (last accessed Nov 24)

93. Department of Health and Social Care. Our Vision for the Women's Health Strategy for England 2021 [Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1042631/dhsc-our-vision-for-the-women_s-health-strategy-for-england.pdf (last accessed June 2022)

94. Hu XH, Markson LE, Lipton RB, Stewart WF, Berger ML. Burden of Migraine in the United States: Disability and Economic Costs. Archives of Internal Medicine. 1999;159(8):813-8.

95. Bonafede M, Cai Q, Cappell K, Kim G, Sapra SJ, Shah N, et al. Factors associated with direct health care costs among patients with Migraine. Journal of Managed Care and Specialty Pharmacy. 2017;23(11):1169-76.

96. Office for National Statistics. Sickness absence in the UK labour market: 2020 2020 [Available from: https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/labourproductivity/articles/sicknessabsenceinthelabourmarket/2020 (last accessed April 2022)

97. The Work Foundation. Society's headache: The socioeconomic impact of migraine: The Work Foundation; 2018 [Available from: https://www.lancaster.ac.uk/media/lancaster-university/content-assets/documents/lums/work-foundation/SocietysHeadacheTheSocioeconomicimpactofmigraine.pdf (last accessed April 2022)

98. NHS Digital. NHS Sickness Absence Rates, November 2021, Provisional Statistics [Available from: https://digital.nhs.uk/data-and-information/publications/statistical/nhs-sickness-absence-rates/november-2021-provisional-statistics (last accessed May 2022)

99. Diener H, Holle-Lee D, Nagel S, et al. Treatment of migraine attacks and prevention of migraine: Guidelines by the German Migraine and Headache Society and the German Society of Neurology. Clinical & Translational Neuroscience. 2019:1-40.

100. Ducros A, de Gaalon S, Roos C, Donnet A, Giraud P, Guégan-Massardier E, et al. Revised guidelines of the French headache society for the diagnosis and management of migraine in adults. Part 2: Pharmacological treatment. Rev Neurol (Paris). 2021;177(7):734-52.

101. Aukerman G, Knutson D, Miser WF. The Management of the Acute Migraine Headache. American Family Physician. 2002;66(11):2123.

102. American Migraine Foundation. Commonly used acute migraine treatments 2019 [Available from: https://americanmigrainefoundation.org/resource-library/commonly-used-acute-migraine-treatments/)

103. Silberstein S. Preventive Migraine Treatment. Continuum (Minneap Minn). 2015;21(4):973-89.

104. Alam A, Munjal S, Reed M, Bostic R, Buse D, Schwedt T, et al. Triptan Use and Discontinuation in a Representative Sample of Persons With Migraine: Results From Migraine in America Symptoms and Treatment (MAST) Study (P4.10-019). Neurology. 2019;92(15 Supplement):P4.10-019.

105. Bonafede M, McMorrow D, Noxon V, Desai P, Sapra S, Silberstein S. Care Among Migraine Patients in a Commercially Insured Population. Neurology and Therapy. 2020:1-11.

106. Sacco S, Braschinsky M, Ducros A, Lampl C, Little P, van den Brink AM, et al. European headache federation consensus on the definition of resistant and refractory migraine : Developed with the endorsement of the European Migraine & Headache Alliance (EMHA). Journal of Headache and Pain. 2020;21(1):76.

107. National Institute for Health and Clinical Excellence. Headaches in over 12s: Diagnosis and management: Clinical Guideline (CG150) Manchester: NICE; 2012 [updated May 2021. Available from: https://www.nice.org.uk/guidance/cg150/chapter/Key-priorities-for-implementation#tensiontype-headache-migraine-and-cluster-headache (last accessed April 2022)

108. Harris L, L'Italien G, O'Connell T, Hasan Z, Hutchinson S, Lucas S. A Framework for Estimating the Eligible Patient Population for New Migraine Acute Therapies in the United States. Adv Ther. 2021;38(10):5087-97.

109. BASH. NATIONAL HEADACHE MANAGEMENT SYSTEM FOR ADULTS 2019. British Association for the Study of Headache; 2019 2019.

110. Viana M, Genazzani AA, Terrazzino S, Nappi G, Goadsby PJ. Triptan nonresponders: do they exist and who are they? Cephalalgia. 2013;33(11):891-6.

111. Dahlöf CGH. Infrequent or Non-Response to Oral Sumatriptan does not Predict Response to Other Triptans—Review of Four Trials. Cephalalgia. 2006;26(2):98-106.

112. Stark S, Spierings EL, McNeal S, Putnam GP, Bolden-Watson CP, O'Quinn S. Naratriptan efficacy in migraineurs who respond poorly to oral sumatriptan. Headache. 2000;40(7):513-20.

113. Färkkilä M, Olesen J, Dahlöf C, Stovner LJ, ter Bruggen JP, Rasmussen S, et al. Eletriptan for the treatment of migraine in patients with previous poor response or tolerance to oral sumatriptan. Cephalalgia. 2003;23(6):463-71.

114. Mathew NT, Kailasam J, Gentry P, Chernyshev O. Treatment of nonresponders to oral sumatriptan with zolmitriptan and rizatriptan: a comparative open trial. Headache. 2000;40(6):464-5.

115. Diener HC, Gendolla A, Gebert I, Beneke M. Almotriptan in migraine patients who respond poorly to oral sumatriptan: a double-blind, randomized trial. Headache. 2005;45(7):874-82.

116. Goldstein J, Tiseo PT, Albert KS, Li C, Sikes CR. Eletriptan in migraine patients reporting unsatisfactory response to rizatriptan. Headache. 2006;46(7):1142-50.

117. Lipton RB, Buse DC, Serrano D, Holland S, Reed ML. Examination of unmet treatment needs among persons with episodic migraine: results of the American Migraine Prevalence and Prevention (AMPP) Study. Headache: The Journal of Head and Face Pain. 2013;53(8):1300-11.

118. Ng-Mak DS, Chen YT, Ho TW, Stanford B, Roset M. Results of a 2-year retrospective cohort study of newly prescribed triptan users in European nationwide practice databases. Cephalalgia. 2012;32(12):875-87.

119. Katić BJ, Rajagopalan S, Ho TW, Chen Y-T, Hu XH. Triptan persistency among newly initiated users in a pharmacy claims database. Cephalalgia. 2011;31(4):488-500.

120. Chen TB, Chen YT, Fuh JL, Tang CH, Wang SJ. Treatment adherence among new triptan users: a 2-year cohort study in Taiwan. Journal of Headache and Pain. 2014;15(1):48.

121. Messali A, Owens G, Bloudek L, Kori S, Cole A, Chia J. Health care resource utilization following initiation of a triptan: A retrospective claims analysis. Journal of Managed Care Pharmacy. 2014;20(4):368-75.

122. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. A meta-analysis. Ann Intern Med. 1991;115(10):787-96.

123. Henry D, McGettigan P. Epidemiology overview of gastrointestinal and renal toxicity of NSAIDs. Int J Clin Pract Suppl. 2003(135):43-9.

124. Hernandez-Diaz S, Rodriguez LA. Association between nonsteroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation: an overview of epidemiologic studies published in the 1990s. Archives of Internal Medicine. 2000;160(14):2093-9.

125. Yarnitsky D, Dodick DW, Grosberg BM, Burstein R, Ironi A, Harris D, et al. Remote Electrical Neuromodulation (REN) Relieves Acute Migraine: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial. Headache: The Journal of Head and Face Pain. 2019;59(8):1240-52.

126. Cooper W, Doty EG, Hochstetler H, Hake A, Martin V. The current state of acute treatment for migraine in adults in the United States. Postgraduate medicine. 2020;132(7):581-9.

127. Wells RE, Markowitz SY, Baron EP, Hentz JG, Kalidas K, Mathew PG, et al. Identifying the factors underlying discontinuation of triptans. Headache. 2014;54(2):278-89.

128. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2000;55(6):754-62.

129. Marmura MJ, Silberstein SD, Schwedt TJ. The Acute Treatment of Migraine in Adults: The A merican H eadache S ociety Evidence Assessment of Migraine Pharmacotherapies. Headache: The Journal of Head and Face Pain. 2015;55(1):3-20.

130. Derry CJ, Derry S, Moore RA. Sumatriptan (oral route of administration) for acute migraine attacks in adults. Cochrane Database Syst Rev. 2012;2012(2):CD008615.

131. Lipton RB, Reed ML, Kurth T, Fanning KM, Buse DC. Framingham-based cardiovascular risk estimates among people with episodic migraine in the US population: Results from the American Migraine Prevalence and Prevention (AMPP) Study. Headache: The Journal of Head and Face Pain. 2017;57(10):1507-21.

132. Buse DC, Reed ML, Fanning KM, Kurth T, Lipton RB. Cardiovascular events, conditions, and procedures among people with episodic migraine in the US population: results from the American Migraine Prevalence and Prevention (AMPP) study. Headache: The Journal of Head and Face Pain. 2017;57(1):31-44.

133. The Neurological Alliance. Hospital Activity Compendium 2017 [Available from: https://www.neural.org.uk/publication/hospital-activity-compendium/ (last accessed June 2022)

134. Doane M, Gupta S, Fang J, et al. The Humanistic and Economic Burden of Migraine in Europe: A Cross-Sectional Survey in Five Countries. Neurol Ther. 2020:1-15.

135. Southwell J, Afridi SK. The burden of migraine on acute and emergency services in a London teaching hospital. Cephalalgia. 2021;41(8):905-12.

136. van Hoogstraten WS, MaassenVanDenBrink A. The need for new acutely acting antimigraine drugs: moving safely outside acute medication overuse. The Journal of Headache and Pain. 2019;20(1):54.

137. Durham PL. CGRP-receptor antagonists--a fresh approach to migraine therapy? N Engl J Med. 2004;350(11):1073-5.

138. Biohaven Pharmaceuticals Inc. Data on File: Clinical study report BHV3000-301: A phase 3, double-blind, randomized, placebo-controlled, safety and efficacy trial of BHV-3000 (rimegepant) for the acute treatment of migraine. 2019.

139. Biohaven Pharmaceuticals Inc. Data on file: Clinical study report BHV3000-303: A Phase 3, Double-blind, Randomized, Placebo-controlled, Safety and Efficacy Trial of BHV-3000 (rimegepant) Orally Disintegrating Tablet (ODT) for the Acute Treatment of Migraine. 2019.

140. Biohaven Pharmaceuticals Inc. Data on File: Clinical study report BHV3000-201: A multicenter, open-label long-term safety study of BHV-3000 in the acute treatment of migraine. 2020.

141. Biohaven Pharmaceuticals Inc. Data on file: Clinical study report BHV3000-302: Clinical Study Report 2020.

142. National Institute for Health and Clinical Excellence. Galcanezumab for preventing migraine: Technology appraisal guidance (TA659): NICE; 2020 [updated 18 November 2020. Available from: https://www.nice.org.uk/guidance/ta659 (last accessed April 2022)

143. National Institute for Health and Clinical Excellence. Erenumab for preventing migraine: Technology appraisal guidance (TA682) Manchester: NICE; 2021 [updated 10 March 2021. Available from: https://www.nice.org.uk/guidance/ta682/resources/erenumab-for-preventing-migraine-pdf-82609376694469 (last accessed April 2022)

144. Candesartan cilexetil 16mg tablets: Summary of Product Characteristics [Available from: https://www.medicines.org.uk/emc/product/7080/smpc#gref (last accessed May 2022)

145. Lai J, Wickizer M, Olson J, Hickman C, Chou J, Patel T, et al. A Retrospective Claims Analysis of Calcitonin Gene-Related Peptides: Utilization, Adherence and Impact on Acute Migraine Therapy Among 4 Million Commercial Members (Poster G44). Journal of Managed Care & Specialty Pharmacy. 2020;24(4-a):S86.

146. Lambru G, Hill B, Murphy M, Tylova I, Andreou AP. A prospective real-world analysis of erenumab in refractory chronic migraine. The Journal of Headache and Pain. 2020;21(1):1-10.

147. Silberstein S, Winner P, Chmiel J. Migraine Preventive Medication Reduces Resource Utilization. Headache. 2003;43(3):171-8.

148. Ansari H, Ziad S. Drug–Drug Interactions in Headache Medicine. Headache: The Journal of Head and Face Pain. 2016;56(7):1241-8.

149. Starling AJ, Dodick DW. Best practices for patients with chronic migraine: burden, diagnosis, and management in primary care. Mayo Clin Proc. 2015;90(3):408-14.

150. Adelman J, Freitag FG, Lainez M, Shi Y, Ascher S, Mao L, et al. Analysis of safety and tolerability data obtained from over 1,500 patients receiving topiramate for migraine prevention in controlled trials. Pain Med. 2008;9(2):175-85.

151. Antonaci F, Ghiotto N, Wu S, Pucci E, Costa A. Recent advances in migraine therapy. Springerplus. 2016;5:637-.

152. Tfelt-Hansen P, Pascual J, Ramadan N, Dahlöf C, D'Amico D, Diener HC, et al. Guidelines for controlled trials of drugs in migraine: third edition. A guide for investigators. Cephalalgia. 2012;32(1):6-38.

153. Hepp Z, Dodick DW, Varon SF, Chia J, Matthew N, Gillard P, et al. Persistence and switching patterns of oral migraine prophylactic medications among patients with chronic migraine: a retrospective claims analysis. Cephalalgia. 2017;37(5):470-85.

154. Hepp Z, Dodick DW, Varon SF, Gillard P, Hansen RN, Devine EB. Adherence to oral migraine-preventive medications among patients with chronic migraine. Cephalalgia. 2015;35(6):478-88.

155. Kawata AK, Shah N, Poon JL, Shaffer S, Sapra S, Wilcox TK, et al. Understanding the migraine treatment landscape prior to the introduction of calcitonin gene-related peptide inhibitors: Results from the Assessment of TolerabiliTy and Effectiveness in Migraine Patients using Preventive Treatment (ATTAIN) study. Headache: The Journal of Head and Face Pain. 2021;61(3):438-54.

156. 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.

157. D'Amico D, Sansone E, Grazzi L, et al. Multimorbidity in patients with chronic migraine and medication overuse headache. Acta Neurol Scand. 2018:1-8.

158. Agostoni E, Barbanti P, Frediani F, Trifirò G, Burgio L, di Nola L, et al. Real-world insights on the management of migraine patients: an Italian nationwide study. Current medical research and opinion. 2019;35(9):1545-54.

159. Delussi M, Vecchio E, Libro G, Quitadamo S, de Tommaso M. Failure of preventive treatments in migraine: an observational retrospective study in a tertiary headache center. BMC Neurology. 2020;20(1):256.

160. Orlando V, Mucherino S, Monetti VM, Trama U, Menditto E. Treatment patterns and medication adherence among newly diagnosed patients with migraine: a drug utilisation study. BMJ Open. 2020;10(11):e038972.

161. FDA. Product insert: AIMOVIG (erenumab-aooe) 2021 [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761077s000lbl.pdf (last accessed May 2022)

162. FDA. Product insert: AJOVY (fremanezumab-vfrm) 2021 [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761089Orig1s000Lbl.pdf (last accessed May 2022)

163. FDA. Product insert: VYEPTI (eptinezumab-jjmr) 2021 [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761119s000lbl.pdf (last accessed May 2022)

164. FDA. Product insert: EMGALITY (galcanezumab-gnlm) 2021 [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761063Orig1s000Lbl.pdf (last accessed May 2022)

165. Novartis Europharm Limited. Summary of Product Characteristics: Aimovig (erenumab) 2021 [Available from: https://www.medicines.org.uk/emc/product/10297/smpc)

166. Eli Lilly Nederland B.V. Summary of Product Characteristics: EMGALITY (galcanezumab) 2021 [Available from: https://www.medicines.org.uk/emc/product/10478#gref (last accessed May 2022)

167. H. Lundbeck A/S. Summary of Product Characteristics: VYEPTI (eptinezumab) 2022 [Available from: https://www.ema.europa.eu/en/documents/product-information/vyepti-epar-product-information_en.pdf (last accessed May 2022)

168. TEVA GmbH. Summary of Product Characteristics: AJOVY (fremanezumab) 2021 [Available from: https://www.medicines.org.uk/emc/product/11630/smpc (last accessed May 2022)

169. Maasumi K, Michael R, Rapoport A. CGRP and Migraine: The Role of Blocking Calcitonin GeneRelated Peptide Ligand and Receptor in the Management of Migraine. Drugs. 2018:1-18.

170. Robblee J, Devick KL, Mendez N, Potter J, Slonaker J, Starling AJ. Real-World Patient Experience With Erenumab for the Preventive Treatment of Migraine. Headache: The Journal of Head and Face Pain. 2020.

171. Aletaha D, Husni ME, Merola JF, Ranza R, Bertheussen H, Lippe R, et al. Treatment Mode Preferences in Psoriatic Arthritis: A Qualitative Multi-Country Study. Patient Prefer Adherence. 2020;14:949-61.

172. University of Manchester. Emotional impact of pandemic could lead to exodus of NHS staff 2021 [updated October 22, 2021. Available from: https://www.manchester.ac.uk/discover/news/pandemic-could-lead-to-exodus-of-nhs-staff/ (last accessed February 23)

173. Pham A, Burch RC. Patients with Migraine Headache who Switch from Erenumab to Galcanezumab Report Similar Improvement. Presented at AHS Conference 2020. 2020.

174. Russo A, Silvestro M, di Clemente FS, Trojsi F, Bisecco A, Bonavita S, et al. Multidimensional assessment of the effects of erenumab in chronic migraine patients with previous unsuccessful preventive treatments: a comprehensive real-world experience. The Journal of Headache and Pain. 2020;21(1):1-14.

175. Scheffler A, Messel O, Wurthmann S, Nsaka M, Kleinschnitz C, Glas M, et al. Erenumab in highly therapy-refractory migraine patients: First German Real-world evidence. 2020.

176. Kanaan S, Hettie G, Loder E, Burch R. Real-world effectiveness and tolerability of erenumab: A retrospective cohort study. Cephalalgia. 2020;40(13):1511-22.

177. Thompson K, Mirzai M, Crabtree T, Zhang J, Thomas J, Kustra LA. Evaluation of persistence, switch patterns, and costs among migraine patients utilizing calcitonin gene-related peptide (cgrp) inhibitors in a u.s. medicaid population. Presented at AMCP conference. 2020.

178. Hines DM, Shah S, Multani JK, Wade RL, Buse DC, Bensink M. Erenumab patient characteristics, medication adherence, and treatment patterns in the United States. Headache: The Journal of Head and Face Pain. 2021.

179. Mansfield C, Gebben DJ, Sutphin J, Tepper SJ, Schwedt TJ, Sapra S, et al. Patient Preferences for Preventive Migraine Treatments: A Discrete-Choice Experiment. Headache: The Journal of Head and Face Pain. 2019;59(5):715-26.

180. Hubig L, Smith T, L'italien G, Harris L, Powell L, Johnston K, et al. Data on File: Patient preferences for calcitonin gene-related peptide (CGRP) inhibitors in the preventive treatment of migraine: A discrete choice experiment in the US and Germany 2022.

181. Johnston K, Harris L, Powell L, Popoff E, Coric V, L'Italien G, et al. Monthly migraine days, tablet utilization, and quality of life associated with Rimegepant – post hoc results from an open label safety study (BHV3000–201). The Journal of Headache and Pain. 2022;23(1):10.

182. Migraine Trust. Migraine: Help at Work 2018 [Available from: https://migrainetrust.org/wp-content/uploads/2021/04/Migraine_Help-at-work-toolkit.pdf (last accessed Nov 24)

183. Zhang L, Losin EAR, Ashar YK, Koban L, Wager TD. Gender Biases in Estimation of Others' Pain. J Pain. 2021;22(9):1048-59.

184. Hunt K, Adamson J, Hewitt C, Nazareth I. Do women consult more than men? A review of gender and consultation for back pain and headache. J Health Serv Res Policy. 2011;16(2):108-17.

185. Hunt K, Ford G, Harkins L, Wyke S. Are women more ready to consult than men? Gender differences in family practitioner consultation for common chronic conditions. J Health Serv Res Policy. 1999;4(2):96-100.

186. Lombard L, Ye W, Nichols R, Jackson J, Cotton S, Joshi S. A Real-World Analysis of Patient Characteristics, Treatment Patterns, and Level of Impairment in Patients With Migraine Who are Insufficient Responders vs Responders to Acute Treatment. Headache. 2020;60(7):1325-39.

187. L'Italien G, Croop R, Stock E, Thiry A, Rosenthal H, Lovegren M, et al. Acute Treatment of Migraine with Oral Rimegepant 75 mg Confers Robust Improvement in Absenteeism, Presenteeism and Productivity: Results from a One Year, Open-Label, Safety Study (BHV3000-201) (1864). Neurology 2020;94(15 Supplement):1864.

188. Office for National Statistics. EMP17: People in employment on zero hours contracts 2021 [Available from: https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/employmentandemployeetypes/datasets/emp17peopleinemploymentonzerohourscontracts (last accessed June 2022)

189. Marcus R, Goadsby PJ, Dodick D, Stock D, Manos G, Fischer TZ. BMS-927711 for the acute treatment of migraine: a double-blind, randomized, placebo controlled, dose-ranging trial. Cephalalgia. 2014;34(2):114-25.

190. Biohaven Pharmaceuticals Inc. Data on File: Clinical study report: Pooled analysis of BHV3000-301, BHV3000-302 and BHV3000-303 (final version). 2021.

191. ClinicalTrials.gov. Safety and Efficacy Trial of BHV3000-310 (Rimegepant) 75 mg for the Acute Treatment of Migraine (NCT04574362) 2017 [updated May 2022. Available from: https://clinicaltrials.gov/ct2/show/NCT04574362?term=NCT04574362)

192. Blumenfeld A, Buse D, Turner I, Stock D, Morris B, Coric V, et al., editors. Rimegepant 75 mg Is More Effective Than Nonsteroidal Anti-inflammatory Drugs for the Acute Treatment of Migraine: Post Hoc Analysis of Data From 2 Phase 3 Trials. Headache; 2019: WILEY 111 RIVER ST, HOBOKEN 07030-5774, NJ USA.

193. Croop R, Jensen C, Thiry A, Stock E, Conway C, Morris B, et al. Rimegepant is Effective for the Acute Treatment of Migraine in Patients Who Have Discontinued or Currently Use Triptans: Results from 3 Phase 3 Clinical Trials (2114). Neurology. 2020;94(15 Supplement):2114.

194. Hutchinson S, Lipton R, Thiry A, BA M, Coric V, Croop R, editors. The Safety and Tolerability of Rimegepant 75 mg Are Similar to Placebo: Results from 3 Phase 3 Trials in

Adults With Migraine. Headache; 2019: WILEY 111 RIVER ST, HOBOKEN 07030-5774, NJ USA.

195. Hutchinson S, Lipton R, Thiry A, Morris B, Coric V, Croop R, editors. Rimegepant 75 mg demonstrates safety and tolerability similar to placebo: results from 3 phase 3 trials in adults with migraine. Cephalalgia; 2019: SAGE PUBLICATIONS LTD 1 OLIVERS YARD, 55 CITY ROAD, LONDON EC1Y 1SP, ENGLAND.

196. Hutchinson S, Schim J, Lipton R, Thiry A, Morris B, Coric V, et al., editors. Safety of rimegepant 75 mg in adults with migraine: No effects of age, sex, or race in 3 phase 3 trials. Cephalalgia; 2019: SAGE PUBLICATIONS LTD 1 OLIVERS YARD, 55 CITY ROAD, LONDON EC1Y 1SP, ENGLAND.

197. Jensen CM, Lipton RB, Blumenfeld A, Croop R, Thiry A, L'Italien G, et al. Rimegepant for the Acute Treatment of Migraine: subgroup Analyses from 3 Phase 3 Clinical Trials by Number of Triptans Previously Tried and Failed. The Journal of Headache and Pain. 2021;22(1).

198. Jensen C, Lipton R, Blumenfeld A, Croop R, Thiry A, L'Italien G, et al. Rimegepant for the Acute Treatment of Migraine in Patients with a History of Triptan Treatment Failure: Pooled Results From 3 Phase 3 Clinical Trials (Poster 4914). Neurology. 2021;96(15 Supplement):4914.

199. Levin M, Buse D, Blumenfeld A, Lipton R, Stock E, Thiry A, et al., editors. Rimegepant 75 mg is Effective for the Acute Treatment of Migraine Regardless of Attack Frequency: Results From 3 Phase 3 Trials (1212). Neurology; 2020: AAN Enterprises.

200. Lipton R, Tepper S, Friedman D, Thiry A, Morris B, Coric V, et al. Rimegepant 75 mg Provides Pain Relief and Return to Normal Function with a Single Dose: Results from 3 Phase 3 Trials in Adults With Migraine. Cephalalgia. 2019;39:195-.

201. Lipton R, Tepper S, Friedman D, Thiry A, Morris B, Coric V, et al. A single dose of Rimegepant 75 mg provides pain relief and return to normal function: Results from 3 phase 3 trials in adults with migraine. Headache. 2019;59:178-9.

202. Lipton RB, Blumenfeld A, Croop R, Jensen CM, Thiry A, Stock EG, et al. Rimegepant is effective for the acute treatment of migraine in subjects who have discontinued or currently use triptans: results from 3 phase 3 clinical trials. Headache. 2020;60:122.

203. McAllister P, Berman G, Kudrow D, Smith T, Lipton R, Stock E, et al. Rimegepant 75 mg Demonstrates Superiority to Placebo on Nausea Freedom: Results from a Post Hoc Pooled Analysis of 3 Phase 3 Trials in the Acute Treatment of Migraine (2402). Neurology. 2020;94(15 Supplement):2402.

204. Pavlovic JM, Dodick D, Newman LC, Lipton RB, Thiry A, Morris BA, et al., editors. A Single Dose of Rimegepant Demonstrates Sustained Efficacy and Low Rescue Medication Use in the Acute Treatment of Migraine: Results From 3 Phase 3 Trials. Headache; 2019: SAGE PUBLICATIONS LTD 1 OLIVERS YARD, 55 CITY ROAD, LONDON EC1Y 1SP, ENGLAND.

205. Pavlovic J, Dodick D, Friedman D, Tepper S, Newman L, Lipton R, et al. Rimegepant 75 mg Provides Early and Sustained Relief of Migraine With a Single Dose: Results from 3 Phase 3 Clinical Trials (2366). Neurology. 2020;94(15 Supplement):2366.

206. Pavlovic J, Dodick D, Newman L, Lipton R, Stock E, Thiry A, et al. Rimegepant is Effective for the Acute Treatment of Migraine in Subjects Taking Concurrent Preventive Medication: Results From 3 Phase 3 Trials (2091). Neurology. 2020;94(15 Supplement):2091.

207. Pavlovic JM, Dodick D, Friedman D, Tepper S, Newman LC, Lipton RB, et al., editors. Rimegepant 75 mg provides early and sustained relief of migraine with a single oral dose: results from 3 phase 3 clinical trials. Headache; 2020: SAGE PUBLICATIONS LTD 1 OLIVERS YARD, 55 CITY ROAD, LONDON EC1Y 1SP, ENGLAND.

208. Schim J, Hutchinson S, Lipton R, Stock E, Thiry A, Conway C, et al. Rimegepant 75 mg Demonstrates Safety and Tolerability Similar to Placebo With No Effects of Age, Sex, or Race in 3 Phase 3 Trials (1609). Neurology. 2020;94(15 Supplement):1609.

209. Smith T, McAllister P, Berman G, Kudrow D, Lipton R, Jensen C, et al. Low Rates of Rescue Medication Usage in Subjects Treated with a Single Dose of Rimegepant 75 mg for the Acute Treatment of Migraine: Results from 3 Phase 3 Clinical Trials (Poster 2342). Neurology. 2021;96(15 Supplement):2342.

210. Turner I, Buse D, Blumenfeld A, Stock E, Stock D, Conway C, et al. Rimegepant 75 mg Is More Effective for Migraine Than Nonsteroidal Anti-inflammatory Drugs: Post Hoc Analysis of Data From 2 Phase 3 Trials (2107). Neurology. 2020;94(15 Supplement):2107.

211. Lipton RB, Croop R, Stock EG, Stock DA, Morris BA, Frost M, et al. Rimegepant, an oral calcitonin gene–related peptide receptor antagonist, for migraine. New England Journal of Medicine. 2019;381(2):142-9.

212. Croop R, Goadsby PJ, Stock DA, Conway CM, Forshaw M, Stock EG, et al. Efficacy, safety, and tolerability of rimegepant orally disintegrating tablet for the acute treatment of migraine: a randomised, phase 3, double-blind, placebo-controlled trial. The Lancet. 2019;394(10200):737-45.

213. Lipton R, Coric V, Stock DA, Gosden R, Forshaw M, Croop R, et al., editors. Efficacy, safety, and tolerability of rimegepant 75mg orally dissolving tablet for the acute treatment of migraine: results from a phase 3, double-blind, randomized, placebo-controlled trial, study 303. Cephalalgia; 2019.

214. Biohaven Pharmaceuticals. Data on File: Clinical study report BHV3000-305-(Final-Week-12-CSR). A Phase 2/3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Rimegepant in Migraine Prevention. 2020.

215. Biohaven Pharmaceuticals Inc. Data on file: Clinical study report addendum to BHV3000-305 CSR: A Phase 2/3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Rimegepant in Migraine Prevention. 2021.

216. Croop R, Lipton RB, Kudrow D, Stock DA, Kamen L, Conway CM, et al. Oral rimegepant for preventive treatment of migraine: a phase 2/3, randomised, double-blind, placebo-controlled trial. The Lancet. 2021;397(10268):51-60.

217. Croop R, Lipton R, Thiry A, Kamen L, Coric V, Goadsby P. A Phase 2/3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Rimegepant for the Preventive Treatment of Migraine (4951). Neurology. 2021;96(15 Supplement):4951.

218. Croop R, Lipton R, Kudrow D, Stock D, Kamen L, Conway C, et al., editors. A Phase 2/3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Rimegepant for the Preventive Treatment of Migraine. Journal of Headache and Pain; 2021.

219. Croop R, Lipton R, Kudrow D, Stock D, Kamen L, Conway C, et al. A phase 2/3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of rimegepant for the preventive treatment of migraine. Headache: The Journal of Head and Face Pain. 2021;61(S1):1-178.

220. Lipton R, Kudrow D, Smith T, Croop R, Jensen C, Kamen L, et al., editors. Onset of Migraine Preventive Effects With Rimegepant in a Phase 2/3, Randomized, Double-Blind, Placebo-Controlled Trial. Journal of Headache and Pain; 2021.

221. ClinicalTrials.gov. Efficacy and Safety Trial of Rimegepant for Migraine Prevention in Adults (BHV3000-305 NCT03732638) 2018 [updated May 2022. Available from: https://clinicaltrials.gov/ct2/show/NCT03732638)

222. Croop R, Berman G, Kudrow D, Mullin K, Stock E, Thiry A, et al. Long-Term Safety of Rimegepant 75 mg for the Acute Treatment of Migraine (Study 201) (4829). Neurology. 2020;94(15 Supplement):4829.

223. Croop R, Ivans A, Stock D, Hould J, Morris B, Stringfellow J, et al. A phase 1 study to evaluate the bioequivalence of oral tablet and orally dissolving tablet formulations of rimegepant in healthy adult subjects under fasting conditions (Abstract PF116LB). Headache: The Journal of Head and Face Pain. 2018;58(8):1303-4.

224. Dowson AJ, Almqvist P. Part III: The convenience of, and patient preference for, zolmitriptan orally disintegrating tablet. Current Medical Research and Opinion. 2005;21(Sup3):S13-S7.

225. Dowson AJ, Charlesworth BR. Patients with migraine prefer zolmitriptan orally disintegrating tablet to sumatriptan conventional oral tablet. Int J Clin Pract. 2003;57(7):573-6.

226. Loder E, Brandes JL, Silberstein S, Skobieranda F, Bohidar N, Wang L, et al. Preference comparison of rizatriptan ODT 10-mg and sumatriptan 50-mg tablet in migraine. Headache: The Journal of Head and Face Pain. 2001;41(8):745-53.

227. ClinicalTrials.gov. Safety and Efficacy Trial of BHV3000-201 (Rimegepant) 75 mg for the Acute Treatment of Migraine (NCT03266588) 2017 [updated May 2022. Available from: https://clinicaltrials.gov/ct2/show/NCT03266588)

228. Biohaven Pharmaceuticals Inc. Data on file: Clinical study report BHV3000-310: A Phase 3: Double-Blind, Randomized, Placebo Controlled, Safety and Efficacy Trial of BHV-3000 (rimegepant) 75 mg for the Acute Treatment of Migraine. 2020.

229. Lipton RB, Conway CM, Stock EG, Morris BA, McCormack BA, Frost M, et al. Efficacy, safety, and tolerability of rimegepant 75 mg, an oral CGRP receptor antagonist, for the actute treatment of migraine: results from a phase 3, double-blind, randomized, placebo-controlled trial, study 301. 60th Annual Meeting of the American Headache Society; 30 June; San Francisco, CA, US2018.

230. Lipton R, Berman G, Kudrow D, Mullin K, Thiry A, Lovegren M, et al. Long-Term, Open-Label Safety Study of Rimegepant 75 mg for the Treatment of Migraine (Study 201): Company evidence submission template for rimegepant for treating or preventing migraine [ID1539]

Interim Analysis of Safety and Exploratory Efficacy (Abstract P235LB). Headache: The Journal of Head and Face Pain. 2019;59(S1):175.

231. Centre for Reviews and Dissemination. Systematic Reviews: CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination, University of York; 2008.

232. ClinicalTrials.gov. Safety and Efficacy Study in Adult Subjects With Acute Migraines Study BHV3000-301 (NCT03235479) 2017 [Available from: https://clinicaltrials.gov/ct2/show/results/NCT03235479 (last accessed May 2022)

233. Harris L, L'Italien G, Croop R, Stock E, Thiry A, Cowrie K, et al. Acute Treatment of Migraine with Oral Rimegepant 75 mg Improves Health Related Quality of Life: Results from a Long-Term, Open-Label Safety Study (BHV3000-201) (Poster 1943). Neurology. 2020;94(15 Supplement):1943.

234. Hutchinson S, Schim J, Lipton R, Croop R, Jensen C, Thiry A, et al., editors. Oral Rimegepant 75 mg is Safe and Well Tolerated in Adults With Migraine and Cardiovascular Risk Factors: Results of a Multicenter, Long-Term, Open-Label Safety Study. American Academy of Neurology; 2021; Virtual.

235. Kudrow D, Mullin K, Berman G, Lipton R, Jensen C, Thiry A, et al. Long-term Use of Rimegepant 75 mg for the Acute Treatment of Migraine Reduces Use of Analgesics and Antiemetics (Poster 5072). Neurology. 2021;96(15 Supplement):5072.

236. L'Italien G, Croop R, Stock E, Thiry A, Lovegren M, Cowie K, et al. Acute Treatment with Oral Rimegepant 75mg Reduces Migraine-Related Disability: Results from a One Year, Open-Label Safety Study (BHV3000-201)(1926). Neurology. 2020;94(15 Supplement):1926.

237. L'Italien G, Popoff E, Johnston K, McGrath D, Conway CM, Powell L, et al. Rimegepant 75 mg for acute treatment of migraine is associated with significant reduction in monthly migraine days: Results from a long-term, open-label study. Cephalalgia Reports. 2022;5:25158163221075596.

238. Mullin K, Hutchinson S, Smith T, Lipton R, Jensen C, Thiry A, et al. Long-Term Safety of Rimegepant 75 mg for the Acute Treatment of Migraine in Adults With a History of Triptan Treatment Failure (Poster 5054). Neurology. 2021;96(15 Supplement):5054.

239. Popoff E, Johnston K, Croop R, Thiry A, Harris L, Powell L, et al. Matching-adjusted Indirect Comparisons of Oral Rimegepant Versus Placebo, Erenumab, and Galcanezumab Examining Monthly Migraine Days and Health-related Quality of Life in the Treatment of Migraine. Headache. 2021;doi: 10.1111/head.14128. Epub ahead of print.

240. Schim J, Hutchinson S, Lipton R, Croop R, Stock E, Thiry A, et al. Rimegepant is Safe and Tolerable for the Acute Treatment of Migraine in Patients Using Preventive Migraine Medications: Results from a Long-Term Open-Label Safety Study (Poster 2370). Neurology. 2021;96(15 Supplement):2370.

241. Johnston KM, L'Italien G, Popoff E, Powell L, Croop R, Thiry A, et al. Mapping Migraine-Specific Quality of Life to Health State Utilities in Patients Receiving Rimegepant. Adv Ther. 2021;38(10):5209-20.

242. Turner I, Pavlovic JM, Lipton RB, Croop R, Stock EG, Thiry A, et al. Patient Preference, Satisfaction, and Improved Clinical Global Impression of Change with

Rimegepant for the Acute Treatment of Migraine: Results from a Long-Term Open-Label Safety Study (Study 201). The IHS and EHF Joint COngress 2021; Sept 8-12; Virtual2021.

243. Biohaven Pharmaceuticals Inc. Data on File: Rimegepant (BHV3000) (Indication Preventive Treatment of Migraine) Module 2.7.3 Summary of Clinical Efficacy. New Haven (CT), USA: Biohaven Pharmaceuticals Inc; 2020.

244. Goadsby PJ, Dodick DW, Ailani J, Trugman JM, Finnegan M, Lu K, et al. Safety, tolerability, and efficacy of orally administered atogepant for the prevention of episodic migraine in adults: a double-blind, randomised phase 2b/3 trial. Lancet neurol. 2020;19(9):727-37.

245. Dias S, Welton NJ, Sutton AJ, Ades A. NICE DSU TECHNICAL SUPPORT DOCUMENT 2: A GENERALISED LINEAR MODELLING FRAMEWORK FOR PAIRWISE AND NETWORK META-ANALYSIS OF RANDOMISED CONTROLLED TRIALS: REPORT BY THE DECISION SUPPORT UNIT. Sheffield (UK): Decision Support Unit, ScHARR, University of Sheffield; 2016.

246. Goadsby PJ, Reuter U, Hallström Y, Broessner G, Bonner JH, Zhang F, et al. A Controlled Trial of Erenumab for Episodic Migraine. New England journal of medicine. 2017;377(22):2123-32.

247. Wang SJ, Roxas AA, Saravia B, Kim BK, Chowdhury D, Riachi N, et al. Randomised, controlled trial of erenumab for the prevention of episodic migraine in patients from Asia, the Middle East, and Latin America: the EMPOwER study. Cephalalgia. 2021.

248. Reuter U, Goadsby PJ, Lanteri-Minet M, Wen S, Hours-Zesiger P, Ferrari MD, et al. Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study. The Lancet. 2018;392(10161):2280-7.

249. Dodick DW, Silberstein SD, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Effect of Fremanezumab Compared With Placebo for Prevention of Episodic Migraine: a Randomized Clinical Trial. Jama. 2018;319(19):1999-2008.

250. Sakai F, Suzuki N, Kim BK, Tatsuoka Y, Imai N, Ning X, et al. Efficacy and safety of fremanezumab for episodic migraine prevention: multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in Japanese and Korean patients. Headache. 2021;61(7):1102-11.

251. Ferrari MD, Diener HC, Ning X, Galic M, Cohen JM, Yang R, et al. Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial. The Lancet. 2019;394(10203):1030-40.

252. Stauffer VL, Dodick DW, Zhang Q, Carter JN, Ailani J, Conley RR. Evaluation of Galcanezumab for the Prevention of Episodic Migraine: The EVOLVE-1 Randomized Clinical Trial. JAMA Neurol. 2018;75(9):1080-8.

253. Detke HC, Millen BA, Zhang Q, Samaan K, Ailani J, Dodick DW, et al. Rapid Onset of Effect of Galcanezumab for the Prevention of Episodic Migraine: Analysis of the EVOLVE Studies. Headache. 2020;60(2):348-59.

254. Skljarevski V, Matharu M, Millen BA, Ossipov MH, Kim BK, Yang JY. Efficacy and safety of galcanezumab for the prevention of episodic migraine: results of the EVOLVE-2 Phase 3 randomized controlled clinical trial. Cephalalgia. 2018;38(8):1442-54.

255. Mulleners WM, Kim BK, Lainez MJA, Lanteri-Minet M, Pozo-Rosich P, Wang S, et al. Safety and efficacy of galcanezumab in patients for whom previous migraine preventive medication from two to four categories had failed (CONQUER): a multicentre, randomised, double-blind, placebo-controlled, phase 3b trial. The Lancet Neurology. 2020;19(10):814-25.

256. Diener H-C, Tassorelli C, Dodick DW, Silberstein SD, Lipton RB, Ashina M, et al. Guidelines of the International Headache Society for controlled trials of preventive treatment of migraine attacks in episodic migraine in adults. Cephalalgia. 2020;40(10):1026-44.

257. Dodick DW, Ashina M, Brandes JL, Kudrow D, Lanteri-Minet M, Osipova V, et al. ARISE: a Phase 3 randomized trial of erenumab for episodic migraine. Cephalalgia. 2018;38(6):1026-37.

258. Stewart-Williams S, Podd J. The placebo effect: dissolving the expectancy versus conditioning debate. Psychological bulletin. 2004;130(2):324.

259. Biohaven Pharmaceuticals Inc. Data on File: Interim Meta-Analysis Results (Continuous Outcomes), Placebo response SLR for migraine preventive therapies. New Haven (CT), USA: Biohaven Pharmaceuticals Inc; 2020.

260. Tepper S, Cirillo J, Kim E, L'Italien G, Tweedie J, Lodaya K, et al., editors. Increased placebo response over time in oral migraine preventive trials: a systematic literature review and meta-analysis. American Headache Society, 64th Annual Scientific Meeting 2022; Denver (CO), USA.

261. Dias S, Sutton A, Welton N, Ades A. NICE DSU TECHNICAL SUPPORT DOCUMENT 3: HETEROGENEITY: SUBGROUPS, META-REGRESSION, BIAS AND BIAS-ADJUSTMENT REPORT BY THE DECISION SUPPORT UNIT. Sheffield (UK): Decision Support Unit, ScHARR, University of Sheffield; 2012.

262. Cameron C, Varu A, Lau A, Gharaibeh M, Paulino M, Rogoza R. Incorporating adjustments for variability in control group response rates in network meta-analysis: a case study of biologics for rheumatoid arthritis. BMC medical research methodology. 2019;19(1):193.

263. ClinicalTrials.gov. Observational Study to Assess Maternal, Fetal and Infant Outcomes Following Exposure to Rimegepant (MONITOR) (BHV3000-402 NCT05046613) 2021 [Available from: https://clinicaltrials.gov/ct2/show/NCT05046613 (last accessed May 2022)

264. Hubig L, Smith T, L'italien G, Harris L, Powell L, Johnston K, et al., editors. P-85 Patient preferences for calcitonin gene-related peptide (CGRP) inhibitors in the preventive treatment of migraine: A discrete choice experiment in the US and Germany American Headache Society; 2022; Denver (CO), USA.

265. L'Italien G, Harris L, Mohajer A, Scripture J, Coric V, Rosen N, editors. Real world evidence of reduction in point prevalence of medication overuse headache after migraine therapy with rimegepant. American Headache Society 64th Annual Scientific Meeting; 2022; Denver (CO), USA.

266. González-Hernández A, Marichal-Cancino BA, MaassenVanDenBrink A, Villalón CM. Side effects associated with current and prospective antimigraine pharmacotherapies. Expert Opin Drug Metab Toxicol. 2018;14(1):25-41.

267. Buse D, Iyer R, Cohen J, et al. Burden of Comorbid Depression and Anxiety on Migraine-specific Health-related Quality of Life in Adult Migraine Patients in the United States (4438). Neurology. 2020;94.

268. Cole J, Lin P, Rupnow M. Minimal important differences in the Migraine-Specific Quality of Life Questionnaire (MSQ) version 2.1. Cephalalgia. 2009;29(11):1180-7.

269. L'Italien G, Popoff E, Harris L, Johnston K, Croop R, Coric V, et al. Acute Treatment with Rimegepant 75 mg Confers Clinically Relevant Improvement in Lost Time (Days) Due to Migraine: Results From a 1-Year, Open-Label Safety Study (BHV3000-201) (Poster 4945). Neurology. 2021;96(15 Supplement):4945.

270. Atlas S, Touchette D, Agboola F, Lee T, Chapman R, Pearson S, et al. Acute treatments for migraine: effectiveness and value 2020 [Available from: http://icer-review.org/material/acute-migraine-evidence-report/ (last accessed Jan 18)

271. Touchette D, Atlas S, Agboola F, Joshi M, Lee T, Chapman R, et al. PND15 LONG-TERM COST-EFFECTIVENESS OF LASMIDITAN, UBROGEPANT AND RIMEGEPANT FOR TREATMENT OF ACUTE MIGRAINE. Value in Health. 2020;23:S261.

272. Johnston KM, L'Italien G, Harris L, Deighton A, Popoff E, Croop R, et al. Novel acute therapies in the treatment of migraine: impact of re-dosing on cost-utility outcomes. J Med Econ. 2021;24(1):512-3.

273. National Institute for Health and Clinical Excellence. Guide to the methods of technology appraisal 2013 Manchester: NICE; 2013 [Available from: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781 (last accessed April 2022)

274. British National Formulary [Available from: https://bnf.nice.org.uk/drug/. (last accessed May 2022)

275. Gillard PJ, Devine B, Varon SF, Liu L, Sullivan SD. Mapping from disease-specific measures to health-state utility values in individuals with migraine. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2012;15(3):485-94.

276. Stafford M, Hareendran A, Ng-Mak D, Insinga R, Xu R, Stull D. EQ-5D™-derived utility values for different levels of migraine severity from a UK sample of migraineurs. Health and Quality of Life Outcomes. 2012;10:65.

277. Vo P, Fang J, Bilitou A, et al. Patients' perspective on the burden of migraine in Europe: a cross-sectional analysis of survey data in France, Germany, Italy, Spain, and the United Kingdom. The Journal of Headache and Pain. 2018;19:82.

278. Schürks M, Rist P, Shapiro R, et al. Migraine and Mortality: A Systematic Review and Meta-Analysis. Cephalalgia. 2011;31(12):1301-14.

279. Office for National Statistics. National life tables, United Kingdom 2018-2020 2021 [Available from:

https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2018to2020 (last accessed January 2022)

280. Johnston K, L'Italien G, Popoff E, Croop R, Thiry A, Harris L, et al. Utility Mapping of Rimegepant by Change in Monthly Migraine Days. American Headache Society and American Academy of Neurology Meetings2020.

281. Jhingran P, Osterhaus J, Miller D, Lee J, Kirchdoerfer L. Development and validation of the Migraine-Specific Quality of Life Questionnaire. Headache. 1998;38(4):295-302.

282. Xu R, Insinga RP, Golden W, Hu XH. EuroQol (EQ-5D) health utility scores for patients with migraine. Quality of life research. 2011;20(4):601-8.

283. Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. Medical care. 2005:203-20.

284. Kind P, Hardman G, Macran S. UK Population Norms for EQ-5D 1999 [Available from: https://www.york.ac.uk/che/pdf/DP172.pdf (last accessed May 2022)

285. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. Medical decision making : an international journal of the Society for Medical Decision Making. 2011;31(6):800-4.

286. 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)

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

288. Office for National Statistics. Employee earnings in the UK: 2021 2021 [updated 26 October 2021. Available from: https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/earningsandworkinghours/bulletins/annualsurveyofhoursandearnings/2021 (last accessed March 2022)

289. Office for National Statistics. Labour market overview, UK: March 2022 2022 [updated 15 March 2022. Available from: https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/employmentandemployeetypes/bulletins/uklabourmarket/march2022 (last accessed March 2022)

290. Mahon R, Lang A, Vo P, Huels J, Cooney P, Danyliv A, et al. Cost-effectiveness of erenumab for the preventive treatment of migraine in patients with prior treatment failures in Sweden. PharmacoEconomics. 2021;39(3):357-72.

291. Lipton RB, Brennan A, Palmer S, Hatswell AJ, Porter JK, Sapra S, et al. Estimating the clinical effectiveness and value-based price range of erenumab for the prevention of migraine in patients with prior treatment failures: a US societal perspective. J Med Econ. 2018;21(7):666-75.

292. Silva C, Monge S, Cooney P, Mahon R, Laires PA. PND56 Cost-Effectiveness of Erenumab for the Prevention of Migraine in Portugal. Value in Health. 2020;23(Supplement 2):S633.

293. Smolen L, Thompson S, Klein T, Cohen J, Gandhi SK. PND37 10-YEAR COST-EFFECTIVENESS ANALYSES OF RESPONSE-BASED USE OF FREMANEZUMAB AS

PREVENTIVE TREATMENT IN CHRONIC AND EPISODIC MIGRAINE FOR PATIENTS WITH INADEQUATE RESPONSE TO PRIOR PREVENTIVE TREATMENTS. Value in Health. 2019;22:S743.

294. Smolen L, Cohen J, Klein T, Gandhi SK, Thompson S. 10-Year cost-effectiveness analyses of fremanezumab compared to erenumab as preventive treatment in episodic migraine for patients with inadequate response to prior preventive treatments. Neurology Conference: 72nd Annual Meeting of the American Academy of Neurology, AAN. 2020;94(15 Supplement).

295. Sussman M, Benner J, Neumann P, Menzin J. Cost-effectiveness analysis of erenumab for the preventive treatment of episodic and chronic migraine: Results from the US societal and payer perspectives. Cephalalgia. 2018;38(10):1644-57.

296. Mahon R, Huels J, Hacking V, Cooney P, Danyliv A, Vudumula U, et al. Economic evaluations in migraine: Systematic literature review and a novel approach. Journal of Medical Economics. 2020:1-13.

297. Ahmed F, Gaul C, García-Moncó JC, Sommer K, Martelletti P. An open-label prospective study of the real-life use of onabotulinumtoxinA for the treatment of chronic migraine: the REPOSE study. J Headache Pain. 2019;20(1):26.

298. Pozo-Rosich P, Lucas C, Watson DPB, Gaul C, Ramsden E, Ritter S, et al. Burden of Migraine in Patients With Preventive Treatment Failure Attending European Headache Specialist Centers: Real-World Evidence From the BECOME Study. Pain and Therapy. 2021.

299. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2010;13(5):509-18.

B.5. Appendices

The following appendices are provided as a standalone document:

Appendix C Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D Identification, selection and synthesis of clinical evidence

Appendix E Subgroup Analysis

Appendix F Adverse reactions

Appendix G Identification, selection and synthesis of cost-effectiveness evidence

Appendix H Identification, selection and synthesis of health-related quality-of-life evidence

Appendix I Identification, selection and synthesis of cost and healthcare resource identification, measurement, and valuation

Appendix J Clinical outcomes and disaggregated results from the model

Appendix K Checklist of confidential information

Appendix L: BHV3000-310 (NCT04574362): summary results

Appendix M: Summary of methodology of relevant studies

Appendix N: Extended description on the distribution of MMD (prevention)

Appendix O: Supplementary information, cost-effectiveness analysis – acute

Appendix P: Supplementary information, cost-effectiveness analysis – prevention

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Rimegepant for treating or preventing migraine [ID1539]

Clarification questions

August 2022

File name	Version	Contains confidential information	Date
ID1539 rimegepant clarification questions to PM for company [ACIC] 09082022	V1.0	ACIC redacted	09/08/2022

Notes for company

Highlighting in the template

Square brackets and [redacted] highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [redacted] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

ACUTE MIGRAINE

Population

A1. Priority question. Please confirm whether the rimegepant marketing authorisation covers any patient with acute migraine attacks or whether its use in the acute setting is also limited to those with episodic migraine (as for preventive use).

According to the SmPC of rimegepant, the acute use is not limited to episodic migraines. It is indicated for “the acute treatment of migraine in adults with or without aura” without further limitation by migraine frequency.[1]

A2. Priority question. The acute clinical trials only include people with moderate-severe migraine attacks. If recommended, would rimegepant also be offered to patients to treat mild attacks?

According to the SmPC, rimegepant is indicated for “the acute treatment of migraine in adults with or without aura”. NICE guidance on headache and migraine diagnosis and treatment classifies migraine pain intensity as “Moderate or severe”, to differentiate migraine from Tension-type headache where pain is “Mild or moderate”,

suggesting that moderate-severe attacks are a feature of migraine and therefore where a migraine treatment would be used.[2,3]

SLR and included clinical evidence

A3. Priority question. The EAG considers that the mITT population is the most appropriate population to inform the analysis, as the randomisation was not stratified for triptan failure and results are similar regardless of triptan failure status, as concluded in the final paragraph of section B.2.7.1.1 of the CS.

Pooled baseline characteristics and results across trials are currently only provided for the different subgroups based on the number of failed triptans (Tables 19 and 20 of the CS). Please provide pooled results and baseline characteristics for the mITT population (currently only provided for each study separately in Tables 13-15 of the CS).

Baseline characteristic of the mITT pooled population of studies 301, 302 and 303 are shown in the table below. These results show baseline characteristics were similar between the pooled rimegepant and placebo groups, and consistent with the previously submitted characteristics for the individual studies, with a mean age around 41 years and the majority of patients being female.

Baseline characteristics for mITT participants in pooled analysis of BHV3000-303, BHV3000-301 and BHV3000-302

Characteristic	pooled mITT 301, 302 and 303	
	Rimegepant (n=[redacted])	Placebo (n=[redacted])
Age in years, mean (SD)	[redacted]	[redacted]
Sex, n (%)		
Males	[redacted]	[redacted]
Females	[redacted]	[redacted]
Race, n (%)		
White	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Multiple	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]

Characteristic	pooled mITT 301, 302 and 303	
	Rimegepant (n=[redacted])	Placebo (n=[redacted])
Native Hawaiian or other Pacific Islander	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Body mass index in kg/m^2, mean (SD)	[redacted]	[redacted]
Migraine history		
Attacks per month, mean (SD)	[redacted]	[redacted]
Duration in hours of untreated attacks, mean (SD)	[redacted]	[redacted]
Migraine with aura, n (%)	[redacted]	[redacted]
Migraine without aura, n (%)	[redacted]	[redacted]
MBS for treated attack, n (%)		
Photophobia	[redacted]	[redacted]
Phonophobia	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Proportion that were taking concomitant prophylactic migraine treatment at baseline	[redacted]	[redacted]
had a history of medication overuse headache[a] (if measured)	[redacted]	[redacted]

[a] Medication overuse headache was not actively probed at enrolment, MOH were reported by two subjects.

Results of outcomes for the pooled mITT 301, 302 and 303 studies are provided below. These are generally consistent with the results seen in the individual studies regardless of prior triptan experience or size of placebo response. However, Pfizer note that the placebo response was typically lower in the triptan failure population and may better reflect this hard-to-treat population.

Primary and secondary endpoint results for mITT participants in acute treatment from mITT pooled population of studies BHV3000-303, BHV3000-301 and BHV3000-302.

	pooled mITT 301, 302 and 303		
	Rimegepant (N=[redacted])	Placebo (N=[redacted])	Risk difference (95% CI) p-value
Co-primary endpoints			
Freedom from pain at 2 hours	[redacted]	[redacted]	[redacted]
Freedom from MBS at 2 hours	[redacted]	[redacted]	[redacted]
Secondary endpoints			

	pooled mITT 301, 302 and 303		
	Rimegepant (N=[redacted])	Placebo (N=[redacted])	Risk difference (95% CI) p-value
Pain relief at 2 hours post-dose	[redacted]	[redacted]	[redacted]
Ability to function normally at 2 hours post-dose	[redacted]	[redacted]	[redacted]
Sustained pain relief from 2 to 24 hours post-dose	[redacted]	[redacted]	[redacted]
Sustained freedom from MBS, 2 to 24 hours post-dose[a]	[redacted]	[redacted]	[redacted]
Use of rescue medication within 24 hours post-dose	[redacted]	[redacted]	[redacted]
Sustained ability to function normally, 2 to 24 hours post-dose[a]	[redacted]	[redacted]	[redacted]
Sustained pain relief, 2 to 48 hours post-dose	[redacted]	[redacted]	[redacted]
Sustained freedom from MBS, 2 to 48 hours post-dose[a]	[redacted]	[redacted]	[redacted]
Sustained ability to function normally, 2 to 48 hours post-dose[a]	[redacted]	[redacted]	[redacted]
Freedom from photophobia at 2 hours post-dose[b]	[redacted]	[redacted]	[redacted]
Ability to function normally at 90 mins post-dose[a]	[redacted]	[redacted]	[redacted]
Pain relief at 90 minutes post-dose[a]	[redacted]	[redacted]	[redacted]
Sustained pain freedom, 2 to 24 hours post-dose	[redacted]	[redacted]	[redacted]
Freedom from MBS at 90 minutes post-dose[a]	[redacted]	[redacted]	[redacted]
Pain freedom at 90 minutes post-dose[a]	[redacted]	[redacted]	[redacted]
Freedom from phonophobia at 2 hours post-dose[b]	[redacted]	[redacted]	[redacted]
Sustained pain freedom from 2 to 48 hours post-dose	[redacted]	[redacted]	[redacted]
Pain relief at 60 minutes post-dose[a]	[redacted]	[redacted]	[redacted]
Ability to function normally at 60 minutes post-dose[a]	[redacted]	[redacted]	[redacted]
Freedom from nausea at 2 hours post-dose[b]	[redacted]	[redacted]	[redacted]
Pain relapse from 2 to 48 hours post-dose[c]	[redacted]	[redacted]	[redacted]

[a] Only assessed in 303.
[b] Based on mITT subjects who have the symptom at migraine onset.
[c] Based on mITT subjects who have pain freedom at 2 hours post-dose.

A table summarising the outcomes research endpoints for the pooled mITT population of 301, 302 and 303 are provided in the table below. Amongst patients that experienced pain relief within 2 hours a higher proportion preferred to remain on rimegepant.

	pooled mITT 301, 302 and 303	
n (%)	**Rimegepant (N=[redacted])**	**Placebo (N=[redacted])**
Preference of medication at 24 hours post-dose (PoM)[a]		
Participants who provided a response, n (%)	[redacted]	[redacted]
Preferred study treatment	[redacted]	[redacted]
Preferred previous treatment	[redacted]	[redacted]
No preference	[redacted]	[redacted]
Participants who responded to treatment[b], n (%)	[redacted]	[redacted]
Preferred study treatment	[redacted]	[redacted]
Preferred previous treatment	[redacted]	[redacted]
No preference	[redacted]	[redacted]
Migraine specific quality of life questionnaire (MQoLQ) at 24 hours post-dose, continuous analysis		
Median total score (min, max)[c]	[redacted]	[redacted]

[a] Migraine preference of medicine (PoM) scale: The PoM is a subject-rated, 5-point scale that measures preference of the study medication compared to the previous medications to treat migraine pain. The eDiary was used to evaluate the PoM
[b] Responders are those subjects who reported a pain score of "no pain" or "mild pain" at 2 hours post-dose and who did not take rescue medication prior to or at 2 hours. [C] Total scores is invalid please see discussion in question A5

A4. Priority question. The EAG does not consider the rationale provided for excluding studies CN170-003 (NCT01430442) and BHV3000-310 (NCT04574362) from the CS to be sufficient (based on being a phase 2 study or geographical location, particularly as geographical location was not an issue in terms of including studies in the NMA for preventive treatment). BHV3000-310, in particular, is important as it provides a second study using the ODT formulation of rimegepant.

Given that these RCTs have similar inclusion criteria to the three included trials, for the mITT population, please perform a sensitivity analysis including these two studies for the following outcomes: freedom from pain at 2 h, pain relief at 2 h, pain severity trajectories over 48 h and adverse events

OR provide stronger rationale as to why one or both of these studies are not relevant:

In addition to CN170-003 (NCT01430442) being a phase 2 study, was the fact that this study excluded those that had no migraine relief from triptans also a reason for exclusion?

While the study design from BHV3000-310 is similar to the other acute trials the focus on Chinese and Korean patients introduced a risk of some heterogeneity, for example due to potential ethnic differences in reporting pain.[4] Furthermore, the study did not capture information on previous triptan attempts, information that is key to understand the generalisability of findings to the positioning of rimegepant in the decision problem, ie. as an option for patients who have had inadequate symptom relief after trials of at least two triptans.

For completeness, Pfizer has provided further analyses as requested by the EAG by pooling of patient level data from the following studies:

- BHV3000-301
- BHV3000-302
- BHV3000-303
- BHV3000-310

But for reason outlined above, we don't believe this pooled analysis should form the basis for the base case analysis.

Study CN170-003 is not appropriate for pooling with these acute studies based on the following rationale:

- Non-equivalent formulations: Study CN170-003 was a Phase 2 rimegepant study that used an early formulation of rimegepant (free-base capsule formulation). This formulation has not been demonstrated as bioequivalent to the commercialized ODT formulation (used in BHV3000-303 and BHV3000-310) or the tablet formulation (used in BHV3000-301 and BHV3000-302). The ODT and tablet formulations have been demonstrated to be bioequivalent.
- Different inclusion/exclusion criteria were used in CN170-003: as patients could be randomized to sumatriptan in this study, the study excluded patients who did not receive migraine relief from triptans as well as patients with cardiovascular contraindications to triptans. The later trials did not have these exclusion criteria.
- Analytical techniques differ: CN170-003 performed primary efficacy analyses based on a Bayesian, hierarchical, logistic regression model of the dose-response relationship of the primary endpoint and used LOCF (Last

Observation Carried Forward). The subsequent studies (301, 302, 303 and 310) classified patients with missing data at 2 hours as failures, as were patients who took rescue medication at or before 2 hours.

A table providing the mITT population pooled results for BHV3000-301, BHV3000-302, BHV3000-303 and BHV3000-310 for freedom from pain at 2 hours and pain relief at 2 hours is provided below.

	Pooled mITT BHV3000-301, BHV3000-302, BHV3000-303 and BHV3000-310		
	Rimegepant, n/N (%)	**Placebo, n/N (%)**	**Risk difference, percentage points (95% CI); p-value**
Freedom from pain at 2 h	[redacted]	[redacted]	[redacted]
Pain relief at 2 h	[redacted]	[redacted]	[redacted]

A table providing the pooled results for BHV3000-301, BHV3000-302, BHV3000-303 and BHV3000-310 for adverse events is provided below. These data show a safety profile consistent with the previously submitted trials with rimegepant having a safety profile similar to that seen in placebo.

	Pooled BHV3000-301, BHV3000-302, BHV3000-303 and BHV3000-310	
	Rimegepant	**Placebo**
Study population	Treated participants	
On-treatment AEs, n (%)	[redacted]	[redacted]
Reported in ≥1% in any group		
UTI	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
On-treatment severe AEs	[redacted]	[redacted]
Reported in >1 participant		
Diarrhoea	[redacted]	[redacted]
On-treatment AEs related to study drug	[redacted]	[redacted]
Reported in ≥1% of any group		
Nausea	[redacted]	[redacted]

On treatment serious AE	[redacted]	[redacted]
On treatment serious AE related to study drug	[redacted]	[redacted]
On treatment AE leading to study drug discontinuation	[redacted]	[redacted]
Deaths	[redacted]	[redacted]

A table providing the post-hoc analysis of pain severity trajectories over 48 h used in cost-effectiveness analyses for the pooled results for BHV3000-301, BHV3000-302, BHV3000-303 and BHV3000-310 is provided below. Data are presented by 2 hour responder status for the rimegepant and placebo patients. Values represent the mean number of hours spent in each pain state over 48 hours and corresponding standard error. Note that this analysis requires subjects to have pain intensity data reported for all scheduled time points between 0-48 hrs (ie no missing data), therefore the sample size for this analysis is smaller than for the mITT population.

	Pooled BHV3000-301, BHV3000-302, BHV3000-303 and BHV3000-310			
	Responders (2-hour)		**Non-Responders (2-hour)**	
Rimegepant	**N=[redacted]**		**N=[redacted]**	
	Mean hours in pain state	**SE**	**Mean hours in pain state**	**SE**
No pain	[redacted]	[redacted]	[redacted]	[redacted]
Mild pain	[redacted]	[redacted]	[redacted]	[redacted]
Moderate pain	[redacted]	[redacted]	[redacted]	[redacted]
Severe pain	[redacted]	[redacted]	[redacted]	[redacted]
BSC	**N=704**		**N=758**	
	Mean hours in pain state	**SE**	**Mean hours in pain state**	**SE**
No pain	[redacted]	[redacted]	[redacted]	[redacted]
Mild pain	[redacted]	[redacted]	[redacted]	[redacted]
Moderate pain	[redacted]	[redacted]	[redacted]	[redacted]
Severe pain	[redacted]	[redacted]	[redacted]	[redacted]

Similar to the pain trajectories pattern observed among triptan failures analysis, responders were found to spend more time in the “no / mild pain” categories than non-responders. The only difference is the standard error are much smaller in the pooled analysis of BHV3000-301, BHV3000-302, BHV3000-303 and BHV3000-310, as expected due to an increase in sample size.

Please also find in Appendix 3, the baseline characteristics of the pooled patient population from BHV3000-301, BHV3000-302, BHV3000-303, and BHV3000-310.

A5. Priority question. For all trials included in the clinical evidence for acute migraine, please add to the baseline characteristics in Table 13 of the CS and provide the following for each study arm:

a) Proportion that were taking concomitant prophylactic migraine treatment at baseline;

The proportion of patients taking concomitant prophylactic migraine treatment at baseline have been added to the contents of Table 13 below along with the baseline characteristics of patients in the BHV3000-310 study.

	BHV3000-303 mITT		BHV3000-301 mITT		BHV3000-302 mITT		BHV3000-310 mITT	
Characteristic	**Rimegepant (n=669)**	**Placebo (n=682)**	**Rimegepant (n=543)**	**Placebo (n=541)**	**Rimegepant (n=537)**	**Placebo (n=535)**	**Rimegepant (n=[redacted])**	**Placebo (n=[redacted])**
Age in years, mean (SD)	40.3 (12.1)	40.0 (11.9)	41.9 (12.3)	41.3 (12.1)	40.2 (11.9)	40.9 (12.1)	[redacted]	[redacted]
Sex, n (%)							[redacted]	[redacted]
Males	101 (15)	103 (15)	79 (14.5)	78 (14.4)	58 (10.8)	63 (11.8)	[redacted]	[redacted]
Females	568 (85)	579 (85)	464 (85.5)	463 (85.6)	479 (89.2)	472 (88.2)	[redacted]	[redacted]
Race, n (%)							[redacted]	[redacted]
White	496 (74)	521 (76)	417 (76.8)	444 (82.1)	394 (73.4)	399 (74.6)	[redacted]	[redacted]
Black or African American	141 (21)	125 (18)	107 (19.7)	80 (14.8)	111 (20.7)[b]	118 (22.1)[b]	[redacted]	[redacted]
Asian	8 (1)	19 (3)	6 (1.1)	7 (1.3)	8 (1.5)	8 (1.5)	[redacted]	[redacted]
Multiple	7 (1)	9 (1)	10 (1.8)	7 (1.3)	14 (2.6)	5 (0.9)	[redacted]	[redacted]
American Indian or Alaska Native	4 (1)	3 (<1)	1 (0.2)	3 (0.6)	4 (0.7)	5 (0.9)	[redacted]	[redacted]
Native Hawaiian or other Pacific Islander	11 (2)	5 (1)	2 (0.4)	0	6 (1.1)	0	[redacted]	[redacted]
Missing	2 (<1)	0	-	-	-	-	[redacted]	[redacted]
Body mass index in kg/m^2, mean (SD)	31.1 (8.2)	30.6 (8.0)	[redacted]	[redacted]	31.0 (7.9)	31.8 (8.5)	[redacted]	[redacted]
Migraine history								
Attacks per month, mean (SD)	4.6 (1.8)[a]	4.5 (1.8)[a]	[redacted]	[redacted]	4.5 (1.9)	4.6 (1.8)	[redacted]	[redacted]
Duration in hours of untreated attacks, mean (SD)	28.7 (21.5)	30.4 (21.7)	[redacted]	[redacted]	32.0 (22.5)	32.9 (21.7)	[redacted]	[redacted]

	BHV3000-303 mITT		BHV3000-301 mITT		BHV3000-302 mITT		BHV3000-310 mITT	
Characteristic	**Rimegepant (n=669)**	**Placebo (n=682)**	**Rimegepant (n=543)**	**Placebo (n=541)**	**Rimegepant (n=537)**	**Placebo (n=535)**	**Rimegepant (n=[redacted])**	**Placebo (n=[redacted])**
Migraine with aura, n (%)	189 (28)	220 (32)	190 (35.0)	183 (33.8)	[redacted]	[redacted]	[redacted]	[redacted]
Migraine without aura, n (%)	480 (72)	462 (68)	353 (65.0)	358 (66.2)	[redacted]	[redacted]	[redacted]	[redacted]
MBS for treated attack, n (%)								
Photophobia	359 (54)	374 (55)	[redacted]	[redacted]	277 (51.6)	279 (52.1)	[redacted]	[redacted]
Phonophobia	108 (16)	101 (15)	[redacted]	[redacted]	72 (13.4	92 (17.2)	[redacted]	[redacted]
Nausea	189 (28)	195 (29)	[redacted]	[redacted]	169 (31.5)	148 (27.7)	[redacted]	[redacted]
Proportion that were taking concomitant prophylactic migraine treatment at baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes:
[a]Restricted to moderate and severe attacks; [b]Race categorised in Study BHV3000-302 as Black

b) Proportion that had medication overuse headache at baseline, or had a history of medication overuse headache (if measured), how this was measured and whether this was addressed (if medication overuse headache was resolved by stopping the treatment) before enrolment in the study;

Across the acute trials two patients were identified with a history of medication overuse headache. However, history of medication overuse headache (MOH) was not pro-actively probed during enrolment. We believe the number with MOH at screening was low due to the inclusion / exclusion criteria and prohibited medication restrictions that were applied in the acute trials: i) not more than 8 attacks of moderate or severe intensity per month within last 3 months; ii) less than 15 days with headache (migraine or non-migraine) per month in each of the 3 months prior to the screening visit. Note the protocols did not require stopping a medication that caused MOH prior to study entry.

c) Baseline values for the Migraine Specific quality of life Questionnaire (MQoLQ) for studies that reported this as an outcome, and clarify why

median (min, max) values were provided rather than means in Table 15 of the CS. Please provide the mean values for comparison.

We believe EAG refers to the MQoLQ at **24 hours post-dose** reported in Table 15 of the CS, as opposed to the **baseline values**, since MQoLQ was not measured at baseline. As per EAG request, the mean values and standard deviations for the MQoLQ at 24 hrs values are shown in the table below.

Please note that a transcription error has recently been identified in the items of the questionnaire for two of the 5 domains which invalidates the total score. Therefore, the total migraine MQoLQ should not be used in this appraisal.

Table migraine specific QoL questionnaire (MQoLQ) at 24 hours post-dose

Characteristic	mITT BHV3000-303		mITT BHV3000-301		mITT BHV3000-302		mITT BHV3000-310	
	Rimegepant (n=669)	Placebo (n=682)	Rimegepant (n=543)	Placebo (n=541)	Rimegepant (n=537)	Placebo (n=535)	Rimegepant (n=[redacted])	Placebo (n=[redacted])
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A6. Priority question. For the included rimegepant acute trials and the long-term safety study, please provide results for discontinuations in each arm across the trial period. Please provide a breakdown of the reasons for discontinuation, including numbers for each reason.

Discontinuation Results taken from Subject Disposition: Enrolled Subjects Studies BHV3000-301[5], 302[6], 303[7] and 310[8]

	303			302			301			310		
	rimegepant n (%)	placebo n (%)	Overall n (%)	rimegepant n (%)	placebo n (%)	Overall n (%)	rimegepant n (%)	placebo n (%)	Overall n (%)	rimegepant n (%)	placebo n (%)	Overall n (%)
Randomised subjects (n)	732	734	1466	594	592	1186	582	580	1162	[redacted]	[redacted]	[redacted]
Not treated Subjects	50 (6.8)	41 (5.6)	91 (6.2)	51 (8.6)	49 (8.3)	100 (8.4)	36 (6.2)	31 (5.3)	67 (5.8)	[redacted]	[redacted]	[redacted]
Reasons not treated/discontinued												
Adverse Event	1 (2)	0	1 (1.1)	0	1 (2)	1 (1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lost To Follow-Up	10 (20)	6 (14.6)	16 (17.6)	11 (21.6)	9 (18.4)	20 (20)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Physician Decision	0	0	0	1 (2)	0	1 (1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Never Experienced Migraine (of Moderate to Severe Intensity)	28 (56)	25 (61)	53 (58.2)	25 (49)	31 (63.3)	56 (56)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-Compliance With Study Drug	0	1 (2.4)	1 (1.1)	0	1 (2)	1 (1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pregnancy	2 (4)	0	2 (2.2)	1 (2)	0	1 (1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protocol Deviation	1 (2)	0	1 (1.10	0	1 (2)	1 (1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal By Subject (Consent)	7 (14)	5 (12.2)	12 (13.2)	3 (5.9)	3 (6.1)	6 (6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	1 (2)	4 (9.8)	5 (5.5)	3 (5.9)	0	3 (3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated Subjects	682 (93.2)	693 (94.4)	1375 (93.8)	543 (91.4)	543 (91.7)	1086 (91.6)	546 (93.8)	549 (94.7)	1095 (94.2)	[redacted]	[redacted]	[redacted]
Completed Acute Phase	679 (99.6)	689 (99.4)	1368 (99.5)	538 (99.1)	542 (99.8)	1080 (99.4)	541 (99.1)	540 (98.4)	1081 (98.7)	[redacted]	[redacted]	[redacted]
Discontinued Acute Phase	3 (0.4)	4 (0.6)	7 (0.5)	5 (0.9)	1 (0.2)	6 (0.6)	5 (0.9)	9 (1.6)	14 (1.3)	[redacted]	[redacted]	[redacted]
Reason for Discontinuation												
Lost To Follow-Up	3 (100)	1 (25)	4 (57.1)	2 (40)	1 (100)	3 (60)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Never Experienced Migraine (of Moderate to Severe Intensity)	0	0	0	1 (20)	0	1 (16.7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Technical problem	0	0	0	1 (20)	0	1 (16.7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protocol Deviation	0	1 (25)	1 (14.3)	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse Event	0	0	0	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	303			302			301			310		
	rimegepant n (%)	placebo n (%)	Overall n (%)	rimegepant n (%)	placebo n (%)	Overall n (%)	rimegepant n (%)	placebo n (%)	Overall n (%)	rimegepant n (%)	placebo n (%)	Overall n (%)
Withdrawal By Subject (Consent)	0	2 (50)	2 (28.6)	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19	0	0	0	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	0	0	0	1 (20)	0	1 (16,7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Analysis Populations												
Treated Subjects (Safety Analysis Population)	682 (93.2)	693 (94.4)	1375 (93.8)	543 (91.4)	543 (91.7)	1086 (91.6)	546 (93.8)	549 (94.7)	1095 (94.2)	[redacted]	[redacted]	[redacted]
mITT Subjects (Efficacy Analysis Population)	669 (91.4)	682 (93)	1351 (92.2)	537 (90.4)	535 (90.4)	1072 (90.4)	543 (93.3)	541 (93.3)	1084 (93.3)	[redacted]	[redacted]	[redacted]

Note: Treated subjects represent the actual treatments received by enrolled subjects. mITT subjects represent the randomized treatments of subjects who took study medication, had a baseline migraine of moderate to severe intensity, and provided at least one post-baseline efficacy data point

Discontinuation Results taken from Subject Disposition – Screened Subjects

Study BHV3000-201[9]

Disposition	Number (%)		
	PRN Dosing (2-8)	PRN Dosing (9-14)	EOD+PRN Dosing (4-14)
	N= 1646	N=862	N=511
Screened	[redacted]	[redacted]	[redacted]
Did not enrol in the long-term treatment period	[redacted]	[redacted]	[redacted]
Did not enter the observational period	[redacted]	[redacted]	[redacted]
Reason for Discontinuation			
Screen Failure	[redacted]	[redacted]	[redacted]
Withdrawal by Subject	[redacted]	[redacted]	[redacted]
Lost to follow up	[redacted]	[redacted]	[redacted]
Non-Compliance	[redacted]	[redacted]	[redacted]
Entered the observational period	[redacted]	[redacted]	[redacted]
Reason for Discontinuation			
Screen Failure	[redacted]	[redacted]	[redacted]
Withdrawal by Subject	[redacted]	[redacted]	[redacted]
Non-Compliance	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]
Eligibility Failure due to baseline laboratory values	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Protocol Deviation	[redacted]	[redacted]	[redacted]

A7. Priority question. Please clarify how (or if) patients from the three acute RCTs currently included in the analysis (BHV3000-301, -302 and -303) continued into the long-term safety study (BHV3000-201):

a) **Do all patients from the acute studies enter BHV3000-201 or only those who respond?**

b) **Can patients who weren't in the acute pooled studies enter BHV3000-201?**

c) **Is it only those that were initially taking rimegepant in the RCTs that can enter BHV3000-201, or may some patients taking placebo in these RCTs then start rimegepant and be included in the long-term safety study?**

Patients from the three acute RCTs (BHV3000-301, -302 and -303) were all eligible for inclusion in BHV3000-201, irrespective of response, and could be evaluated for inclusion. Patients from the three acute RCTs had to satisfy the inclusion/exclusion criteria for BHV3000-201 to enter the long-term safety study.

Patients who weren't in the acute studies (BHV3000-301, -302 and -303) could also enter BHV3000-201, as long as they satisfied the inclusion/exclusion criteria for BHV3000-201.

A8. **Please provide an excluded studies list (with rationale for exclusion) for the acute migraine SLR, as has been done for migraine prevention.**

The entire list contains more than 500 studies, and it is reported on a separate Appendix 1.

A9. For all included trials, please provide a breakdown (with numbers of patients excluded for each reason) of the exclusion reasons of participants from the mITT population (i.e. if the main reason was that they did not have a migraine attack of moderate to severe pain intensity, did not take a dose of study treatment or did not have ≥1 efficacy assessment after dose administration).

The response is included within the answer to Question A6.

A10. Please provide a risk of bias assessment for the long-term safety study (BHV3000-201), as has been done for RCTs already in Appendix D.5 of the CS.

Study BHV3000-201 is a non-comparative, open-label, long term safety study, and as such is non-randomised. Patients were assigned to one of three different enrolment groups according to baseline MMD, dosing schedule and duration of follow-up:

1. PRN (MMD 2-8 at baseline) – 52 weeks follow-up
2. PRN (MMD 9-14 at baseline) – 52 weeks follow-up
3. EOD + PRN (MMD 4-14 at baseline) – 12 weeks follow up

The primary and secondary outcomes from the study were safety related and descriptively summarised per enrolment group and across all enrolment groups.

A summary of the risk of bias assessment using the NICE assessment tool has been provided below along with relevant notes relating to the study design.

Table showing risk of bias assessment for BHV3000-201.

Study ID and name	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blind to treatment allocation, what might be the likely impact on the risk of bias (for each outcome)?	Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Also consider whether the authors of the study publication declared any conflicts of interest/study funding.
BHV3000-201	N/A -study design was non-randomised	N/A – study design was open label	N –patients were allocated to enrolment groups based on baseline MMD	N – open label study design	The following numbers of patients discontinued treatment during the long-term treatment period: PRN (2-8): [redacted]. PRN (9-14): [redacted] EOD+PRN: [redacted]	N	N/A analysis performed on safety population	Y

As the EAG have also requested information on the BHV3000-310 study, as risk of bias assessment has also been provided for this RCT in the table below.

Table showing risk of bias assessment for BHV3000-310.

Study ID and name	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blind to treatment allocation, what might be the likely impact on the risk of bias (for each outcome)?	Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Also consider whether the authors of the study publication declared any conflicts of interest/study funding.
BHV3000-310	Y	Y	Y	Y	N	N	Y	N/A

Analysis and pooling

A11. Priority question. The EAG's clinical experts were concerned that efficacy may differ with different formulations of rimegepant, as can be observed for other acute migraine treatments in practice.

a) **Please confirm whether, if recommended, it would be the oro-dispersible (ODT) formulation of rimegepant that is prescribed to patients (and the tablet formulation is not available)?**

The oro-dispersible (orally disintegrating tablet (ODT)) formulation of rimegepant (identified as oral lyophilisate in the SmPC) is the sole formulation available for prescription to patients. The tablet formulation has not been included in the MHRA marketing authorization and SmPC. The clinical efficacy of the formulations can be seen in Table 14 in Doc B[10]. Trial 303 is assessing the ODT and Trials 301 and 302 is assessing the tablet formulation. The results of both primary endpoints in each trial are very similar to each other. Freedom from pain at 2 hours saw 21.2%, 19.2%, and 19.6% of participants for trials 303, 301, and 302 respectively. The second primary endpoint for freedom from MBS at 2 hours saw 35.1%, 36.6%, and 37.6% trials 303, 301, and 302 respectively. Additionally, regulators in Europe and UK have been satisfied by the bioequivalence (C_{max} and AUC) of the ODT and tablet formulations. However, the T_{max} of the ODT is approximately 30 minutes faster than the tablet, which may explain the faster pain relief observed in 303 and 310 (see question A13).

b) **For the mITT population, please provide pooled results (for freedom from pain at 2 h, pain relief at 2 h, pain severity trajectories over 48 h and adverse events outcomes) from trials using the ODT formulation only (including the additional trial mentioned in question A4 above) and comment on whether these are comparable to when all trials, regardless of formulation, are included.**

The trials included in the pooled analysis using the ODT formulation were:

- BHV3000-303
- BHV3000-310

These have been pooled using the patient level data and the pooled results for freedom from pain at 2 h and pain relief at 2 h provided in the table below.

	Pooled mITT populations of BHV3000-303 and BHV3000-310		
	Rimegepant, n/N (%)	**Placebo, n/N (%)**	**Risk difference, percentage points (95% CI); p-value**
Freedom from pain at 2 h	[redacted]	[redacted]	[redacted]
Pain relief at 2 h	[redacted]	[redacted]	[redacted]

The pooled results for the pain trajectory outcomes over 48 hours are provided in the following table. As discussed previously in Question A4, this analysis requires subjects to have pain intensity data reported for all scheduled time points between 0-48 hrs (ie no missing data), therefore the sample size for this analysis is smaller than for the mITT population.

	Pooled populations of BHV3000-303 and BHV3000-310			
	Responders (2-hour)		**Non-Responders (2-hour)**	
Rimegepant	**N=**[redacted]		**N=**[redacted]	
	Mean	**SE**	**Mean**	**SE**
No pain	[redacted]	[redacted]	[redacted]	[redacted]
Mild pain	[redacted]	[redacted]	[redacted]	[redacted]
Moderate pain	[redacted]	[redacted]	[redacted]	[redacted]
Severe pain	[redacted]	[redacted]	[redacted]	[redacted]
BSCPlacebo	**N=**[redacted]		**N=**[redacted]	
	Mean	**SE**	**Mean**	**SE**
No pain	[redacted]	[redacted]	[redacted]	[redacted]
Mild pain	[redacted]	[redacted]	[redacted]	[redacted]
Moderate pain	[redacted]	[redacted]	[redacted]	[redacted]
Severe pain	[redacted]	[redacted]	[redacted]	[redacted]

The safety data from the treated participants of the pooled analyses of the BHV3000-303 and BHV3000-310 are provided in the table below. These data show that rimegepant was well tolerated in adult subjects with moderate to severe migraine, and a safety profile consistent with the previously submitted trials, having a safety profile comparable to placebo.

	Pooled BHV3000-303 and BHV3000-310	
	Rimegepant	**Placebo**
Study population	Treated participants	
On-treatment AEs, n (%)	[redacted]	[redacted]
Reported in ≥1% in any group		
UTI	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
On-treatment severe AEs	[redacted]	[redacted]
Reported in >1 participant		
Diarrhoea	[redacted]	[redacted]
On-treatment AEs related to study drug	[redacted]	[redacted]
Reported in ≥1% of any group		
Nausea	[redacted]	[redacted]
On treatment serious AE	[redacted]	[redacted]
On treatment serious AE related to study drug	[redacted]	[redacted]
On treatment AE leading to study drug discontinuation	[redacted]	[redacted]
Deaths	[redacted]	[redacted]

Comparison of pooled ODT only formulation with pooled analyses including ODT and tablet formulations. The studies included in these two pooled analyses are summarised in the table below:

Trial	ODT only pooled analysis	ODT and tablet pooled analysis
BHV3000-301	Excluded	Included
BHV3000-302	Excluded	Included
BHV3000-303	Included	Included
BHV3000-310	Included	Included

The results of the two pooled analyses show consistent data for rimegepant across the outcomes of freedom from pain at 2 h and pain relief at 2 h and safety. As per the point raised previously in A11a, the faster T_{max} of the ODT formulation may have

contributed to a slightly higher percentage of patients receiving pain relief at 2 hours than compared to the combined tablet and ODT formulation pooled analysis: in the ODT pooled analysis for freedom from pain at 2 hours was seen in [redacted] of rimegepant patients and [redacted] of placebo patients. For the pooled analysis of ODT and tablet formulations, freedom from pain at 2 hours was seen in [redacted] of rimegepant patients and [redacted]% of placebo patients. For the pain relief at 2 hours endpoint, the ODT pooled analysis showed [redacted] for rimegepant and [redacted] for placebo. For the pooled analysis of ODT and tablet formulations, the results were similar at [redacted] for rimegepant and [redacted] for placebo. The results for the safety data were also similar: for the percentage of patients with an on-treatment adverse event on the ODT pooled analysis: rimegepant ([redacted]) and placebo ([redacted]); for the ODT and tablet pooled analysis: rimegepant ([redacted]) and placebo ([redacted]). Similarly, on-treatment adverse events related to study drug for the ODT pooled population were: rimegepant ([redacted]) and placebo ([redacted]), while for the ODT and tablet pooled analysis, they were: rimegepant ([redacted]) and placebo ([redacted]).

A12. Priority question. For the overall mITT population, please provide Forest plots for pooled analyses of each outcome (including any additional pooled analyses requested at clarification) so that heterogeneity across studies can be visualised. Please include I^2 values in these Forest plots. Please justify why fixed or random effects were considered the most appropriate for the pooled analyses.

Patient level data are available to the sponsor of the studies for rimegepant, in such circumstances it is preferable to pool data at the individual patient level and therefore there is no need to resort to the use of meta-analytical techniques based on the aggregate data from each study. The acute studies were pooled using patient level data and stratified by study and use of prophylactic treatment within study to provide the pooled results. An assessment of homogeneity for the pooled outcomes of the co-primary endpoint of freedom from pain at 2 hours and the outcome used in the economic model to assess response to acute treatment (pain relief at 2 hours) has been provided using the Breslow-Day test for homogeneity of odds ratios between studies; the results are presented as the Chi-square and p-value. The p-values

indicate the lack of any statistically significant heterogeneity for these outcomes regardless of the pooled population analysed.

	Pooled mITT populations of BHV3000-301, BHV3000-302, BHV3000-303			Pooled mITT populations of BHV3000-301, BHV3000-302, BHV3000-303 and BHV3000-310			Pooled mITT populations of BHV3000-303 and BHV3000-310		
	Rimegepant, n/N (%)	**Placebo, n/N (%)**	**Risk difference, percentage points (95% CI); p-value**	**Rimegepant, n/N (%)**	**Placebo, n/N (%)**	**Risk difference percentage points (95% CI); p-value**	**Rimegepant, n/N (%)**	**Placebo, n/N (%)**	**Risk difference, percentage points (95% CI); p-value**
freedom from pain at 2 h	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
freedom from pain at 2 hrs Breslow-Day test for homogeneity of odds Ratios between studies: Chi-square (p-value)		[redacted]			[redacted]			[redacted]	
pain relief at 2 h	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
pain relief at 2 h Breslow-Day test for homogeneity of odds Ratios between studies: Chi-square (p-value)		[redacted]			[redacted]			[redacted]	

A13. Please provide subgroup results from each trial for prophylactic use vs no prophylactic medication use as has been done for other subgroup analyses in Table 37 of the CS appendices.

Co-primary endpoint: subgroup analysis by prophylactic medication use[11]

	Study BHV3000-303			Study BHV3000-301			Study BHV3000-302			Study BHV3000-310		
	RIM	PBO	RD (95% CI)	RIM	PBO	RD (95% CI)	RIM	PBO	RD (95% CI)	RIM	PBO	RD (95% CI)
Prophylactic medication use = Yes												
Pain freedom at 2 hours post-dose (%)												
MBS freedom at 2 hours post dose (%)												
Prophylactic medication use = No												
Pain freedom at 2 hours post-dose (%)												
MBS freedom at 2 hours post dose (%)												

A14. In Table 11 of the CS, a sensitivity analysis accounting for missing data was described for study BHV3000-302. Please provide results of this sensitivity analysis and a discussion of whether results for this trial were affected.

Due to software issues with e-diaries (fixed with a patch on 13 September 2017) there was a modest loss of data for patients who had a qualifying migraine before 13 September 2017. To explore the potential impact, a sensitivity analyses was performed for the primary endpoints (pain freedom at 2 hrs post dose and freedom from MBS at 2 hrs post dose) on the mITT populations of two groups of patients:

- Patients with a qualifying migraine on or before 13 September 2017
- Patients with a qualifying migraine after 13 September 2017

The sample size of the patients with a qualifying migraine on or before 13 September 2017 (rimegepant n=[redacted], placebo n=[redacted]) was notably smaller than that of patients with a qualifying migraine after 13 September 2017 (rimegepant n=[redacted], placebo n=[redacted]).

Despite the difference in sample sizes, the results for pain freedom at 2 hrs and freedom from MBS at 2 hours for the two sensitivity analyses show [redacted] (see table below for comparison of the sensitivity results and the mITT analyses from study 302).

Table of results of the sensitivity analyses of study BHV3000-302 comparing the mITT results with results from patients with migraine onset prior to or on 13 September 2017 and migraine onset after 13 September 2017.

	Rimegepant	Placebo	Risk difference rimegepant vs placebo
mITT population			
N			
pain freedom at 2 hrs (n/N)			
common risk			
ASE			
95% CI			
p-Value			
Freedom from MBS at 2 hrs (n/N)			
common risk			
ASE			
95% CI			
p-Value			
Date of Study Migraine Onset : Prior to or on 13 September 2017			
N			
pain freedom at 2 hrs (n/N)			
common risk			
ASE			
95% CI			
p-Value			
Freedom from MBS at 2 hrs (n/N)			
common risk			
ASE			
95% CI			
p-Value			
Date of Study Migraine Onset: After 13 September 2017			
N			
pain freedom at 2 hrs (n/N)			
common risk			
ASE			
95% CI			
p-Value			
Freedom from MBS at 2 hrs (n/N)			
common risk			
ASE			
95% CI			
p-Value			

A15. Please provide a definition of 'AEs associated with potential abuse' (Table 45 of the CS for the long-term safety study). Does this include some events that could be considered medication overuse? If so, please provide the number of these events.

'AEs associated with potential abuse' were defined as one of the following:

- Drug abuse, dependence and withdrawal" Standardized MedDRA Query (SMQ): All preferred terms (PTs).

- Preferred Terms based on clinical review of AE PTs in the depressant, stimulant, and psychotomimetic categories of the General Disorders and Administration Site Conditions SOC, Nervous System Disorders SOC, and Psychiatric Disorders SOC, as recommended in Section V.B of the FDA Guidance for Industry Assessment of Abuse Potential of Drugs. Note that some Preferred Terms in this list are also part of the "Drug abuse, dependence and withdrawal" SMQ.

- Preferred Terms of dizziness only if concurrent with any euphoria-related AE.

AEs associated with potential abuse were monitored in subjects with migraine treated with Rimegepant 75mg in the long term, open-label safety study 201 and prevention study 305. The types and frequency of on-treatment AEs categorised as associated with potential drug abuse were generally consistent across enrolment groups of study 201. The most frequently reported on-treatment AEs categorised as associated with potential drug abuse (greater than or equal to 1% of subjects overall) were fatigue ([redacted]) and somnolence ([redacted]). MoH (reported verbatim term of rebound headaches; considered possibly related to study drug was reported for [redacted] subject in study 201.

In the pivotal Phase 2/3 migraine prophylaxis study 305, no potential drug abuse AEs were reported in greater than or equal to 1% of subjects treated with rimegepant. The most frequently reported on-treatment potential drug abuse were depression (0.9%), fatigue (0.7%), insomnia (0.6%), and somnolence (0.4%). There were no reports of medication overuse headache among subjects treated with Rimegepant in this study.[12]

MIGRAINE PREVENTION

SLR and included clinical evidence

A16. Priority question. For all trials included in the clinical evidence for migraine prevention, please add to the baseline characteristics in Tables 25 and 32 of the CS and provide the proportion in each study arm that:

a) **Had medication overuse headache at baseline, or had a history of medication overuse headache (if measured), and whether this was addressed (if medication overuse headache was resolved by stopping the treatment) before enrolment in the study.**

This data was not widely available across the included clinical evidence studies and has not been extracted.

b) **With prior preventive treatment failures (and mean number of failed treatments if reported).**

Unfortunately, this data was not extracted during the systematic literature review. Please refer to question **A18** for the proportion of patients with prior prevention treatment history.

A17. Priority question. Please provide baseline characteristics for the rimegepant trial (Table 25 in the CS) separately for those with episodic migraine (excluding those with chronic migraine), including any additional characteristics requested above in question A16.

Baseline characteristics for the post-hoc analysis of the treated population of patients with episodic migraine are included in the table below and were similar to those for the combined population of EM and CM previously presented in CS Table 25. Episodic migraine was defined as the absence of chronic migraine from history or entry criteria.

Demographics and Rimegepant Baseline Characteristics Episodic Migraine Double-Blind Treated Subjects (BHV3000-305): DBT population

Characteristic	BHV3000-305 double-blind treated population episodic migraine identified by using history or entry criteria	
	Rimegepant (n=[redacted])	Placebo (n=[redacted])
Age in years, mean (SD)	[redacted]	[redacted]
Gender, n (%)		
Women	[redacted]	[redacted]
Men	[redacted]	[redacted]
Race, n (%)		
White	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Multiple	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]
Native Hawaiian or other Pacific Islander	[redacted]	[redacted]
Weight (kg), mean (SD)	[redacted]	[redacted]
Height (cm), mean (SD)	[redacted]	[redacted]
BMI in kg/m^2, mean (SD)	[redacted]	[redacted]
Migraine history		
Age at disease onset in years, mean (SD)	[redacted]	[redacted]
Moderate or severe attacks per month, mean (SD)	[redacted]	[redacted]
Duration in hours of untreated attacks, mean (SD	[redacted]	[redacted]
Primary migraine type n (%)		
Without aura	[redacted]	[redacted]
With aura	[redacted]	[redacted]
Proportion that was taking concomitant prophylactic migraine treatment at baseline n (%)	[redacted]	[redacted]
Proportion that failed previous treatment	[redacted]	[redacted]
Episodic migraine evaluable mITT population	[redacted]	[redacted]
MMD in the observation period, mean (SD)*	[redacted]	[redacted]

Abbreviations: BMI, body mass index; IQR, interquartile range; SD, standard deviation *baseline MMD data for the observational period are not available for Episodic Migraine treated patients; values shown are for the Episodic Migraine evaluable mITT subjects.

References: Demographics and baseline characteristics [13]; migraine history[14] concomitant prophylactic migraine treatment[15] MMD in the observation period[16]

A18. Priority question. The EAG does not consider a trial being phase 2 a valid reason for exclusion from the NMA (Table 30 of the CS appendices). Please provide sensitivity analyses with these studies included (including results for fixed and random effects models for all outcomes in the NMA with and without

baseline adjustment, and parameters for each of these models e.g. between-trial heterogeneity, DIC and plots to assess convergence):

- **NCT02025556 - Bigal 2015;**
- **CGAN - NCT02959177 - Sakai 2020;**
- **NCT02630459 - Sakai 2019;**
- **CGAB - NCT02163993 - Skljarevski 2018.**

The following study was also excluded because it was a phase 2 study but it also used a dose different to those recommended by NICE - please confirm whether this is considered a reason for exclusion and update Table 30 of the CS appendices as appropriate:

- **ART-01 - NCT01625988 - Dodick 2014.**

NOTE: Following EAG Addendum clarification questions received on 25 July, the NMA has been amended, the new revised base case NMA are presented in the response to Addendum 3 question, the response to question A18 has been amended to reflect the revised results.

Study screening

The full text publications of the five studies listed in priority question A18 (NCT02025556 - Bigal 2015, CGAN - NCT02959177 - Sakai 2020, NCT02630459 - Sakai 2019, CGAB - NCT02163993 - Skljarevski 2018 and ART-01 - NCT01625988 - Dodick 2014**)** were screened again by two independent reviewers for inclusion into the NMA sensitivity analysis, while relaxing the study design criteria for Phase 2/3 or Phase 3 trials only, and thus allowing inclusion of Phase 2 trials. The first four studies met PICOS criteria and were included.

Dodick 2014 (ART NCT01625988) examined a dose of galcanezumab (LY2951742) not authorised for use in the UK (150 mg dose) and was excluded. Therefore, the reason for exclusion in Table 30 should be updated from “study design” to “intervention” as per the table below.

Excluded study	Reason for exclusion
NCT02025556 Bigal 2015[1]	**Study design**: Phase 2
CGAJ NCT02614287 Camporeale 2018[2]	**Outcomes**: Safety endpoints only
ARISE NCT02483585 Dodick 2018[3]	**Intervention**: Erenumab 70 mg dose, not recommended by NICE
ART-01 NCT01625988 Dodick 2014[4]	**Intervention:** Galcanezumab (LY2951742) 150 mg dose, not authorised in UK
HALO LT NCT02638103 Goadsby 2020[5]	**Outcomes:** Safety endpoints only
CGAP NCT02959190 Hirata 2021[6]	**Outcomes**: Safety endpoints only
CGAN NCT02959177 Sakai 2020[7]	**Study design**: Phase 2
NCT03303105 Sakai 2021[8]	**Outcomes**: Safety endpoints only
NCT02630459 Sakai 2019[9]	**Study design**: Phase 2
CGAB NCT02163993 Skljarevski 2018	**Study design**: Phase 2
NCT01952574 Sun 2016[10]	**Intervention**: Erenumab 70 mg dose, not recommended by NICE
NCT03812224 Takeshima 2021[11]	**Intervention:** Erenumab 70 mg dose, not recommended by NICE

Abbreviations: NIOCE, National Institute for Health and Care Excellence; NMA, network meta-analysis

Interventions

For the Phase 2 trials considered in this sensitivity analysis, only NICE recommended doses were included, as outlined in the table below. To note, Bigal et al. 2015 did study the higher dose of fremanezumab (675mg) however at monthly administration frequency, not quarterly as is approved by the EMA and recommended by NICE. Therefore, the higher 675mg dose from Bigal 2015 was not included in the evidence base given the difference in dosing frequency, irrelevance to UK clinical practice, and discordance with the other included fremanezumab trials. Of the other three Phase 2 trials two examined the efficacy of galcanezumab 120 mg

monthly subcutaneous injection, and one studied erenumab 140 mg monthly subcutaneous injection.

Phase 2 trial	Therapy and dose studied (NICE recommended doses only)
NCT02025556 Bigal 2015[1]	Fremanezumab 225mg monthly, subcutaneous injection
CGAN NCT02959177 Sakai 2020[7]	Erenumab 140mg monthly, subcutaneous injection
NCT02630459 Sakai 2019[9]	Galcanezumab 120 mg monthly, subcutaneous injection
CGAB NCT02163993 Skljarevski 2018	Galcanezumab 120 mg monthly, subcutaneous injection

Patient population

The baseline patient characteristic table from the original CS (Table 32) was updated to include the additional Phase 2 mAb trials. The patient populations of these Phase 2 trials are largely consistent with those included in the original evidence base. Bigal 2015 enrolled a study population with 'high frequency episodic migraine' which is reflected in the relatively higher mean baseline MMD of 11.5. However, this is still within the baseline MMD range of the original trials included in the NMA. Sakai 2019 and Sakai 2020 were both conducted in primarily Asian populations, at various study sites across Japan. The proportion of patients with prior preventive medication use, and the proportion on concurrent preventive therapies in the Phase 2 studies are within the range of the original evidence base, and therefore are not anticipated to add additional sources of heterogeneity.

Table 32. Baseline patient characteristics for included studies, migraine prevention NMA, Phase 2 sensitivity analysis

Trial	Study arm	Pts treated (n)	Mean Age (SD) years	Sex (% Female)	Race (% White)	Migraine with aura (%)	EM (%)	Mean migraine duration, years (SD)	Mean MMD (SD) at baseline	Preventive treatment, prior use (%)	Preventive treatment, current use (%)
STRIVE NCT02456740 Goadsby 2017	**ERE 140**	319	40.4 (11.1)	85.3	NR	NR	100	NR	8.3 (2.5)	38.9	2.5
	PBO	319	41.3 (11.2)	85.9	NR	NR		NR	8.2 (2.5)	41.1	3.1
EMPOwER NCT03333109 Wang 2021	**ERE 140**	224	37.1 (9.6)	82.1	15.6	73.7	100	11.2 (9.7)	8.3 (3.1)	53.1	NR
	PBO	338	38.0 (10.1)	83.1	17.8	67.2		12.6 (10.2)	8.4 (2.8)	53	NR
LIBERTY NCT03096834 Reuter 2018	**ERE 140**	121	44.6 (10.5)	80	93	35	100	NR	9.2 (2.6)	100	0
	PBO	125	44.2 (10.6)	82	92	36		NR	9.3 (2.7)	100	0
HALO EM NCT02629861 Dodick 2018	**FRE 225**	290	42.9 (12.7)	84.1	NR	NR	100	20.7 (12.9)	8.9 (2.6)	NR	21.4
	FRE 675	291	41.1 (11.4)	86.3	NR	NR		20.0 (12.1)	9.3 (2.7)	NR	19.9
	PBO	294	41.3 (12.0)	84	NR	NR		19.9 (11.9)	9.1 (2.7)	NR	21.1
NCT03303092 Sakai 2021	**FRE 225**	121	44.4 (9.5)	83.5	NR	NR	100	22.0 (12.9)	8.6 (2.5)	NR	19.8
	FRE 675	119	41.9 (10.1)	84.9	NR	NR		18.3 (11.4)	8.7 (2.5)	NR	19.3
	PBO	117	44.2 (10.7)	85.5	NR	NR		19.4 (13.3)	9.0 (2.8)	NR	18.8
FOCUS NCT03308968 Ferrari 2019	**FRE 225**	283	45.9 (11.1)	84	93	NR	40	24.0 (13.7)	14.1 (5.6)*	100	0
	FRE 675	276	45.8 (11.0)	83	95	NR		24.3 (12.8)	14.1 (5.6)*	100	0
	PBO	279	46.8 (11.1)	84	94	NR		24.3 (13.6)	14.3 (6.1)*	100	0
EVOLVE-1 NCT02614183 Stauffer 2018	**GAL 120**	213	40.9 (11.9)	85	79.3	NR	100	12.1 (13.0)	9.2 (3.1)	62.4	NR
	PBO	443	41.3 (11.4)	83.6	82.2	NR		19.9 (12.3)	9.1 (3.0)	59.4	NR
EVOLVE-2 NCT02614196 Skljarevski 2018	**GAL 120**	231	40.9 (11.2)	85.3	71.9	NR	100	19.9 (11.7)	9.1 (2.9)	68	NR
	PBO	461	42.3 (11.3)	85.3	70.5	NR		21.2 (12.8)	9.2 (3.0)	64.6	NR
CONQUER NCT03559257	**GAL 120 (EM)**	137	45.9 (11.2)	82	86	47	100^	21.7 (12.7)	9.5 (3.0)	100	0
		132	46.3 (11.8)	89	87	42		22.9 (13.1)	9.2 (2.7)	100	0

Trial	Study arm	Pts treated (n)	Mean Age (SD) years	Sex (% Female)	Race (% White)	Migraine with aura (%)	EM (%)	Mean migraine duration, years (SD)	Mean MMD (SD) at baseline	Preventive treatment, prior use (%)	Preventive treatment, current use (%)
Mulleners 2020	**PBO (EM)**										
NCT03732638 Croop 2021	**RIM 75**	370	41.3 (13.0)	81	80	41	77	18 (range: 14-28)	10.3 (3.2)	[redacted]	[redacted]
	PBO	371	41.1 (31.1)	84	83	39		18 (range: 13-28)	10.1 (3.1)	[redacted]	[redacted]
Phase 2 trials											
NCT02025556 Bigal 2015	**FRE 225**	96	40.8 (12.4)	91	77	NR	100	18.9 (12.9)	11.5 (1.9)	33^^	34
	PBO	104	42.0 (11.6)	88	82	NR		21.1 (14.1)	11.5 (2.24)	27	27
NCT02630459 Sakai 2019	**ERE 140**	137	45 (range: 23-64)	81.8	NR	27	100	NR	8.1 (2.4)	56.2	10.9
	PBO	136	45 (range: 21-61)	86.8	NR	24.3		NR	7.7 (2.3)	55.9	9.6
CGAN NCT02959177 Sakai 2020	**GAL 120**	115	43.2 (10.0)	82.6	NR	NR	100	21.1 (11.8)	8.6 (2.8)	59.1	0
	PBO	230	44.2 (10.0)	85.2	NR	NR		21.2 (11.6)	8.6 (3.0)	60.9	0
CGAB NCT02163993 Skljarevski 2018	**GAL 120^^^**	273^^^	40.6 (11.9)^^^	84.6^^^	NR	NR	100	NR	6.7 (2.6) ^^^	NR	NR
	PBO	137	39.5 (12.1)	79.6	NR	NR		NR	6.6 (2.7)	NR	NR

Abbreviations: EM=episodic migraine, ERE=erenumab; FRE=fremanezumab; GAL=galcanezumab; MMD=monthly migraine day; NR=not reported; PBO=placebo; RIM=Rimegepant
Notes:
*note that baseline characteristics in FOCUS trial were only reported for mITT population, EM subgroup not reported separately
**BHV300-305 CSR
^EM subgroup only (stratified by EM/CM)
^^Reported as the proportion who discontinued prior preventives due to lack of efficacy
^^^Baseline not provided specifically for GAL 120 dose; estimates are for all patients receiving GAL

Trial endpoints

To align with the endpoint considered in the original NMA, the specific efficacy endpoint definition of CFB *at 12-weeks* and the proportion achieving 50% reduction from baseline *average over 12-weeks* were extracted from the Phase 2 trials. In three studies this required digitizing mean CFB measures and dispersion estimates from line graphs. Bigal 2015 was the only Phase 2 study that reported the 50% responder endpoint averaged over 12-weeks (located in the trial appendix; post-hoc analysis). In Sakai 2019, we were able to impute the endpoint from the monthly values published in the manuscript. Sakai 2020 only reported 50% responder rate over 1-6 months, therefore we were not able to include data from this trial for this endpoint. Similarly, Skljarevski 2018 reported the proportion achieving 50% reduction at 3-months, but not at months 1 and 2, therefore we were unable to calculate the average reduction over the 12-week study period. To summarize, all four phase 2 trials contributed data to the CFB endpoint, but only Bigal 2015 and Sakai 2019 were incorporated into the 50% responder NMA.

Trial	CFB in MMD		Percent with ≥50% MMD reduction from baseline	
	At 12-weeks*	Average over 12-weeks	At 12-weeks	Average over 12-weeks*
STRIVE NCT02456740 Goadsby 2017	Yes	No	Yes	Yes (Imputed from Goadsby 2017[248])
EMPOwER NCT03333109 Wang 2021	Yes	No	Yes	Yes (Imputed from Wang 2021[247]
LIBERTY NCT03096834 Reuter 2018	Yes	No	Yes	Yes (Imputed from Reuter 2018[248])
NCT02630459 Sakai 2019	Yes	No	Yes	Yes (imputed from Sakai 2019)
HALO EM NCT02629861 Dodick 2018	Yes	Yes	Yes	Yes
NCT03303092 Sakai 2021	Yes	Yes	No	Yes
FOCUS NCT03308968 Ferrari 2019	Yes**	Yes	No	Yes**

Trial	CFB in MMD		Percent with ≥50% MMD reduction from baseline	
	At 12-weeks*	Average over 12-weeks	At 12-weeks	Average over 12-weeks*
NCT02025556 Bigal 2015	Yes	No	Yes (post-hoc)	Yes (post-hoc)
EVOLVE-1 NCT02614183 Stauffer 2018	Yes	No	No	Yes (Imputed from Detke 2020[253])
EVOLVE-2 NCT02614196 Skljarevski 2018	Yes	No	No	Yes (Imputed from Detke 2020[253])
CONQUER NCT03559257 Mulleners 2020	Yes	Yes	No	Yes
CGAN NCT02959177 Sakai 2020	Yes	No	No	No
CGAB NCT02163993 Skljarevski 2018	Yes	No	Yes	No
NCT03732638 Croop 2021	Yes	Yes	No	Yes (From BHV3000-305 CSR)

Raw efficacy data from all included trials, migraine prevention NMA

The raw efficacy data are presented in the table below, including the Phase 2 trials considered in this sensitivity analysis. The phase 2 erenumab trial (Sakai et al. 2019) had the lowest placebo effect of any included trial in the network, for mean CFB in MMD (mean [SE]: 0.0 [0.31]). The placebo effect in the phase 2 galcanezumab trial by Sakai et al. 2020 was also relatively low compared to others in the evidence base for mean CFB in MMD (0.65 [0.28]). In both of these trials, over 50% of patients had prior experience with preventative migraine medications. As discussed in the CS, clinical feedback from the advisory board indicated that patients who have experienced lack of response or intolerability to prior preventive therapies, may in turn have lower expectations for the benefits of a subsequent study drug, which may be a contributing factor to the low placebo response observed in these trials.

Trial	Treatment	N	CFB in MMD, mean (SE)	≥50% reduction in MMD, n (%)
STRIVE NCT02456740 Goadsby 2017	PBO	316	-1.70 (0.21)	[redacted]
	ERE 140	318	-3.51 (0.21)	[redacted]
EMPOwER NCT03333109 Wang 2021	PBO	330	-3.10 (0.25)	[redacted]
	ERE 140	219	-4.79 (0.30)	[redacted]
LIBERTY NCT03096834 Reuter 2018	PBO	124	-0.20 (0.40)	[redacted]
	ERE 140	119	-1.80 (0.40)	[redacted]
HALO EM NCT02629861 Dodick 2018	PBO	290	-2.69 (0.28)	81 (27.93)
	FRE 225	287	-3.89 (0.28)	137 (47.74)
	FRE 675	288	-3.70 (0.30)	128 (44.44)
NCT03303092 Sakai 2021	PBO	116	-1.59 (0.44)	13 (11.21)
	FRE 225	121	-4.33 (0.38)	50 (41.32)
	FRE 675	117	-3.88 (0.44)	53 (45.30)
FOCUS NCT03308968 Ferrari 2019	PBO	278	-0.58 (0.35)	24 (8.63)
	FRE 225	283	-4.09 (0.36)	97 (34.28)
	FRE 675	276	-3.40 (0.39)	95 (34.42)
EVOLVE-1 NCT02614183 Stauffer 2018	PBO	433	-2.99 (0.27)	[redacted]
	GAL 120	213	-4.66 (0.54)	[redacted]
EVOLVE-2 NCT02614196 Skljarevski 2018	PBO	461	-2.19 (0.22)	[redacted]
	GAL 120	231	-3.77 (0.26)	[redacted]
CONQUER NCT03559257 Mulleners 2020	PBO	132	-0.59 (0.39)	23 (17.42)
	GAL 120	137	-2.80 (0.36)	57 (41.61)
NCT03732638 Croop 2021	PBO	347	-3.50 (0.20)	[redacted]
	RIM 75	348	-4.30 (0.26)	[redacted]
New Phase 2 trials				
NCT02025556 Bigal 2015	**FRE 225**	95	-6.27 (0.55)	45 (53.94)
	PBO	104	-3.46 (0.53)	28 (28.0)
NCT02630459 Sakai 2019	**ERE 140**	136	-1.74 (0.31)	[redacted]
	PBO	136	0.0 (0.31)	[redacted]
CGAN NCT02959177 Sakai 2020	**GAL 120**	115	-3.72 (0.40)	NR
	PBO	230	-0.65 (0.28)	NR
CGAB NCT02163993 Skljarevski 2018	**GAL 120**	70	-4.89 (0.36)	NR
	PBO	137	-3.54 (0.29)	NR

Abbreviations: CFB=change from baseline; ERE=erenumab; FRE=fremanezumab; GAL=galcanezumab; MMD=monthly migraine day; PBO=placebo; RIM=Rimegepant
Notes:
*imputed from monthly 50% responder rates, for Months 1-3**From ; BHV300-305 CSR

NMA results: Phase 2 sensitivity analysis

≥50% reduction in MMD outcome

Plots assessing convergence have been provided in Appendix 2.

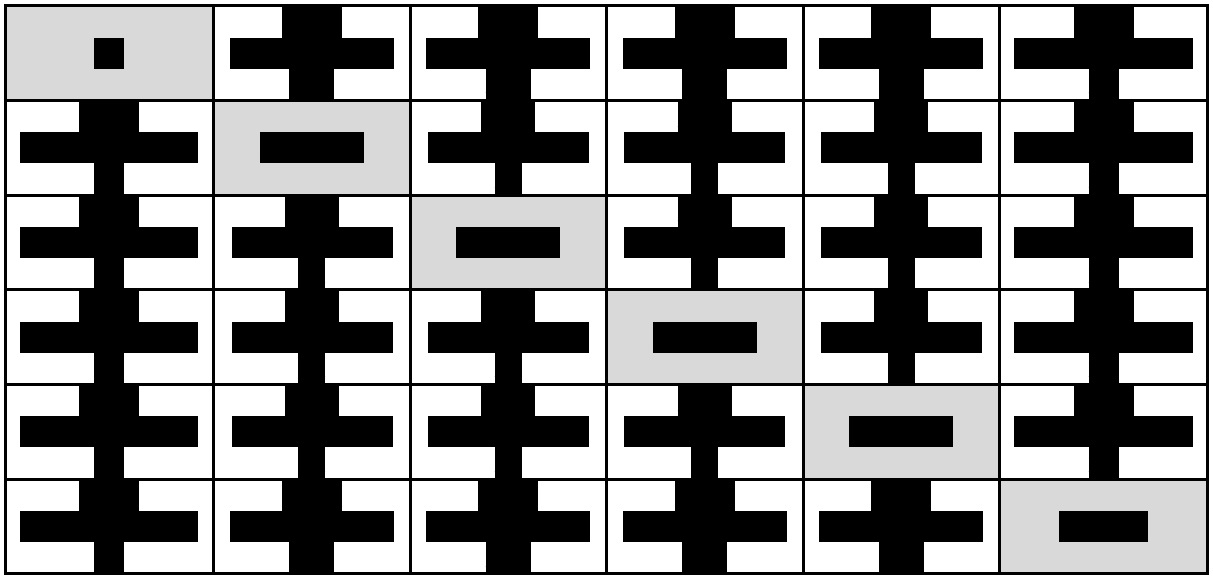
For ≥50% reduction in baseline MMD outcome, the fixed effects baseline adjusted model was chosen based on DIC values presented below. The model results are consistent with the base case analysis.

Table of DICs, ≥50% reduction in MMD outcome

Model	DEV	pD	DIC
FE	[redacted]	[redacted]	[redacted]
RE	[redacted]	[redacted]	[redacted]
FE_PBO	[redacted]	[redacted]	[redacted]
RE_PBO	[redacted]	[redacted]	[redacted]

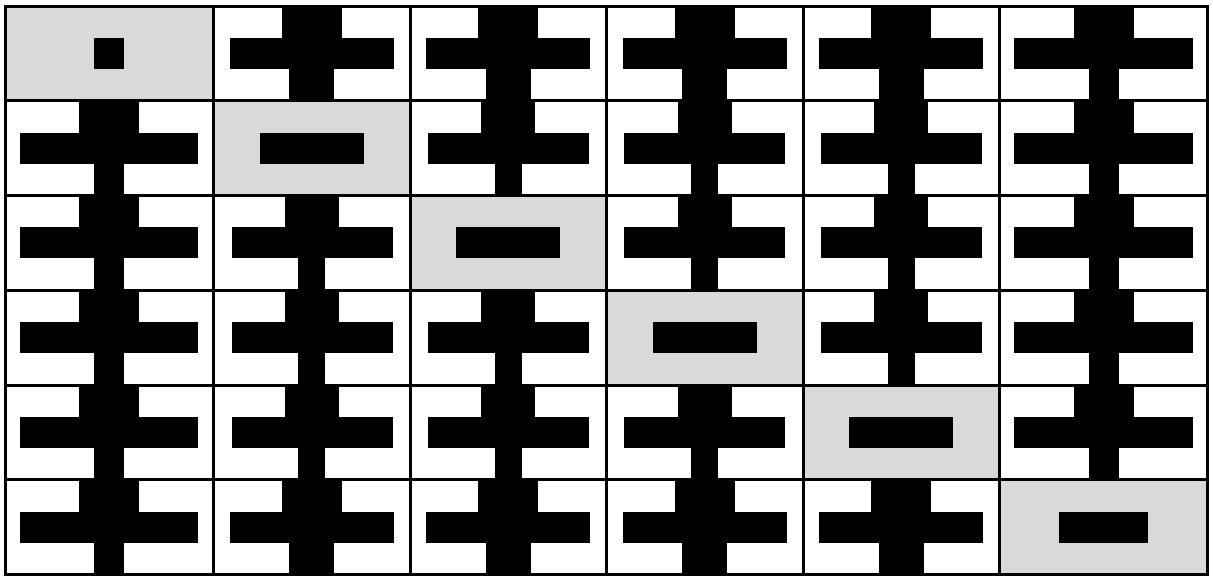
Abbreviations: Dbar = deviance; DIC = deviance information criterion; FE = fixed-effects; MMD = monthly migraine days; pD = effective number of parameters; RE = random-effects
Notes: green highlighted values indicate chosen model based on DIC

Proportion achieving 50% reduction from baseline MMD, Phase 2 sensitivity analysis, fixed effects baseline adjusted (chosen model based on DIC)



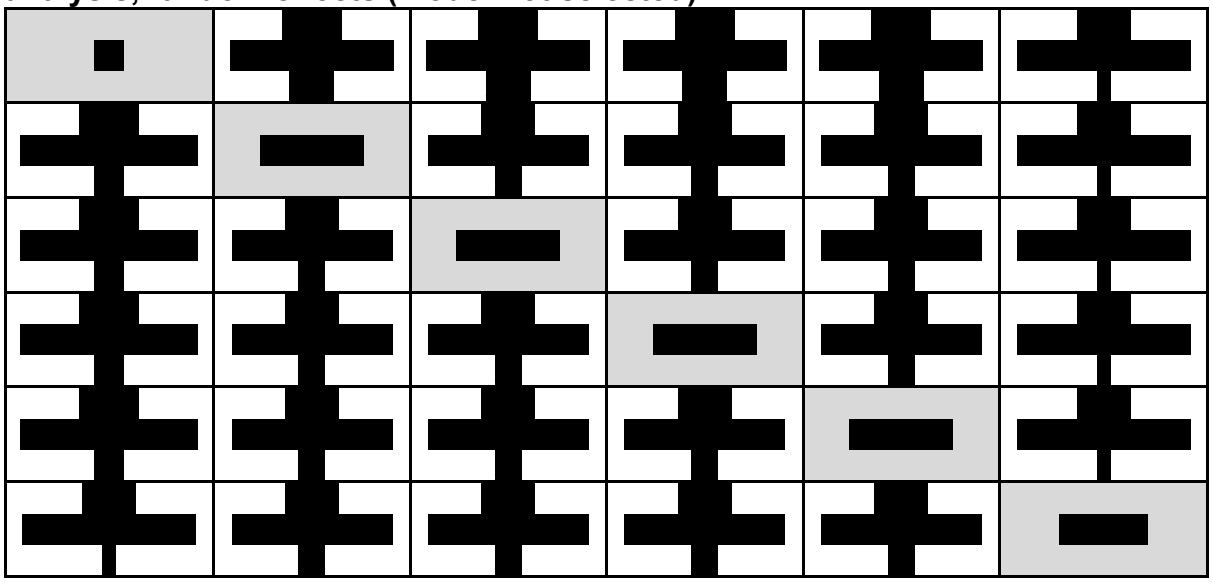
Abbreviations: CrI, credible interval; ERE, erenumab; FRE, fremanezumab; GAL, galcanezumab; PBO, placebo; RIM, Rimegepant
Notes:
Estimates are odds ratios (95% CrI). Bolded values are significant at a 5% level.

Proportion achieving 50% reduction from baseline MMD, Phase 2 sensitivity analysis, fixed effects (model not selected)



Abbreviations: CrI, credible interval; ERE, erenumab; FRE, fremanezumab; GAL, galcanezumab; PBO, placebo; RIM, Rimegepant
Notes:
Estimates are odds ratios (95% CrI). Bolded values are significant at a 5% level.

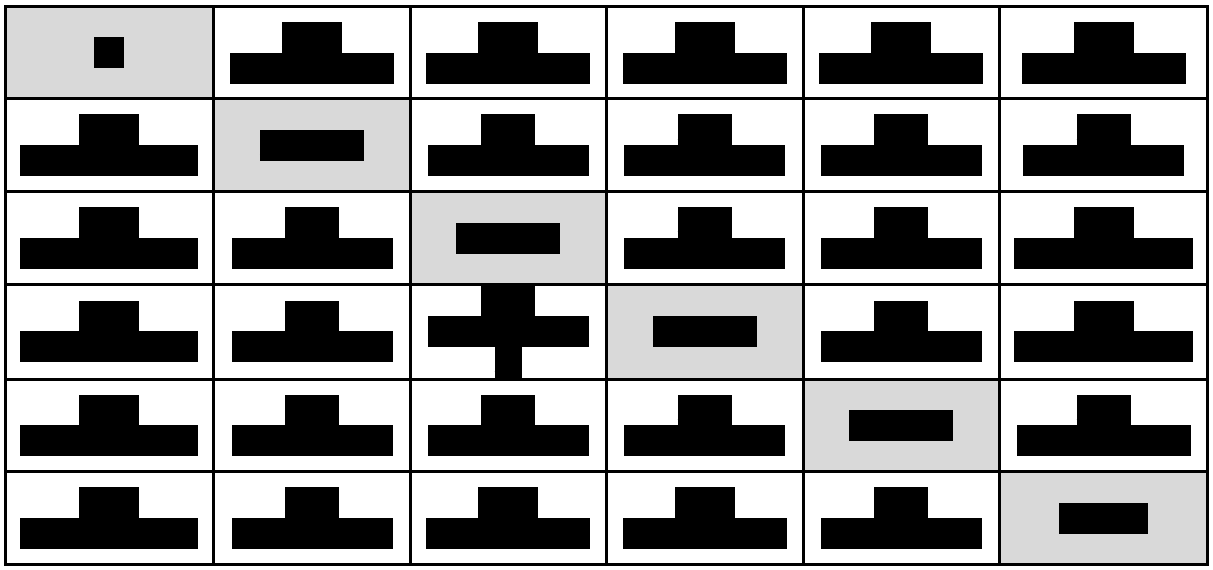
Proportion achieving 50% reduction from baseline MMD, Phase 2 sensitivity analysis, random effects (model not selected)



Abbreviations: CrI, credible interval; ERE, erenumab; FRE, fremanezumab; GAL, galcanezumab; PBO, placebo; RIM, Rimegepant
Notes:
Estimates are odds ratios (95% CrI). Bolded values are significant at a 5% level.

The between-trial heterogeneity parameter for this model, sd [median (95% CrI)] was: [redacted]**Proportion achieving 50% reduction from baseline MMD,**

Phase 2 sensitivity analysis, random effects baseline adjusted (model not selected)



Abbreviations: CrI, credible interval; ERE, erenumab; FRE, fremanezumab; GAL, galcanezumab; PBO, placebo; RIM, Rimegepant
Notes:
Estimates are odds ratios (95% CrI). Bolded values are significant at a 5% level.

The between-trial heterogeneity parameter for this model, sd [median (95% CrI)] was:

[redacted]

Mean change from baseline in monthly migraine days outcome

Plots assessing convergence can be found in Appendix 2.

For the MMD reduction outcome, the random effects model was chosen based on DIC values presented below. The model results are consistent with the base case analysis. There were no substantial differences between treatments with only the 95% CrI for rimegepant 75 mg vs fremanezumab 225mg marginally remaining above the null value of zero ([redacted]). We note the Bigal 2015 included only high frequency episodic migraine, which may have introduced further heterogeneity and this study was not used to inform decision making in previous fremanezumab appraisal [TA631, TA764].

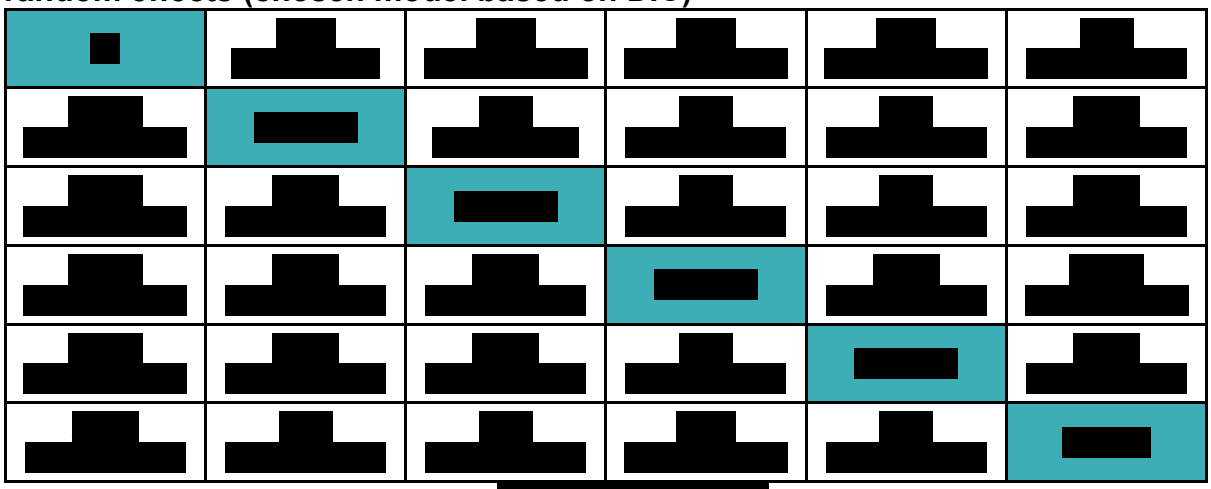
Table of DICs, change from baseline in monthly migraine day out come

Model	Dbar	pD	DIC
FE	[redacted]	[redacted]	[redacted]

RE	[redacted]	[redacted]	[redacted]
FE_BL adj	[redacted]	[redacted]	[redacted]
RE_BL adj	[redacted]	[redacted]	[redacted]

Abbreviations: Dbar = deviance; DIC = deviance information criterion; FE = fixed-effects; MMD = monthly migraine days; pD = effective number of parameters; RE = random-effects
Notes: green highlighted values indicate chosen model based on DIC

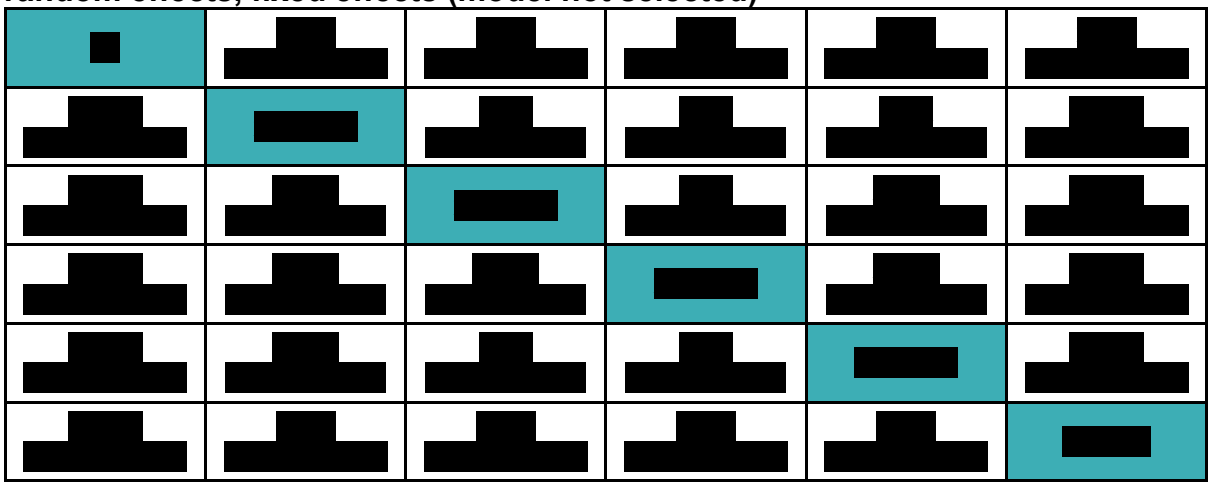
Change from baseline in monthly migraine days, Phase 2 sensitivity analysis, random effects (chosen model based on DIC)



median *sd* (95% credible interval): [redacted]

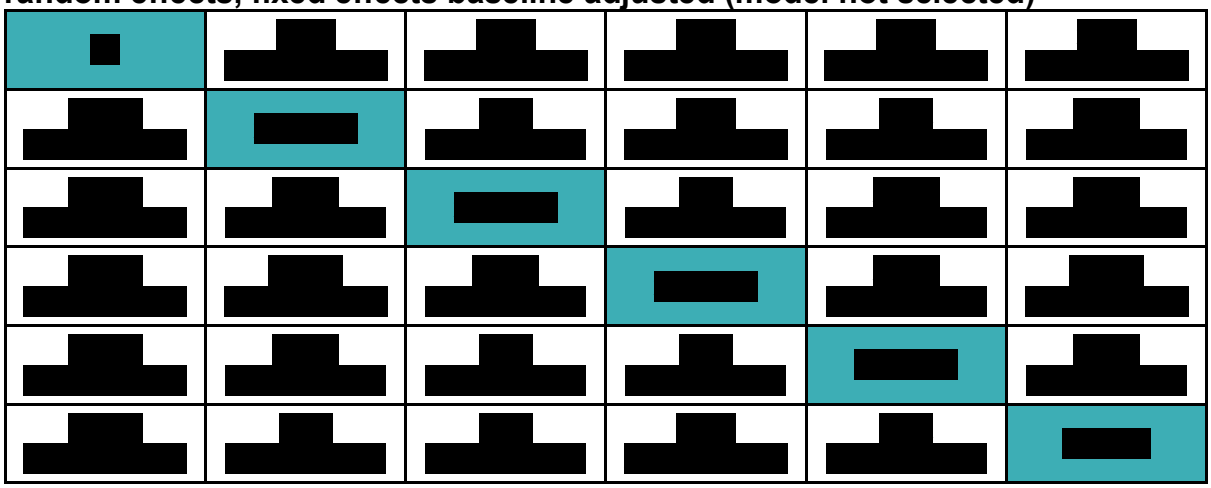
Abbreviations: CrI, credible interval; ERE, erenumab; FRE, fremanezumab; GAL, galcanezumab; PBO, placebo; RIM, Rimegepant
Notes:
Estimates are mean differences (95% CrI). Bolded values are significant at a 5% level.

Change from baseline in monthly migraine days, Phase 2 sensitivity analysis, random effects, fixed effects (model not selected)



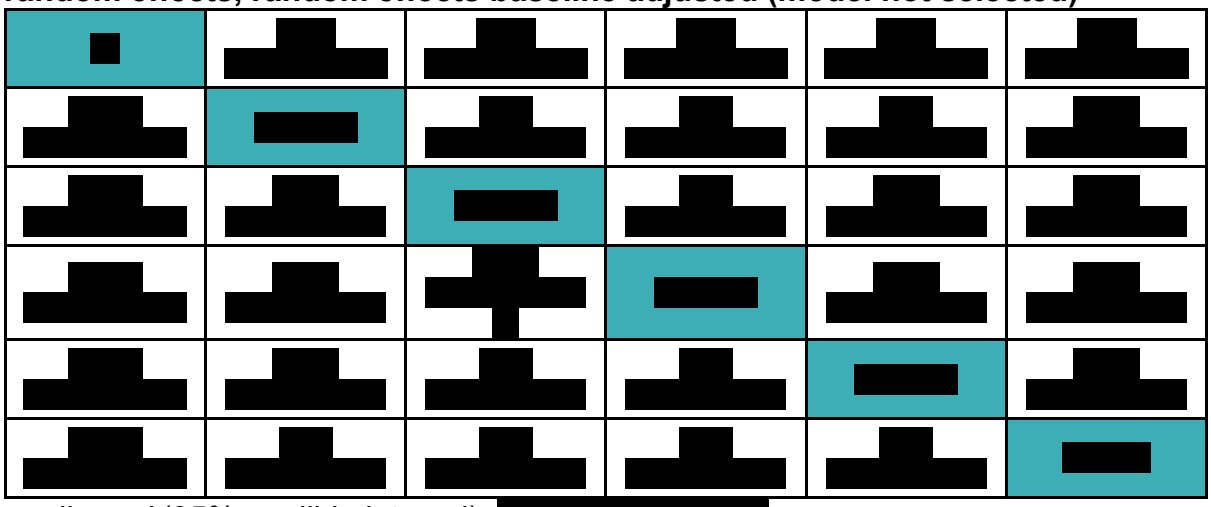
Abbreviations: CrI, credible interval; ERE, erenumab; FRE, fremanezumab; GAL, galcanezumab; PBO, placebo; RIM, Rimegepant
Notes:
Estimates are mean differences (95% CrI). Bolded values are significant at a 5% level.

Change from baseline in monthly migraine days, Phase 2 sensitivity analysis, random effects, fixed effects baseline adjusted (model not selected)



Abbreviations: CrI, credible interval; ERE, erenumab; FRE, fremanezumab; GAL, galcanezumab; PBO, placebo; RIM, Rimegepant
Notes:
Estimates are mean differences (95% CrI). Bolded values are significant at a 5% level.

Change from baseline in monthly migraine days, Phase 2 sensitivity analysis, random effects, random effects baseline adjusted (model not selected)



median *sd* (95% credible interval): [redacted]

Abbreviations: CrI, credible interval; ERE, erenumab; FRE, fremanezumab; GAL, galcanezumab; PBO, placebo; RIM, Rimegepant
Notes:
Estimates are mean differences (95% CrI). Bolded values are significant at a 5% level.

A19. Priority question. For the included rimegepant trial (BHV3000-305) and the long-term safety study (BHV3000-305 open label phase up to 64 weeks), please provide results for discontinuations in each arm across the trial period. Please provide a breakdown of the reasons for discontinuation, including numbers for each reason (for example, the number that discontinued due to poor

compliance as defined in Table 23 of the CS or discontinuation due to adverse events).

305: Overall, 1,591 subjects were enrolled in this study. Of these, 747 subjects were randomized, and 741 subjects were treated with Rimegepant 75 mg (370 subjects) or placebo (371 subjects) in the DBT phase. The reasons that 6 subjects were randomized but not treated were due to protocol deviations (2 rimegepant subjects and 2 placebo subjects) and lost to follow-up (1 rimegepant subject and 1 placebo subject).

There are no on-going treated subjects in the DBT phase. The majority of treated subjects (626/741, 84.5%) completed the DBT phase. The most common reasons for the 115 treated subjects not completing the DBT phase were: withdrawal by subject (11 rimegepant subjects and 22 placebo subjects), lost to follow-up (19 rimegepant subjects and 12 placebo subjects), and eligibility failure due to baseline laboratory values (8 rimegepant subjects and 13 placebo subjects).

Of the 747 randomized subjects, 695 were included in the evaluable mITT population. Reasons for exclusion from the evaluable mITT population included: <14days of efficacy data in all 3 months in DBT phase only ([redacted] subjects) and not treated with double-blind treatment ([redacted] subjects). There are no ongoing evaluable mITT subjects in the DBT phase. Most of the evaluable mITT subjects [redacted] completed the DBT phase. The most common reasons for the [redacted] evaluable mITT subjects not completing the DBT phase were: withdrawal by subject ([redacted] rimegepant subjects and [redacted] placebo subjects), lost to follow-up ([redacted] rimegepant subjects and [redacted] placebo subjects), and non-compliance ([redacted] rimegepant subjects and [redacted] placebo subjects).

Open label up to 64 weeks: A total of [redacted] treated subjects ([redacted] rimegepant, [redacted] placebo) continued to the OLE phase of the study. The majority of these subjects [redacted] completed the OLE phase. The most common reasons for the [redacted] subjects not completing the OLE phase were withdrawal by subject ([redacted] subjects), lost to follow-up ([redacted] subjects), non-compliance ([redacted] subjects), adverse event ([redacted] subjects), and physician decision ([redacted] subjects).

Discontinuation results for BHV3000-305 and the long-term safety study (BHV3000-305 open label phase up to 64 weeks) [17]

	rimegepant	Placebo
Enrolled in Study	**N=1591**	
Randomized	**N=747**	
Randomized Subjects (subjects entering acute phase)	373 (49.9)	374 (50.1)
Not Treated Subjects	3 (0.4)	3 (0.4)
Reason Not Treated/Discontinued		
Lost to follow up	1 (33.3)	1 (33.3)
Protocol Deviation	2 (66.7)	2 (66.7)
Treated Subjects	370 (99.6)	371 (99.6)
Completed DBT Phase	626 (84.5)	
Did not complete DBT Phase	115 (15.5)	
Reason for not completing		
Lost to follow-up	19 (16.5)	12 (10.4)
Eligibility Failure due to baseline laboratory values	[redacted]	[redacted]
Withdrawal by Subject	11 (9.6)	22 19.1)
Other	30 (26.1)	
Included in evaluable mITT population	695 (93)	
Excluded in evaluable mITT population	52 (7)	
<14 days of efficacy data in all 3 months in DBT phase	[redacted]	
Not treated with double-blind treatment	[redacted]	
Evaluable mITT population completing DBT phase	[redacted])	
Evaluable mITT population not completing DBT phase	[redacted]	
Reason for not completing	[redacted]	[redacted]
Withdrawal by Subject	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Non-Compliance	[redacted]	[redacted]
Other	[redacted]	
Included in OLE phase of study	[redacted]	[redacted]
Completed OLE phase	[redacted]	
Did not complete OLE phase	[redacted]	
Reason for not completing	[redacted]	

	rimegepant	Placebo
Enrolled in Study	**N=1591**	
Randomized	**N=747**	
Withdrawal by Subject	[redacted]	
Lost to follow-up	[redacted]	
Non-Compliance	[redacted]	
Adverse Event	[redacted]	
Physician Decision	[redacted]	
Other	[redacted]	

A20. For the included rimegepant trial, please provide a breakdown (with numbers of patients excluded for each reason) of the exclusion reasons of participants from the evaluable mITT population (i.e. if the main reason was they did not take a dose of study treatment or did not have ≥14 days eDiary efficacy data in both the observation period and at least one month in the double-blind treatment phase).

Inclusion and Exclusion From the Evaluable mITT Population[18]

Reason: n (%)	Rimegepant (N=373)	Placebo (N=374)	Overall (N=747)
Inclusion in the evaluable mITT population sample	348 (93.3)	347 (92.8)	695 (93.0)
Exclusion from the evaluable mITT population sample	25 (6.7)	27 (7.2)	52 (7.0)
Not mITT	[redacted]	[redacted]	[redacted]
Not treated with DBT	[redacted]	[redacted]	[redacted]
Treated with DBT but randomized more than once	[redacted]	[redacted]	[redacted]
mITT but not evaluable	[redacted]	[redacted]	[redacted]
< 14 days of efficacy data in OP only	[redacted]	[redacted]	[redacted]
< 14 days of efficacy data in all 3 months in DBT Phase only	[redacted]	[redacted]	[redacted]
< 14 days of efficacy data in both OP and in all 3 months in DBT Phase	[redacted]	[redacted]	[redacted]

Evaluable subjects are those with >= 14 days of eDiary efficacy data (not necessarily consecutive) in both the Observational Period (OP) and >=1 month (4-week interval) in the Double-Blind Treatment (DBT) Phase.

A21. Please provide a risk of bias assessment for the long-term safety study (open label phase of BHV3000-305), as has been done for RCTs already in Appendix D.10 of the CS.

BHV3000-305 was a RCT with an open label phase for the long-term collection of safety data. A risk of bias assessment for the study open label extension is provided below.

Table showing risk of bias assessment for open label phase of BHV3000-305.

Study ID and name	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blind to treatment allocation, what might be the likely impact on the risk of bias (for each outcome)?	Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Also consider whether the authors of the study publication declared any conflicts of interest/study funding.
BHV3000-305	N/A open label phase was non-randomised	N open label phase	N/A single study group only (75 mg rimegepant EoD)	N	N/A – single study group only	N	mITT used for open label phase (subjects who received at least one open label dose of rimegepant)	Y

Analyses and results

A22. Priority question. The EAG's clinical experts have noted that efficacy can differ between episodic and chronic migraine. Within the rimegepant trial (BHV3000-305), please perform a within-trial analysis of episodic vs chronic migraine to determine whether the results for the following outcomes differ between these two groups:

In the absence of adequate and validated biomarkers, the diagnosis of migraine as episodic or chronic is determined based on historical frequency of migraines. However, migraine frequency is known to vary within individuals with time; data from the CaMEO study found that 73.4% of patients diagnosed with CM at baseline had at least one three month period once over the course of a year where they did not meet the 15 or more headache days per month criteria for CM.[19] Since the diagnosis of EM vs CM is not an enduring characteristic, the unambiguous classification of a migraine patient as EM or CM can be considered challenging at best.

Furthermore, the current threshold used to define chronic migraine (15 or more monthly headache days) is somewhat arbitrary. Evidence suggests that there is a considerable overlap between EM patients with 8-14 migraine headache days per month and CM patients with 15-23 migraine headache days per month in levels of health care resource utilisation, interictal burden, depression and moderate and severe disability[20]. This has led to debate as to whether the threshold for the current definition of CM should be lowered to 8 or more headache days per month.[21]

With respect to the design of BHV3000-305, the subgroup of patients diagnosed as CM was relatively small (22.7%) and analyses were not stratified by EM and CM diagnosis. The previously requested analysis of the baseline characteristics of the EM patients from BHV3000-305 (A17), demonstrated that the EM population had baseline characteristics that were very similar to those of the overall mITT population.

The post-hoc analyses below requested by the EAG demonstrate that the any differences in treatment effect between the EM and CM patients are small, with no evidence of statistically significant differences between the populations. As such, the results of these analyses do not change the interpretation of the results from the mITT analyses of BHV3000-305. This is consistent with the subgroup analysis presented in the primary publication for the 50% reduction in moderate and severe MMD at 12 weeks and presentation of the mITT data in the SmPC.[22,23]

a) Proportion with 50% reduction in MMD - average over 12 weeks;

The table below shows odds ratios for the reduction of monthly migraine days by 50% or more, over 12 weeks, for subjects from BHV3000-305 with a history of episodic migraine and for subjects with a history of chronic migraine.

As seen in the table, for subjects with a history of episodic migraine, the odds of not achieving a better than 50% response when treated with rimegepant are about [redacted] of the odds of subjects treated with placebo. For subjects with a history of chronic migraine, the odds of not achieving a better than 50% response when treated with rimegepant are about [redacted] of the odds of subjects treated with placebo.

The table also shows there is a substantial overlap in the 95% confidence intervals for two odds ratios. In addition, the Breslow-Day test for the homogeneity of odds ratios was [redacted] ([redacted]).

[redacted]

Table showing the sample sizes, response rates with asymptotic standard errors (ASE), the odds ratio and associated Chi-squared and p-values for rimegepant vs placebo for the EM and CM patients. The results of the Breslow-Day test for the homogeneity of odds ratios for EM vs CM are also shown.

	Statistic	Rimegepant (N=348)	Placebo (N=347)	Test Statistics
Episodic Migraine	Response Rate (n/N)	[redacted]	[redacted]	[redacted]
	Risk (ASE)	[redacted]	[redacted]	[redacted]
	Odds Ratio (95% CI)			[redacted]
	Table Chi-Square			[redacted]
	P-value			[redacted]
Chronic Migraine	Response Rate (n/N)	[redacted]	[redacted]	[redacted]
	Risk (ASE)	[redacted]	[redacted]	[redacted]
	Odds Ratio (95% CI)			[redacted]
	Table Chi-Square			[redacted]
	P-value			[redacted]
Homogeneity of Odds Ratios	Breslow-Day Chi-Square			[redacted]
	P-value			[redacted]

All Chi-Square tests have 1 degree of freedom
Evaluable subjects are those with >= 14 days of eDiary efficacy data (not necessarily consecutive) in both the Observational Period and >= 1 month (4-week interval) in the Double-Blind Treatment Phase.
Subjects must have >= 1 total migraine day in the Observational Period to be responders.
* Subjects must also be evaluable (have >= 14 days of eDiary efficacy data not necessarily consecutive) in the month to be responders.

b) Change from baseline in MMD at 12 weeks.

Analyses of the change from the observation period in total Monthly Migraine Days (MMDs) for both subjects with a history of CM and those with EM at month 3 (ie > 8 to <= 12 weeks) are presented in the table below. This shows that the treatment effect in month 3 was [redacted] days for EM subjects and [redacted] for CM subjects.

As can be seen in the table, the confidence intervals for CM and EM subjects overlap. In fact, the confidence interval for the EM subjects is almost entirely contained within the confidence interval for CM subjects. The last row of the table shows the difference of the treatment effects, as well as the asymptotic standard error (ASE), 95% confidence interval (CI) and p-value. [redacted]. The p-value of [redacted]. [redacted]

Table showing the treatment effects, and difference of treatment effects, with asymptotic standard errors (ASE), 95% confidence intervals (95% CI), and p-values

c)

	Treatment effect at month 3	ASE*	95% CI	P-value

Chronic Migraine	[redacted]	[redacted]	[redacted]	[redacted]
Episodic Migraine	[redacted]	[redacted]	[redacted]	[redacted]
Difference	[redacted]	[redacted]	[redacted]	[redacted]

* ASEs,95% Cis and p-values for EM and CM subjects were calculated using General Linear Mixed Effects Models (GLMEM). The ASE for the difference was calculated by pooling the GLMEM ASEs with equal weights. The P-value for the difference was found by using a normal approximation for the critical ratio (difference / ASE).

A23. Priority question. Please discuss what effect the variation across trials in terms of the proportion using concurrent prophylactic medications (0.0-21.4%, described in section B.2.9.1.4 under patient population) may have on the results. If it may affect results, please consider performing an appropriate sensitivity analysis to account for this.

Pfizer are not aware of extensive published evidence to indicate that concurrent prophylactic medication is an independent treatment effect modifier. However, subgroup analyses from BHV3000-305 indicated that the likelihood of achieving a 50% reduction in total MMD was similar regardless of concurrent medication status.

>=50% reduction in MMD over 12 weeks	**Rimegepant (n/N, %)**	**Placebo (n/N, %)**	**Risk Difference (95% CI)**
Prophylactic migraine medication use at randomisation (i.e., IWRS randomization strata) Yes	[redacted]	[redacted]	[redacted]
Prophylactic migraine medication use at randomisation (i.e., IWRS randomization strata) No	[redacted]	[redacted]	[redacted]

A24. Priority question. Please provide measures of between-trial heterogeneity for all NMA models where possible (random effects with or without baseline adjustment), as currently this is not provided for the following NMA models:

Note; The responses to this question have been updated to reflect the amendment to the NMA analysis following the Addendum 3 clarification questions.

a) **For the 50% reduction in MMD outcome:**

   i. **Random effects model base case;**

      0.08 (0.00, 0.31) random effect with adjustment to placebo

      0.30 (0.06, 0.71) random effect without adjustment

   ii. **Random effects model, sensitivity analysis with Sakai *et al.* 2021 study excluded;**

      0.29 (0.04, 0.83)

   iii. **Adjusted random effects model, sensitivity analysis with Sakai *et al.* 2021 study excluded.**

      0.07 (0.00, 0.34)

b) **For the MMD change from baseline outcome:**

   i. **Adjusted random effects model, sensitivity analysis with Sakai *et al.* 2021 study excluded.**

      0.57 (0.08, 1.80)

c) **Please also provide this for any additional analyses performed as a result of clarification questions.**

   50% reduction in MMD – including phase II trials

   random effects: 0.29 (0.06, 0.64)

   random effects baseline adjusted: 0.07 (0.00, 0.25)

   CFB in MMD – including phase II trials

   random effects: 0.52 (0.12, 1.06)

   random effects baseline adjusted: 0.44 (0.09, 0.93)

A25. Priority question. Please perform an NMA of treatment discontinuation, which can be used to inform treatment-specific long-term discontinuation rates in the economic model (see question B42). If a treatment-specific

discontinuation rate cannot be estimated, please consider a class-based discontinuation rate for the injectable mABs vs rimegepant.

Publicly available data regarding the long-term discontinuation of mAbs is limited (redacted in prior appraisals). A cross-sectional NMA of treatment discontinuation may be feasible at the 12-week timepoint for rimegepant and the subset of mAb trials that report such data, however there are multiple considerations as to why these results would not be useful for input into the economic model:

1. 12-week discontinuation rates do not represent an accurate proxy for the long-term annual discontinuation rates needed in the economic model. Individual patient-level data (not available in the public domain) would be necessary from the mAb trials to conduct an NMA which would allow for the extrapolation of discontinuation rates
2. The economic model requires discontinuation rates specific to those patients who responded during the double-blind treatment phases (achieved a ≥50% reduction in baseline MMD). These data are not available in the public domain for the mAb trials.

Given the limitations with the current evidence base and requirements of the economic model the proposed analysis has not been undertaken.

A26. Please provide the following in relation to the NMA:

a) **Further details of the methods used for meta-regression analysis performed as part of the NMA models that were adjusted for baseline risk**;

The JAGS code used in running the baseline risk adjusted models can be found in appendix D (D.8.7.3, D.8.7.4, D.8.8.3, and D.8.8.4). In summary:

- A common covariate effect was assumed throughout all the models.

- An uninformative prior was used for the meta-regression covariates [*Normal*(mean = 0, precision = 0.0001)

- For the binomial models, *mean_mu1* was computed as mean(ln(*p*/(1-*p*)), where *p* is a vector containing all placebo responses (in %s) across all trials in the network.

- For the Normal models, *mean_mu1* was computed as the average CFB from the placebo arms across all trials in the network.

b) **Details of the initial values that were used for each chain in the NMA analyses;**

For both the ≥50% reduction in baseline MMD and change from baseline in MMD outcomes, the following initial values were used:

- Chain 1: d = 0, mu = 0, sd = 0.5 (for RE models)

- Chain 2: d was sampled from a uniform(-1, 1) distribution, mu was sampled from a uniform(-1, 1) distribution, sd = 1 (for RE models)

c) **NICE DSU TSD 2 recommends at least 3 chains are run for NMA models. Please justify why 2 chains were selected and how this may affect results**;

A large number of iterations with thinning in addition to widely different initial values for each of the 2 chains resulted in excellent convergence between the 2 chains, indicating that further chains were not necessary. The incorporation of additional chains is expected to have very minimal impact to the results.

d) **Model convergence plots for all NMA models tested for each outcome (not just those for chosen models already in Table 32 of the CS appendices). Please also provide these for any new NMA analyses supplied as a result of clarification**.

Please find these plots in the accompanying Word document (Convergence plots for additional NMA models.docx): Appendix 2 (see separate file]

A27. Although proper convergence for the final selected models was said to have been achieved in section D.8.9 P of the CS appendices, we note that the

lines in the Gelman-Rubin plots (Table 32 of the CS appendices) fluctuate after initially stabilising for the following comparisons:

a) **≥50% reduction in MMD outcome: fremanezumab vs placebo (particularly the 675 mg dose)**;

It is important to note the shrink factor scale on the y-axis here. In the case of the fremanezumab 675 mg dose, the scale ranges from 1 to 1.015; whereas in the plot above for example which examines fremanezumab 225 mg, the y-axis ranges from 1 to 1.04. Therefore, the fremanezumab 675 mg dose estimate is in fact not of concern and holding steady around a shrink factor of 1.

b) Change from baseline in MMD outcome: galcanezumab vs placebo.

Please comment on, and provide your rationale for, why this is not a concern.

As stated in the response to a), the shrink factor scale is again very tight and ranges from 0.994 to 1.004. Therefore, the estimate for galcanezumab is in fact holding steady around a shrink factor of 1.

A28. Please clarify why ORs generated from the NMA (e.g. in Figure 11) are provided as medians rather than means.

As we are dealing with converged symmetrical posterior distributions, there should not be much difference in using the median compared to the mean. However, medians were provided as they are more robust to sampling outliers compared to means.

A29. Were informed priors considered for use in the NMA, as provided in the reference below? If not, please clarify why, and consider performing a sensitivity analysis using your preferred prior:

a) Turner RM, Jackson D, Wei Y, Thompson SG, Higgins JP. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. Stat Med 2015; 34: 984-98

Informed priors were not considered, as the NICE DSU 2 guidance suggests incorporating vague priors for mu and d throughout as to not unjustly bias the choice of reference treatment used in each network. As stated in the NICE DSU

2 document: "*While the likelihood is not altered by a change in which treatment is taken to be "Treatment 1", the choice of the reference treatment can affect the posterior estimates because priors cannot be totally non-informative. However, for the vague priors we suggest throughout for μi and d1k (see below) we expect the effect to be negligible.*"

In addition, the NICE DSU 2 document states the following related to the between trial variance parameter (σ): "*It has become standard practice to also set vague priors for the between-trial variances.*"

Finally, the Turner et al reference incorporates and tests informative priors in the context of a single meta-analysis. Further research would be necessary to fully evaluate the impact of similar priors used in the context of network meta-analysis.

A30. Please provide a definition of 'AEs associated with potential abuse' (page 39 of the addendum provided for BHV3000-305 CSR). Does this include some events that could be considered medication overuse? If so, please provide the number of these events.

Cases of abuse of study medication are defined in the CSR as subjects taking study drug for non-therapeutic purposes, e.g. for psychoactive effects such as a high or euphoria.[24]

Preferred terms for AEs associated with potential abuse were drawn from Medical Dictionary for Regulatory Activities (MedDRA) Version 21.1 and included: Affect lability, Anger, Asthenia, Confusional state, Depressed level of consciousness, Depressed mood, Depression, Disturbance in attention, Fatigue, Frustration tolerance decreased, Hypnagogic hallucination, Hypoaesthesia, Insomnia, Irritability, Major depression, Memory impairment, Overdose, Somnolence and Syncope. [25]

Potential drug abuse AEs were reported in [redacted] rimegepant subjects and [redacted] placebo subjects. The majority were mild in severity, with only 1 severe event (overdose in the placebo group). The most common potential drug abuse AEs were depression ([redacted] in the rimegepant group and [redacted] in the placebo group) and fatigue ([redacted] in the rimegepant group and [redacted] in the placebo group).

The safety profile demonstrated during the double-blind treatment period is consistent with prior clinical studies of rimegepant in migraine, with no new safety issues identified. The clinical data do not indicate adverse events suggestive of abuse potential related to rimegepant.

Section B: Clarification on cost-effectiveness data

Please note

If as a result of the responses to the clarification questions the company revises its base case, please indicate what assumptions are considered for the revised base case and provide updated results including updated probabilistic sensitivity analyses, deterministic sensitivity analyses and scenario analyses.

Please provide the ICER and net monetary benefit using willingness-to-pay thresholds of £20,000 and £30,000 when presenting these results. The NHB is not required. When presenting the results of OWSA, please provide the ICER (rather than the NHB).

Please provide all requested scenario analyses as options in the economic model and on top of any revised assumptions.

ACUTE MIGRAINE

[redacted]

[redacted]

[redacted]

	[redacted]			[redacted]		
Population	**Δ Cost**	**Δ QALY**	**ICER**	**Δ Cost**	**Δ QALY**	**ICER**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

CS Table 1: Revised base-case results <u>acute</u> treatment of migraine

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weighted across migraine event distribution observed in Study BHV3000-201 (≥2 triptan failure group)					
Rimegepant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]			

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

[redacted]

CS Table 2: Results of the probabilistic sensitivity analysis for rimegepant vs BSC <u>acute</u> treatment of migraine

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rimegepant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]			

Abbreviations: BSC, best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs, versus

[redacted]

CS Table 3: Results of the deterministic sensitivity analysis for rimegepant versus BSC <u>acute</u> treatment of migraine

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BL, baseline; BSC, best supportive care; hr, hour; ICER, incremental cost-effectiveness ratio; Max, maximum; MMD, monthly migraine days; NA, not applicable; vs, versus

CS Table 4: Scenario analysis: rimegepant vs BSC (using Study BHV3000-201 MMD distribution option) acute treatment of migraine

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; mITT, modified intention to treat; PRN, *pro re nata* (as needed); QALYs, quality adjusted life year

B1. Priority question. The model includes two approaches to estimate cost-effectiveness: 1) mean MMD and 2) mean 201 distribution.

The methods and results based on the mean MMD approach are not mentioned in the CS, please explain why?

The 201 distribution approach was included as the base case; variation in MMD only influences the cost-effectiveness of rimegepant in the acute setting when the relationship between baseline MMD and the potential association with reduced MMD frequency is taken into account (as it is assumed in the base case scenario) and to fully account for the impact of this reduction in migraine frequency it is informative to account for the proportion of patients with high-frequency migraine episodes, which is only achievable by considering the full distribution. However, the model does allow for results to be generated for any selected MMD value; it is a weighted average of such values that is used to generate results under the distributional approach.

a) **The results based on the mean 201 distribution (ICER £18,221) are more favourable for rimegepant than the results based on the mean MMD (ICER £20,553), please explain what is driving this discrepancy in the model?**

This is related to the points raised in the response to B1a): specifically, that the distribution approach includes a proportion of patients with higher-frequency migraine, and the relationship between MMD and ICER is non-linear due to a reduction in migraine frequency with rimegepant observed for MMD greater than approximately 8. Because the 201 distribution approach includes a wider range of potential MMD values for whom impacts of reduced MMD frequency are greater and ICER therefore lower, the weighted average ICER of this distribution is lower than that of an individual mean MMD approach.

b) **Please add annotations to the VBA module "MMD_Distribution".**

The model will be updated accordingly.

c) **Please clarify why the costs and QALYs associated with a MMD of 0 ('MMD distribution'C49:N49) equal the results based on the mean MMD ('MMD distribution'C46:N46 and 'Results'E16:F21).**

This was incorrect, thank you for flagging (i.e. as noted, values associated with the mean MMD value and not MMD=0). Given that the distribution % associated with MMD=0 is 0% it did not impact the results; it will be corrected in the updated model.

B2. Priority question. As noted in question A3, the EAG considers the mITT population to be the most appropriate population to inform the analysis. However, the EAG finds the cost-effectiveness results obtained from the mITT population using the mean 201 distribution to be questionable

a) **Please explain why the ICER decreases from £18,221 to £16,058 when the analysis is based on the mean 201 distribution and increases from £20,553 to £21,761 based on the mean MMD. The EAG would expect the ICER to increase when considering how the clinical effectiveness data is impacted by the different populations. If the company is using inconsistent sources to inform the baseline mean MMD and distribution of MMD at baseline, please ensure a consistent approach is used.**

Given the differences in patient characteristics, efficacy outcomes, and MMD distributions across patient populations we would not a priori anticipate a particular directional impact on results of mITT vs. 2+ triptan failure and as such do not believe that the above trends in results a cause for validity concern.

b) **For all subsequent requests in this clarification letter please focus on using inputs from the mITT population and provide results using both modelling approaches.**

Noted for responses below. As requested by EAG, all the responses below will present the results using the efficacy results, i.e responder and pain trajectory from selected mITT population in addition to the CS triptan refractory patient population.

For comparison, the table below reproduces the base case results for the triptan refractory patient (2+ triptan failures) submitted in the CS, in the next row, we

present the updated model base case addressing the addendum 2 question around MMD vs migraine attack (please refer to the response in Addendum 2)

	Mean MMD			MMD distribution		
Population	**Δ Cost**	**Δ QALY**	**ICER**	**Δ Cost**	**Δ QALY**	**ICER**
2+ triptan failures	£10,627	0.52	£20,553	£8,872	0.49	£18,221
	Mean migraine event			**Migraine event distribution (Revised Base Case)**		
Population	**Δ Cost**	**Δ QALY**	**ICER**	**Δ Cost**	**Δ QALY**	**ICER**
2+ triptan failures	£7,681	0.41	£18,570	£7,307	0.43	£17,160

	Mean migraine event (Efficacy from mITT, migraine distribution from 201)			Migraine event distribution (From 201)		
Population	**Δ Cost**	**Δ QALY**	**ICER**	**Δ Cost**	**Δ QALY**	**ICER**
mITT (301-303)	£4,220	0.26	£16,515	£4,154	0.25	£16,312

B3. Priority question. As a scenario analysis, please provide cost-effectiveness results using the data requested in question A4 (including studies CN170-003 and BHV3000-310).

As per EAG request, the scenario analysis using the mITT efficacy data from all the acute studies (301, 302, 303, and 310) is provided below. There is a negligible impact on the base-case cost-effectiveness results submitted in the CS.

	Mean migraine event			Migraine event distribution		
Population	**Δ Cost**	**Δ QALY**	**ICER**	**Δ Cost**	**Δ QALY**	**ICER**
mITT including 310	£4,418	0.23	£19,600	£4,350	0.23	£19,285
2+ triptan failures[a]	£7,681	0.41	£18,570	£7,307	0.43	£17,160

[a] only included studies 301, 302, &303. Study 310 does not allow to determine the triptan failures status.

[redacted]

[redacted]

We do not feel this would be an appropriate distribution to consider, given that the acute pooled trials employed inclusion criteria limiting participants to 2-8 moderate to severe migraine attacks and as such do not reflect the full distribution amongst migraine patients

B4. Priority question. As a scenario analysis, please provide cost-effectiveness results using the data requested in question A11 (pooled results from trials using the ODT formulation only) if these results are considered to be significantly different (clinically or statistically) from the base case analysis

As discussed in question A4, study CN170-003 is not appropriate for pooling with the other acute studies (301, 302, 303, and 310) due to major differences described in the response to question A4. The scenario analysis using the pooled efficacy results from the ODT formulation trials only, i.e. 303 and 310, is provided below.

	Mean migraine event			Migraine event distribution		
Population	**Δ Cost**	**Δ QALY**	**ICER**	**Δ Cost**	**Δ QALY**	**ICER**
mITT ODT only	£4,571	0.20	£22,731	£4,499	0.20	£22,645
2+ triptan failures	£7,681	0.41	£18,570	£7,307	0.43	£17,160

[redacted]

a) **Please clarify if the list price will be the same for both formulations.**

As discussed in Question A11 a, the ODT formulation is the only marketed formulation in the UK.

MMD distributions

B5. Priority question. Please clarify why a parametric distribution was not used to estimate the distribution of MMD at baseline, as per the prevention model.

a) **Please explore parametric distributions and provide scenario analyses based on the best fitting models. In your response, please provide figures comparing the parametric distributions versus the observed distribution and goodness of fit statistics.**

Given the direct availability of a parametric distribution from BHV3000-201, this was felt to be the most relevant input source and avoids any concern with generating estimates outside of the 0-28 MMD bounds (which, with the updated framework, translates to 0-14 migraine events) (see Addendum 2), and this remains the base case source for the distributional analysis. We have added parametric models using negative binomial and Poisson approaches, and results, shown below, are similar to the base case.

		Mean migraine event			Migraine event distribution		
Description	**Population**	**Δ Cost**	**Δ QALY**	**ICER**	**Δ Cost**	**Δ QALY**	**ICER**
MMD distribution: Neg Bin	mITT excl 310	£4,220	0.26	£16,515	£4,125	0.25	£16,278
	2+ triptan	£7,681	0.41	£18,570	£7,292	0.42	£17,400
MMD distribution: Poisson	mITT excl 310	£4,220	0.26	£16,515	£4,174	0.25	£16,387
	2+ triptan	£7,681	0.41	£18,570	£7,447	0.42	£17,729
MMD empirical	mITT excl 310	£4,220	0.26	£16,515	£4,154	0.25	£16,312
	2+ triptan	£7,681	0.41	£18,570	£7,307	0.43	£17,160

[redacted]

B6. Priority question. As noted in question A7, the EAG is unclear how (or if) patients from the three acute RCTs currently included in the analysis

(BHV3000-301, -302 and -303) continued into the long-term safety study (BHV3000-201).

a) **Please clarify if patients from the three acute RCTs who continued into the long-term safety study contributed to the distribution of MMD at baseline.**

Yes, n=[redacted] patients from BHV3000-301, -302, and -303 were also included in BHV3000-201 and of these [redacted] were triptan failure patients.

b) **Please assess the impact of including and excluding these patients on the distribution of MMD at baseline.**

Below is the distribution of BHV3000-201, with and without the 301/2/3 acute trial patients included. The MMD distribution is higher with the patients excluded, as expected given that the acute trials restricted inclusion to 2-8 MMD while the long-term safety study was less restrictive.

MMDs	% - 201 overall	% - 201 with 301/2/3 patients excluded
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
7	[redacted]	[redacted]
8	[redacted]	[redacted]
9	[redacted]	[redacted]
10	[redacted]	[redacted]
11	[redacted]	[redacted]
12	[redacted]	[redacted]
13	[redacted]	[redacted]
14	[redacted]	[redacted]
15	[redacted]	[redacted]
16	[redacted]	[redacted]
17	[redacted]	[redacted]
18	[redacted]	[redacted]
19	[redacted]	[redacted]
20	[redacted]	[redacted]
21	[redacted]	[redacted]
22	[redacted]	[redacted]
23	[redacted]	[redacted]

MMDs	% - 201 overall	% - 201 with 301/2/3 patients excluded
24	[redacted]	[redacted]
25	[redacted]	[redacted]
26	[redacted]	[redacted]
27	[redacted]	[redacted]
28	[redacted]	[redacted]
Total	[redacted]	[redacted]

B7. Priority question. Please provide a scenario using the acute pooled trials to estimate the distribution of MMD at baseline. As per question B5, please consider using a parametric distribution.

We do not feel this would be an appropriate distribution to consider, given that the acute pooled trials employed inclusion criteria limiting participants to 2-8 moderate to severe migraine attacks and as such do not reflect the full distribution amongst migraine patients.

B8. The EAG has identified a discrepancy between the baseline MMD calculation applied in model (e.g. 'Rim'W16: 9.2 MMD *2/28) and CS (page 152: 9.2 MMD ÷ (365 days/12 months) x 2), please clarify which calculation should be used.

The value used in the model is correct and reflects a 28-day month as standard for calculating MMD. The formula provided in the CS assuming a MMD based on a 30.4-day month is incorrect.

Baseline patient characteristic

B9. Priority question. The patient characteristics from the long-term safety study are only provided for the ≥2 triptan failures subgroup, 'Settings'R25:50 and Table 50 of the CS, please explain why.

Given the proposed positioning of rimegepant in the decision problem baseline characteristics for the population considered most relevant were provided.

a) **Please provide inputs for the mITT population (treated population) and include these as an option in the model.**

These characteristics have been added as options within the revised model.

B10. Priority question. The EAG considers the distribution of pain severity at baseline to be unequal across treatment arms (rimegepant: [redacted] moderate, [redacted] severe; placebo: [redacted] moderate, [redacted] severe).

a) **Please clarify how the proportion of moderate baseline pain (vs severe) in 'Settings'R40 ([redacted]) is taken from acute pooled studies when the acute pooled studies report a proportion of [redacted] ('Settings'P40);**

The [redacted]% was incorrect and will be updated in the model to [redacted]%.

b) **Please clarify exactly how the proportion of moderate baseline pain (vs severe) has been calculated and include this as a calculation in the model, it is currently hard-coded;**

The proportion of moderate or severe pain severity were not "calculated". They were sourced from the individual patient level data from the trial.

c) **Please clarify if, and how, any adjustments are made in the model to account for the imbalances in pain severity across the treatment arms at baseline. If no adjustment was made, the EAG would urge the company to correct for this in their revised base case and ensure the starting population is balanced appropriately for any discrepancies.**

In the base case, the regression-based approach is taken to estimating QALH values for rimegepant and UC, which adjusts for severity at baseline (i.e. severity as a covariate) and includes a common value for both treatment arms.

B11. Age and sex inputs in the model, 'Settings'J26,28, are taken from the long-term safety study and not the pooled acute studies as stated in the CS, please clarify which source should be used in the base case and why.

The long-term safety study had broader inclusion criteria and likely reflects a population more similar to the real-world migraine population eligible for rimegepant. Therefore, values from 201 were selected for use in the base case.

Treatment efficacy

B12. Priority question. Please clarify why a 2-hour stopping rule is included in the economic analysis when no stopping rule is included in the rimegepant SMPC.

NICE recommendations from prior appraisals for the mAbs have included stopping rules to focus long term treatment on those patients who benefit the most.[26],[27],[28] Discussions with clinical experts indicated that rimegepant would only be continued long term in those patients achieving sufficient symptom relief, with pain relief at 2-hours considered most reflective of response. This is consistent with post-hoc analyses of preference data from BHV3000-303 that indicated a greater preference for continuing rimegepant amongst patients that achieved 2-hour pain relief.

B13. Priority question. The EAG considers the long-term reductions in MMD with PRN rimegepant to be highly uncertain as this is based on *a post-hoc* analysis of the long-term safety study which may suffer from confounding (including but not limited to a possible placebo effect).

a) **Please identify comparative evidence to inform a more robust estimate of treatment effectiveness, as recommended in NICE DSU TSD 17, and implement these results in a scenario analysis;**

Collecting comparative data on the long-term effects of acute migraine treatment are not possible within the context of the single attack study design typically used for RCTs in acute treatment. As such, the evidence for the long-term reduction in MMD with PRN rimegepant come from the open label extension safety trial 201. While we acknowledge the lack of a comparator arm in the study design of 201 is a limitation, post-hoc analyses of these data showing the long-term reductions in MMD are available in a number of peer reviewed publications that collectively support the effect using a variety of outcomes and analytical approaches.

- In an analysis of the three treatment regimens of 201 (PRN use in patients with baseline MMD of 2 to 8 (n=1033); PRN use in patients with baseline MMD of 9 to 14 (n=286) and EOD use in patients with baseline MMD of 4-14 (n=481)) Johnston et al 2021[29] demonstrated a larger MMD reduction from baseline in patient groups with higher MMD baseline frequency with

rimegepant PRN use at 52 weeks. While the 2-8 MMD PRN group showed a mean change from baseline of -0.47 (95% CI: -0.84 to -0.11), the 9-14 MMD PRN group showed a mean change from baseline MMD of -2.94 (95% CI -3.65 TO -2.24).

- An analysis of 1044 patients from study 201 with ≥6 MMD taking rimegepant 75mg PRN showed that long term acute treatment resulted in a reduced migraine frequency over up to a year of dosing[30]. This post-hoc analysis using Cox proportional hazards models reported a median time to ≥30% reduction in MMD from baseline of 12 weeks (IQR: 4-40 weeks) and a median time to ≥50% reduction in MMD from baseline of 32 weeks (IQR: 12-NR).
- A separate analysis on the same cohort of 1044 patients also demonstrated that, together with the decrease in MMD there was no increase in tablet utilization frequency, when rimegepant was used on a PRN basis, showing lack of indication for rimegepant to cause medication overuse headache. The mean monthly tablet use remained stable throughout the 12 months of follow up, with a trend towards decreasing use (mean of 7.9 tablets in weeks 4-8, and a mean of 7.3 tablets in weeks 48-52)[31].

Importantly, these data should also be considered in the context of the biological plausibility of rimegepant having a preventative effect for migraine based on the RCT evidence in the prevention indication[32]. This evidence has been presented extensively in the submission, and shows that for rimegepant taken EOD vs placebo, there is a significant reduction in MMD from baseline in weeks 9-12 (least squares mean difference −0·8 days, 95% CI −1·46 to −0·20; p=0·0099).

When the data supporting the reduction in MMD by PRN rimegepant were discussed with UK clinicians, the feedback was unanimously supportive of the inclusion of this effect in the economic model. It was noted that in the context of other available acute treatments, the lack of an observed association with MoH for rimegepant with frequent use provides a unique benefit in the context of reducing MMD in the acute setting.[33]

b) Please provide a scenario removing the long-term reductions in MMD, as per the approach in the ICER evidence report (Atlas *et al.* 2020). Please consider time horizons of 2 years and 20 years.

Scenario #6 of CS Table 68 showed that exclusion of the long term reduction in MMD increased the ICER from £18,221/QALY to £22,199/QALY over a 20 year time horizon. The table below provides updated results reflecting requested amendments to the model and inclusion of a 2 year time horizon. Results are consistent with CS submitted in scenarios using time horizons reflecting the NICE reference case, i.e over 20 year time horizon. The scenario with the shorter time horizon of 2 year may not be long enough to capture the full benefits of rimegepant.

		Mean migraine event			Migraine event distribution		
Description	**Population**	**Δ Cost**	**Δ QALY**	**ICER**	**Δ Cost**	**Δ QALY**	**ICER**
No prevention (2-year time horizon)	mITT excl 310	£1,713	0.05	£33,066	£1,712	0.05	£33,659
	2+ triptan	£2,271	0.08	£27,334	£2,271	0.08	£27,851
No prevention (20-year time horizon)	mITT excl 310	£5,229	0.23	£22,978	£5,226	0.22	£23,391
	2+ triptan	£8,507	0.38	£22,110	£8,505	0.38	£22,529

[redacted]

B14. Priority question. In the acute model, BSC responders are assumed to transition to BSC non-responder trajectories after 12 months. Additionally, patients who discontinue rimegepant over the longer term are assumed to follow the trajectory of BSC responders for 12 months, and then transition to BSC non-responder trajectories after this point.

a) Please explain why BSC responders do not transition to baseline trajectories after 12 months, as per the justification from TA764 provided in Table 48 of the CS, "*committees' preferred assumptions for fremanezumab,143 where the treatment effect for people who responded to BSC (placebo) diminished to baseline over 1 year*";

The acute setting is distinct from prevention, in that efficacy is characterized by 48-hour pain trajectories, and these trajectories are not known at baseline – the only

relevant available data are pain trajectories for rimegepant vs. best supportive care patients (with placebo effect thus unable to be directly measured) and as such, best supportive care response rates are used to estimate potential placebo effect and plausible interpretation of “return to baseline”.

b) Please explain why no linear reversion (gradual loss of benefit) is applied (as per Figure 21 for prevention);

As, above, given that the exact definition of return to baseline is unknown, a viable approach for “gradual return” was not identified. As an acknowledged area of uncertainty this was explored in Scenario analyses within the CS. Scenario #12 in CS Table 68 showed that immediately reverting rimegepant discontinuers to BSC non-responders at discontinuation modestly increased the ICER from £18,221/QALY to £19,287/QALY. As a further alternative to the placebo non-responder values that are used in the base case, placebo all-comers values will be added as an option to the updated model (see results in c). Similarly, Scenario #13 in CS Table 68 showed that varying the time point at which benefit was lost between 6 and 18 months (base case 12 months) had a limited impact on cost-effectiveness (£18,250/QALY - £18,181/QALY).

c) Please provide a scenario exploring the suggestion in part b.

Scenarios showing results for rimegepant responder discontinuers transitioning to placebo all comers, reflecting an intermediate between the CS base case and CS Scenario #12. Rimegepant remained cost-effective using both the pooled and triptan failure datasets.

		Mean migraine event			Migraine event distribution		
Description	**Population**	**Δ Cost**	**Δ QALY**	**ICER**	**Δ Cost**	**Δ QALY**	**ICER**
Placebo all-comer QALH 12 months after discontinuation	mITT excl 310	£4,220	0.24	£17,346	£4,154	0.24	£17,112
	2+ triptan	£7,681	0.40	£19,292	£7,307	0.41	£17,769

[redacted]

B15. For the reduction in MMD frequency regression:

a) **Please list all covariates that were considered for inclusion and why any statistically significant covariates were excluded**;

All covariates which were considered were listed in section B.3.3.2.5. Additional variables that were considered, but not included in the final model included: linear time, non-linear time, presence of the subject in a previous rimegepant single-event acute trial (BHV3000-301, BHV3000-302, or BHV3000-303), age, and sex. None of these variables were statistically significant.

b) Please clarify if a stepwise approach was taken to choose the covariates (and if not, please justify this decision);

Yes, a stepwise approach was taken.

c) Please clarify if removing the covariate Proph_mig_meds (insignificant in the multivariate regression) results in a better fitting model;

The Proph_mig_meds covariate was included due to both the clinical significance of the covariate and alignment with the primary outcome of Study BHV3000-305. Model fits were comparable with and without this covariate included.

d) Please clarify why the covariate Pills_per_migraine is associated with a value of 1 ('Efficacy'S22), is this based on an assumption or study data?

This is an assumption, based on alignment with the model in which the cost of one rimegepant tablet is added for each migraine attack.

Discontinuation

B16. Priority question. In the CS it states, *"Long term discontinuation in the post assessment period was informed by the subset of patients from the pooled acute studies (responders with ≥2 triptan failures from Studies BHV3000-301,302,303) who continued into the long-term safety study (BHV3000-201) and received rimegepant 75 mg PRN for 52-weeks".* As noted in question A7, the EAG is unclear how (or if) patients from the three acute RCTs

currently included in the analysis (BHV3000-301, -302 and -303) continued into the long-term safety study (BHV3000-201).

a) **If the statement in the CS is correct, please clarify if patients informing the long-term discontinuation rate responded to treatment at 2 hours. If not, please provide these data and implement it in the model as a scenario analysis. As per the request in question B2, please provide results for the mITT population (treated population).**

Confirmed that this rate was calculated for patients who responded to treatment at 2 hours. A discontinuation rate of [redacted] will be included in the model for the mITT population.

b) **Please provide the annual rate of discontinuation according to the reason for discontinuation, for example, due to adverse events, lack of efficacy or withdrawal by participant and where the data informing these can be found in the CSR.**

Discontinuation rates for responders amongst the triptan failure population were calculated for patients who responded in BHV-3000 301,302,303 and continued into the long-term safety study (BHV3000-201). They are as follows:

- Adverse events [redacted]
- Lack of efficacy [redacted]
- Withdrawal by subject [redacted]

B17. Priority question. When a rimegepant patient follows the BSC responder pain trajectories for 12 months a one-off QALY adjustment is applied. Please explain why no adjustment is made for HCRU.

Due to the complexity of the one-off calculation, and the relative low impact of HCRU in ICER results, the conservative assumption was made to not adjust for HCRU in the discontinuation calculation. HCRU represents <10% of total costs and excluding HCRU from the model altogether results in approximately £1K difference in the ICER; thus the impact of this adjustment is expected to be negligible.

B18. Priority question. The EAG considers there to be inconsistencies between the long-term discontinuation assumptions made in the acute model and the prevention model. In the acute model, patients who discontinue rimegepant

over the longer term follow the trajectory of BSC responders for 12 months, and then transition to BSC non-responder trajectories after this point. In the prevention model, patients who discontinue rimegepant or comparator treatment over the longer term immediately return to the baseline distribution of MMD.

a) **Please explain why the reversion to non-responder trajectories is not immediate in the acute model;**

Following discussion with clinicians it was assumed that a “placebo effect” for the usual care arm (characterized by 2-hour responders retaining this responder pain trajectory) would be maintained for up to 12 months. Given this, if rimegepant patients who discontinued were to transition directly to placebo non-responder status it would paradoxically create a situation where patients who initially responded to rimegepant and discontinued would then have poorer outcomes than patients who responded to placebo and didn’t initiate an active treatment. As such, the 12-month response for rimegepant is defined to be consistent with the placebo assumptions, with equivalent benefits observed post-discontinuation as are assumed for placebo patients.

b) **Please explain why all patients are assumed to respond to BSC when they discontinue rimegepant in the acute model;**

Initial response status to rimegepant was assumed to be informative of subsequent response, with rimegepant responders assumed to be analogous to placebo responders and non-responders to placebo non-responders. As such, patients who do not respond to rimegepant and are assumed to immediately discontinue treatment immediately revert to placebo non-responders, while those patients who have an initial response and then discontinue are subsequently assumed to follow a trajectory equivalent to placebo responders. This avoided the paradoxical scenario outlined in question B18a above.

c) **Please provide a scenario analysis where the proportion of patients following the trajectory of BSC responders for 12 months in the acute**

model is based on the proportion of patients who responded to BSC at the 2-hour assessment.

Please refer to the results presented for question B14c. Assuming that rimegepant response was not informative to future BSC response; rimegepant responder discontinuers were allocated the trajectory of BSC all comers in order to reflect a mix of responders and non-responders to BSC. Rimegepant remained cost-effective using both the pooled and triptan failure datasets.

B19. Please clarify why the per cycle discontinuation rate has been calculated as 1-EXP(-2/365*rim_disc_live) = 0.0531% and not as 1-(1-rim_disc_live)^(2/365) = 0.0559%.

The formula in the submission model erroneously treated the discontinuation data as a rate not a probability. This will be corrected in the updated model.

Health-related quality of life

B20. Priority question. Please explain why the QALH regression analysis was chosen to inform the base case and not the raw QALH calculation (scenario 7, Raw data: Pain intensity x hour). Please provide the strengths and limitations of these different approaches.

The base case included the QALH regression as it allows for adjustment for patient characteristics – particularly, as noted in Question B10c), the proportion with moderate vs. severe pain at baseline, which in the base case triptan failure population varied between rimegepant and usual care. The primary advantage of the raw QALH calculation option within the model is that it allows for testing alternative utility values by pain category; due to the nature of the data, these utilities must be pre-specified in order to fit the regression models outside of Excel and imported into the model and thus the regression method is not amenable to ad-hoc adjustments to utility values. Furthermore, use of regression analysis was found to be a conservative approach in scenario 7 (Table 68 of the CS).

B21. Priority question. For the QALH regression:

a) **If the BL_severity represents the proportion of patients reporting moderate vs severe migraine, does a higher proportion infer less severe migraines at baseline?**

The BL_severity coefficient represents the proportion of severe migraines at baseline (vs. moderate), i.e. higher proportion reflects greater severity.

b) **If so, please clarify why the BL_severity coefficient indicates a negative relationship with QALH.**

As per the note above, the negative relationship with QALH is to be expected as it reflects decreased QALH for greater severity.

B22. Priority question. The EAG considers the company's approach to incorporate baseline utility data from BHV3000-201 to be unduly complex.

a) **Please explain why the "pain free" utility value from Stafford *et al.* 2012 or Xu *et al.* 2011 (as per the ICER evidence report) was not used to inform the baseline value;**

The "pain free" value is focussed on experience of migraine pain only and does not incorporate other elements of interictal burden or social or emotional impact of migraine. As such and given that the MSQ data from BHV3000-201 provides a direct EQ-5D mapping for the relevant patient population, it was felt that this was a more representative estimate of utility for the population, and literature-based pain-specific values were adjusted accordingly, to avoid the implausible scenario of interictal utility being lower than pain-related utility during the course of a migraine event.

b) **Please provide scenarios exploring the suggestion in part a for both sources;**

As described above, these scenarios are not felt to be relevant, as BHV3000-201 provides a direct estimate of utility for the patient population. For completeness, results are provided below.

		Mean migraine event			Migraine event distribution		
Description	**Population**	**Δ Cost**	**Δ QALY**	**ICER**	**Δ Cost**	**Δ QALY**	**ICER**

Stafford utilities + raw-data. Interictal = Stafford pain free	mITT excl 310	£4,220	0.28	£15,091	£4,154	0.27	£15,577
	2+ triptan	£7,681	0.53	£14,368	£7,307	0.51	£14,383
Xu utilities + raw-data. Interictal = Xu pain free	mITT excl 310	£4,220	0.11	£39,705	£4,154	0.09	£45,277
	2+ triptan	£7,681	0.24	£31,644	£7,307	0.21	£35,491

Note: Appendix 4 provides options and dropdowns in the model that need to be changed to generate this result.

c) Please explain why UK general population utility values (using Ara and Brazier 2010) were not used to inform the baseline value;

It was not felt that UK population norms are appropriate, given the reduction in utility associated with migraine (including interictal periods). Lower overall quality of life across the population may reflect the proportion of days in which a migraine is experienced, as well as the mental health implications of fearing potential onset of a migraine on any given day. Patients with migraine experience additional HRQoL impact of migraine in-between attacks, for example due to lifestyle changes made to avoid triggers, anticipation of future attacks, lost work opportunities, emotional impacts including anger, depression, and anxiety. UK community-based EQ-5D scores for individuals with migraine have been reported to be 0.750 (mean, unadjusted value) and 0.796 (median, adjusted value), which are more closely aligned with the baseline utility values observed in BHV3000-201, providing further justification for their use in the model.

d) Please provide scenarios exploring the suggestion in part c. Please consider calculating the utilities associated with severe, moderate and mild pain from Stafford *et al.* 2012 and Xu *et al.* 2011 multiplicatively from the "pain free" baseline.

As described above, these scenarios are not felt to be relevant, as BHV3000-201 provides a direct estimate of utility for the patient population. For completeness, results are provided below.

		Mean migraine event			Migraine event distribution		
Description	**Population**	**Δ Cost**	**Δ QALY**	**ICER**	**Δ Cost**	**Δ QALY**	**ICER**

Stafford utilities + raw-data. Interictal = UK gen pop	mITT excl 310	£4,220	0.29	£14,723	£4,154	0.27	£15,258
	2+ triptan	£7,681	0.57	£13,476	£7,307	0.54	£13,648
Xu utilities + raw-data. Interictal = UK gen pop	mITT excl 310	£4,220	0.11	£39,467	£4,154	0.09	£44,913
	2+ triptan	£7,681	0.24	£31,713	£7,307	0.21	£35,474

Note: Appendix 4 provides options and dropdowns in the model that need to be changed to generate this result.

As discussed in section B3.4.3.A of the CS, we consider that Xu et al lacks face validity for modelling the UK population, the utility of 0.4 associated with 'severe pain' is implausibly high, given the EQ-5D score by setting the pain dimension to the highest level, and assuming perfect health on all dimensions would result in a hypothetical maximal utility value of 0.264 (< 0.4). This conclusion was supported in discussion with UK clinical experts.[34]

B23. Priority question. In the CS it states, "*Study BHV3000-201 did include MSQv2 responses which were mapped to EQ-5D utilities. These mapped utilities inform the baseline values and the values for patients who do not experience migraine in each 48-hour cycle, based on MMDs*."

a) Please clarify if episodic migraine model 1 from Gillard *et al.* 2012 was used to generate EQ-5D scores;

The episodic migraine model 1 from Table 6 from Gillard et al. 2012 was used.

b) Given that the MSQv2 has a four week recall period for patients answering the questions, please explain why it was considered appropriate to use these data to inform the utility of patients who do not experience migraine in each 48-hour cycle;

The MSQv2 focusses on the overall experience of patients over the course of the month, rather than the specific impact of pain, which is the focus of the Stafford published values. As such, we considered that it was reasonable to assume that the mapped MSQv2 utilities represent a constant background utility value over the course of the month, similar to the approach taken in prior migraine prevention submissions to NICE.

c) **Please clarify if migraines could be double counted by using the MSQv2 to inform the baseline utility.**

In mapping the MSQv2 mapping values to the pain-free state and applying pain decrements for acute migraines on top, we acknowledge the limitation of potential double counting disutilities; there is no available data source that addresses both interictal and pain-specific disutility for migraine patients. However, this is unlikely to impact results, as the overall utilities would be shifted up or down analogously for both treatment arms, and no differential survival is associated with rimegepant.

B24. In the acute model, age-related utility decrements are not applied, "*given that migraine severity may decrease with age, it is unclear whether the standard population-based decrease in utility would be relevant vs. offset by improvements in migraine-specific utility. In the absence of direct data to support these complex relationships over time, a constant age-based utility was retained*". However, age-related utility decrements are applied in the prevention model. Please clarify why this argument was not made in the prevention model.

Given multiple steps to generate utilities in the acute model and no differential mortality this was not included. To align with prevention, age-adjustment will be added to the acute model.

B25. The baseline utility value obtained from BHV3000-201 (0.695) is lower than the Stafford *et al.* 2012 pain free utility (0.87) and the UK community-based EQ-5D values reported by the company when making the case for Stafford *et al.* 2012 (0.740 [mean, unadjusted value] and 0.796 [median, adjusted value]). Please provide a clinical rationale why the utility obtained from BHV3000-201 could be lower than the values in these other sources.

The baseline utility value from the subgroup of BHV3000-201 is reflective of their triptan-refractory status and baseline MMD. As discussed in response to question B23, the data from BHV3000-201 reflect a hard to treat, triptan resistant population, who have exhausted treatment options. Triptan failure patients have a significantly greater HRQOL burden in terms of higher levels of disability as measured by the MIDAS, and reduced MSQv2 and EQ-5D scores.[35]

Furthermore, HRQoL is known to decrease with monthly migraine frequency,[36,37,38] which is likely contributing to the lower utility value observed among patients from BHV3000-201, with a baseline MMD of [redacted].

B26. Please provide the standard error, lower bound of 95% CI, upper bound of 95% CI and p-value associated with each term in Tables 55 and 58. Also clarify how these covariates were identified and chosen.

Please find updated tables below.

Updated CS Table 55

Term	Coefficient	Standard error	conf.low	conf.high	p.value
(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex = Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
trip_lines1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
trip_lines2+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Updated CS Table 58

Term	Estimate	Standard error	conf.low	conf.high	p.value
(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex = Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
trip_lines1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
trip_lines2+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Resource use and costs

B27. Priority question. Please clarify why no rimegepant-specific monitoring costs are included in the model.

a) **If rimegepant is expected to be initiated and monitored in secondary care, please include these costs.**

There are no monitoring requirements outlined in the SmPC for rimegepant, therefore treatment-specific monitoring costs were excluded.

B28. Priority question. Non-responders in the first cycle who discontinue incur the cost of a whole pack. Please clarify why tablets are costed individually for subsequent attacks (that is, there is no pack wastage). Please provide a scenario analysis including pack wastage for subsequent attacks.

It is assumed that for an oral medication, patients who discontinue (with the exception of initial non-responders) would complete their final package. In addition, given that only a proportion of patients experience a migraine each cycle, it is felt to be unnecessarily complex to estimate cumulative dosing and potential pack wastage over time.

B29. According to Vo *et al.* 2018, the p-value for the non-migraine control group vs the 4-7 EM and 8-14 EM groups was not considered statistically significant for hospitalisations.

a) **With this in mind, please explain why hospitalisations were included in the resource use estimates;**

Hospitalizations were included to align with the prevention model, and prior TAs in migraine. While hospitalization are relatively rare with migraine, they represent a significant use of health care resources.[39] Therefore, any cost offsets due to reduced migraine hospitalizations are considered relevant.

It should also be noted that any uncertainty in Vo et al estimates of mean hospitalizations (e.g., standard error), is propagated through the PSA.

b) Please explain how the control group is taken into account when considering which health care resources to include;

The control group was not taken into account when considering which health care resources to include. This is aligned with the prior NICE TAs in migraine.

c) Please justify costing for only the severe migraines when Vo *et al.* 2018 does not single out these as the only EMs resulting in resource use.

We acknowledge that this is a limitation to the current evidence base, that we were unable to account for potential increases in resource use that would arise from migraine with lower pain severity at 24 hours. Prior work by Atlas et al. and the ICER model from the United States informed our approach. We consider the assumption that patients with no, mild, or moderate pain at 24 hours following pain onset would have a low probability of accessing ED, GP, or hospital specifically to that migraine event, compared to a patient in severe pain, who required medical assistance for management of their symptoms as reasonable.

B30. In Table 61 of the CS, the HRG code for emergency department visits is VB09Z and the unit cost is £188.07. In Table 80, the HRG code for emergency department visits is VB08Z and the unit cost is also £188.07. Furthermore, TA260 and TA764 both refer to a HRG code of VB09Z. Please clarify the correct unit cost and HRG code for emergency department visits.

Thank you for identifying this discrepancy. The intended HRG code for both models is VB08Z, with a unit cost of £188.07. This was the cost applied in both models, but as noted by EAG, there is a typo in Table 61. This is now changed from VB09Z to VB08Z as below.

Resource	Unit costs (£)	Description	Source
General practitioner visit	39.23	Based on cost per patient contact lasting 9.22 minutes	PSSRU
Emergency department visit	188.07	HRG code VB08Z	NHS reference costs
Hospitalisation	643.29	Weighted average of HRG codes AA31C, AA31D, and AA31E	NHS reference costs

Abbreviations: HRG, healthcare resource group; PSSRU, Personal Social Services Research Unit

B31. The lost productivity parameters and costs reported in the CS (Table 62) and model ('Costs;F54:F56) are very different, please explain why.

The values in the CS table 62 are the most up-to-date and correct. Model values will be updated to match table in CS.

MIGRAINE PREVENTION

[redacted]

CS Table 5: Base-case results prevention

[redacted]								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]						

Abbreviations: Dominated, strictly or extendedly dominated; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years
Notes: NMB: Net monetary benefit (mAbs vs rimegepant): a negative value indicating rimegepant is cost-effective compared with the alternative at the given WTP threshold.

CS Table 86: Probabilistic base-case results prevention

[redacted]								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]						

Abbreviations: Dominated, strictly or extendedly dominated; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years

Notes: NMB: Net monetary benefit: a negative value indicating rimegepant is cost-effective compared with the alternative at the given WTP threshold.

[redacted]

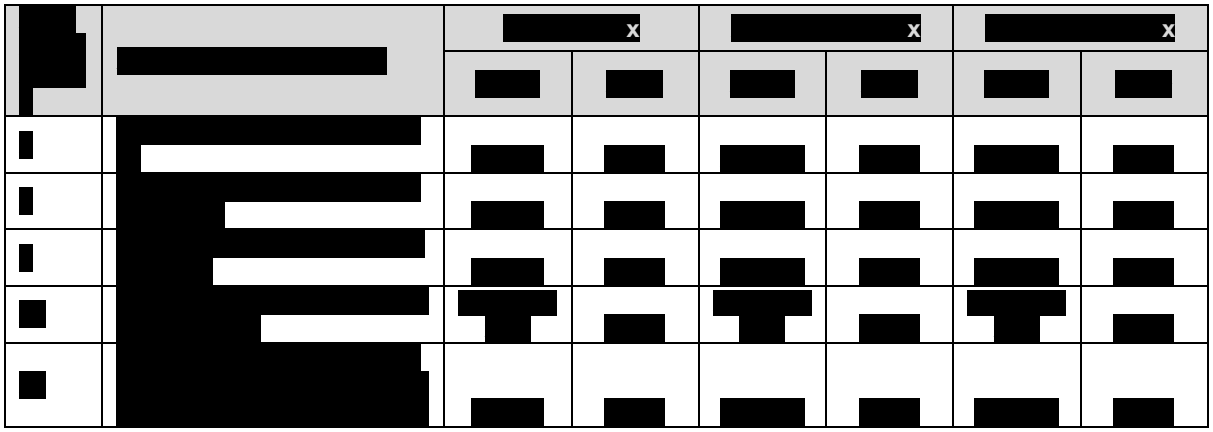
CS Table 6: Ranges for most influential parameters for ICER galcanezumab versus rimegepant (migraine prevention)

[redacted]	[redacted]		
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

CS Table 7: Pairwise ICERs and NMB (rimegepant vs mAbs) for scenario analyses

[redacted]	[redacted]	[redacted]x		[redacted]x		[redacted]x	
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]



Abbreviations: BSC, best supportive care; HCRU, healthcare resource use; ICER, incremental cost-effectiveness ratio; MMD, monthly migraine day(s); NHWS, national health and Wellbeing Survey; NMA, network meta-analysis; NMB, net monetary benefit; OR, odds ratio

[1]:

B32. Priority question. Based on your response to the request in question A22 (a within-trial analysis of episodic vs chronic migraine) please comment on how the results of the economic analysis could be impacted by having a full episodic population.

As discussed in question A22, the diagnosis of EM vs CM is not an enduring characteristic, the unambiguous classification of migraine patient as EM or CM is challenging. Furthermore, as shown in the post-hoc analysis provided in question there is no statistically significant evidence that the odd-ratios differ between the EM and CM subjects as assessed by the Breslow-Day test. As such, we do not anticipate any impact on the economic model. Please also refer to the response to question B35.b that indicated minimal impact of truncation of the MMD distribution range to episodic migraine (4-14 MMD).

B33. Priority question. At the end of a 40-year time horizon, [redacted] of patients have died in the model. Please enable the model to analyse a lifetime time horizon and provide these results in scenario analysis.

A proportion of subjects remain alive at the end of a 40-year time horizon. However, as discussed in Document B, section B.3.2.2.P table 71, given the discontinuation rate, only a negligible proportion of patients are expected to remain on treatment beyond 20 year. For completeness the model capacity has been extended to a time

horizon of 60 years – approximately 100 years of age for the base case population. Given the extent of discontinuation at twenty years, though absolute costs and QALYs increase there is negligible impact on incremental analyses.

The following table provides results for the 60-year analyses in the updated model with all other model settings as per the original submission base case.

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus rimegepant (£/QALY)	Base case ICER (£/QALY)
Galcanezumab	33,113	13.201	6,076	0.053	115,199	115,211
Fremanezumab	32,326	13.192	5,289	0.044	118,890	118,883
Erenumab	30,254	13.183	3,217	0.035	92,676	92,671
Rimegepant	27,037	13.148	0	0.000	na	na

[redacted]

MMD distributions

B34. Priority question. Please clarify why a normal distribution was chosen to estimate the distribution of MMD at baseline.

a) **Please clarify if a number of parametric distributions were assessed to estimate the distribution of MMD at baseline;**

b) **In your response please provide figures comparing the parametric distributions versus the observed distribution and goodness of fit statistics.**

Alternative parametric distributions were not considered. The normal distribution was provided alongside the observed data as it appeared this had been favoured in a previous appraisal. According to AIC the Poisson distribution appears to provide a slightly better fit than the normal distribution, with results similar to those when using the observed baseline MMD data. These options will be added to the updated model.

Distribution of MMD at baseline: Model AIC results

Model	AIC
Poisson	
Beta-binomial	
Normal	

B35. Priority question. In the CS, episodic migraine is defined as at least four migraine days per month but fewer than 15 headache days per month.

a) **Please clarify why the distribution of MMD at baseline was not truncated to this definition;**

The figure presented in Question B34 b depicts the baseline MMD distribution for the group without a history of chronic migraine. This shows migraine frequency in the observation period for patients with episodic migraine out with the 4-14 range. This reflects the natural tendency for there to be some variability outside this range in an episodic migraine population. An option will be included in the updated model to truncate baseline MMD of 4-14.

b) **Please provide a scenario analysis truncating the distribution of MMD at baseline to at least four migraine days per month but fewer than 15 headache days per month.**

The following table provides results from the scenario truncating the MMD distribution to 4-14 MMD. These are consistent with the original unrestricted base case.

Table Model scenario based on restricting the MMD baseline range to 4-14:

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Scenario ICER versus rimegepant (£/QALY)	Revised Base case ICER (£/QALY)
Galcanezumab	25,620	9.164	6,072	0.051	120,236	115,211
Fremanezumab	24,832	9.156	5,284	0.043	124,061	118,883
Erenumab	22,763	9.147	3,215	0.033	96,751	92,671
Rimegepant	19,548	9.114	0	0.000	na	na

[redacted]

B36. Priority question. Please explain why the distribution of MMD in cycles 1 (week 0-3) and 2 (week 4-8) is not adjusted according to response status when the NMA outcome is based on the average response over 12 weeks. Please provide a scenario analysis including this adjustment in cycles 1 and 2.

All patients are modelled to remain on treatment through 12 weeks. Consequently, distinguishing between responders and non-responders in these earlier cycles is unnecessary as the model reflects the overall effect in the total population (both responders and non-responders). In contrast the post 12-week period relies on separate estimates for those who are responders and continue on treatment and non-responders who will not. Therefore, we have not revised the model in order to perform the requested scenario analysis.

B37. **Please clarify why a Week 4 covariate was not included in the count regressions for MMD (Table 81 of appendix P).**

As in the fremanezumab, erenumab, and galcanezumab submissions, we set baseline MMD according to the frequencies observed in the trial, rather than predict those using a regression, with statistical distributions used to model subsequent

MMD. The potential for week eight and week 12 MMD to differ from week four is accounted for, with the week four MMD represented in the model constant.

Treatment efficacy

B38. Median ORs were used to inform the economic analysis:

a) **Please clarify if the OR for GAL 120 versus rimegepant should be [redacted] (CS Table 39 and 'Response'H29) or [redacted] (CS Table 75);**

b) **Please clarify if the OR for FRE 225 versus rimegepant should be [redacted] (CS Table 39 and 'Response'H30) or [redacted] (CS Table 75);**

c) **Please explain why mean ORs were not used to inform the economic analysis.**

There appears to have been a transposition error in Table 75, with the GAL 120 and FRE 225 odds ratios being swapped with one another for the fixed effect. The data employed in the economic model is as intended.

a) The OR for GAL 120 versus rimegepant should be [redacted].

b) The OR for FRE 225 versus rimegepant should be [redacted].

c) As we are dealing with converged symmetrical posterior distributions, there should not be much difference in taking the median compared to the mean. However, medians were provided as they are more robust to sampling outliers compared to means.

B39. Priority question. Please explain why the probability of response for rimegepant is based on the response at 12 weeks (0.491) and not the average response over 12 weeks (0.331). The EAG considers the company's approach to be inconsistent with the NMA outcome (average response over 12 weeks). Please provide a scenario analysis using the approach suggested by the EAG (if this does not form part of the revised base case).

The approach adopted in the submission base case is based on the supposition that best response *at* 12 weeks is the more clinically meaningful criteria in practice by which to assess response for the purpose of determining continued treatment. We

believe this is appropriate for the *absolute* response probabilities irrespective of the means by which *relative* treatment effects for response are to be estimated. Had the data to inform the NMA been complete in terms of response at 12 weeks this would have been the data that would have informed the NMA. However, due to the limited availability of *at* week 12 data, we performed the NMA using data *over* the 12-week period, rather than *at* 12 weeks. As we noted in the submission, the relative treatment effects estimated by the two different approaches (where both *at* and *over* 12-week data are available), were consistent with one another. On this basis we apply estimates of *relative* treatment effects based on the *over* 12-week data (the more complete evidence set), to the *absolute* probability of response based on the *at* 12-week referent probability (the more clinically meaningful criteria). A scenario analysis is presented below in which the Rimegepant response of [redacted] based on the over-12 week criterion is applied. Results are consistent with the CS base case.

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Scenario ICER versus rimegepant (£/QALY)	Revised Base case ICER (£/QALY)
Galcanezumab	24,114	9.040	5,416	0.053	102,997	115,211
Fremanezumab	23,313	9.031	4,614	0.044	104,939	118,883
Erenumab	21,516	9.021	2,818	0.034	82,960	92,671
Rimegepant	18,698	8.987	0	0.000	na	na

[redacted]

B40. Priority question. Please use CODA from the NMA to inform the probabilistic analysis and generate revised probabilistic results. Please ensure the same iteration (row) is used for each treatment to preserve the correlation between the treatments.

CODA has been added to the model. Please note the NMA is based on a run of 20,000 draws. A random sample of 1,000 is applied as the CODA, and there are

therefore minor differences versus the medians tabulated per CS Table 75. Results are consistent with the CS base case.

[redacted]

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Scenario ICER versus rimegepant (£/QALY)	Revised Base case ICER (£/QALY)
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	115,211
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	118,883
Erenumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	92,671
Rimegepant	[redacted]	[redacted]				

[redacted]

B41. Priority question. Please provide a clinical rationale why non-responders on active treatment (at 12 weeks) revert to baseline MMD over 12 months after assessment. The EAG cannot identify this assumption in TA764.

Though we do not include BSC as a relevant comparator in this submission, the model was informed by models that did. In TA764 “the treatment effect for people whose migraine responded to best supportive care diminished to baseline over 1 year.” We apply this gradual reversion to both BSC responders and non-responders. Were an active treatment then to be compared with BSC, a similar gradual reversion would be necessary (rather than penalising active therapies by immediately returning all non-responders to baseline). We recognise the reference to TA764 does not fully account for the approach taken, but the gradual reversion to baseline (rather than immediate full reversion at any single time point) is informed by TA764. Furthermore, in the appraisal of galcanezumab patients who do not achieve a response over the

first 3-months transition to the off-treatment health state where they have the mean change in monthly MHDs of a non-responder and return to baseline monthly MHDs over time. Due to redaction of the submissions and subsequent Technical reports there is some uncertainty as to the period over which this return to baseline occurs. Assumptions of immediate reversion to baseline for non-responders may also have been tested.

In the CS model base case a gradual return to baseline was implemented. The tables below present results from scenario analyses where all reversion to baseline occurred at 12 months and all reversion to baseline occurred at assessment (12 weeks). In each case the ICERs vs the CS base case are similar.

All reversion to baseline occurs 12 months after response assessment:

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Scenario ICER versus rimegepant (£/QALY)	Revised Base case ICER (£/QALY)
Galcanezumab	25,978	9.089	6,065	0.051	117,948	115,211
Fremanezumab	25,192	9.081	5,278	0.043	121,705	118,883
Erenumab	23,124	9.072	3,211	0.034	94,883	92,671
Rimegepant	19,913	9.038	0	0.000	na	na

[redacted]

All reversion to baseline occurs at assessment (12 weeks):

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Scenario ICER versus rimegepant (£/QALY)	Revised Base case ICER (£/QALY)
Galcanezumab	25,995	9.082	6,060	0.054	112,932	115,211
Fremanezumab	25,209	9.074	5,274	0.045	116,533	118,883
Erenumab	23,142	9.064	3,207	0.035	90,830	92,671

Rimegepant	19,935	9.029	0	0.000	na	na

[redacted]

a) Please rewrite the reversion rate to baseline, 'Settings'J34 (7.69%), as a calculation, this is currently hard-coded.

Please note with the new features added in the model, 'Settings' J34 (7.69%) is now moved to "Settings"J41 (7.69%); the formula has been added to the cell.

b) Please explain why a linear reversion was preferred compared to other options, e.g. an exponential reversion.

The rate of 7.69% reflects a linear decline over 13 cycles (the hard coding will be revised in the updated model). An option to revert exponentially will also be added – note this represents a more immediate reversion to baseline).

B42. Priority question. Please use the NMA requested in question A25 to inform a scenario using treatment-specific long-term discontinuation rates.

As discussed in question A25, data regarding the long-term discontinuation among the mAbs patients who responded during the double-blind treatment phases are not publicly available, the NMA comparing this outcome cannot be undertaken.

B43. Priority question. The EAG cannot validate the long-term discontinuation data informing Figure 23 of the CS with the CSR. Please provide the annual rate of discontinuation according to the reason for discontinuation, for example, due to adverse events, lack of efficacy or withdrawal by participant and where this data can be found in the CSR.

The discontinuation data included in the model is based upon those who were on rimegepant and also responded during the double-blind period of 301/2/3. This was a post-hoc analysis for the model and is not reported in the CSR. The table below provides the reasons for discontinuation.

Reason	Count	Percentage
ADVERSE EVENT	[redacted]	[redacted]
DEATH	[redacted]	[redacted]
NON-COMPLIANCE	[redacted]	[redacted]

OTHER	[redacted]	[redacted]
PHYSICIAN DECISION	[redacted]	[redacted]
PREGNANCY	[redacted]	[redacted]
WITHDRAWAL BY SUBJECT	[redacted]	[redacted]

Note that the reasons censored as trial-related were "LOST TO FOLLOW-UP" (n = [redacted]) and "STUDY TERMINATED BY SPONSOR" (n = [redacted]).

Health-related quality of life

B44. Please clarify how the covariates in Table 77 of the CS were identified and chosen.

An effect of MMD is expected, and the coefficient for treatment, adjusting for MMD, was also statistically significant. Further covariates were not considered. This is consistent with previous appraisals of erenumab and fremanezumab.

B45. **Given the mAb treatments have a different method of action to rimegepant, please provide a clinical rationale why mAbs would have the same 'on-treatment' utility as rimegepant**.

As stated in Doc B, the mechanism of action of rimegepant and mAbs is similar in that both target and act as calcitonin gene-related peptide (CGRP) blockers. They both work by blocking CGRP and thereby inhibiting the biologic activity of the CGRP neuropeptide resulting in vasodilation and minimizing vasoconstriction.[40]

The utilities of rimegepant could be higher due to the differentiated oral nature of the drug, which would decrease adverse events and have lower discontinuation rates. However, with the modelling we have taken a conservative approach and kept the on-treatment utility similar.

B46. Please explain why the baseline utility multiplier for age is implemented differently in the BSC engine compared to the other treatment engines (column I). Please correct as necessary.

The implementation in the BSC engine was in error and has been corrected. There is no implication for the analysis, however, as BSC is not considered as a relevant comparator.

Resource use and costs

B47. Please clarify why no treatment-specific monitoring costs are included in the model.

As discussed on B27, there are no monitoring requirements outlined in the SmPC for rimegepant, therefore treatment-specific monitoring costs were excluded.

B48. Please clarify why acute medication (as labelled in Table 81 of the CS) uses values from the fremanezumab submission (TA764) for the NHWS I source when all the other values are taken from the erenumab submission (TA682).

The data employed in the submission did contain this error, and this element of the data will be updated to reflect the data in the Erenumab submission. The unit cost for other medication will be taken from the submission and uprated for Hospital & Community Health Services cost inflation.

B49. The NHWS I data obtained from the erenumab submission (TA682) appears to be rounded to 2 decimal places. For consistency, please use the exact resource use values reported in Table 59 of the erenumab CS (page 158 of 201 in the committee papers)

a) **Please clarify why 90 days has been used to represent 3 months of resource use and amend as necessary.**

[The decimal places have been adjusted. The model applies data for 28-day cycles; the reference to 90 days in the model relates to the period covered for the estimates supplied. The following scenario analysis employs the corrected acute medication data (B48) and the adjusted decimal places as requested.

This analysis will constitute the revised base case in the second response].

Section C: Textual clarification and additional points

C1. Table 44 of the CS suggests that for study -302, there were [redacted] on-treatment severe AEs in rimegepant and placebo groups respectively.

a) **However, this differs from the CSR for this study (page 63), which reports [redacted] in rimegepant and placebo groups. Are the results in the CSR correct?**

This was a typographical error in Table 44 of the CS, [redacted] vs [redacted] are the results for on treatment SAEs (serious AEs) not severe AEs. The numbers reported in the CSR are correct, on-study severe AEs in treated subjects were reported in [redacted] rimegepant subjects and [redacted] placebo subjects. The severe events were diarrhoea, hematemesis, and nausea ([redacted]).

b) **There also appears to be results for this study in the CSR where 'NR' has been included in Table 44 (e.g. on-treatment AEs related to study drug).**

Please refer to the CSR in study 302.[41]

On-study treatment-related AEs were reported in [redacted] rimegepant subjects and [redacted] placebo subjects. As with overall on-study AEs, the most frequently reported treatment-related AE was nausea ([redacted] rimegepant subjects and [redacted] placebo subjects.

C2. Please review the models and ensure one year has been defined as 365.25 days throughout. For example, 365.00 is used in the acute model in 'Rim'M13.

This has been reviewed for the acute and prevention model. Amendment has been made in "RimN13" in the acute model

C3. From cycle 9 in the model engines ('Rim'P24), the sum of the cohort does not equal the starting cohort, please clarify.

We have closely examined this issue and note that it occurred for both the rimegepant and usual care arms in selected cycles. Based on a number of tests including simplifying transitions and turning mortality on and off, we are confident that the reason for this discrepancy is due to the limits of Excel rounding (coupled with very small mortality probabilities associated with 2-day model cycles). We have

included a check in the trace calculations of the death state, in which there is a check if the trace sums to one and if not, as long as the discrepancy in the trace is less than 10E-10 it is then defined as one minus the remaining health state occupancy (such that the trace sums to 1 by definition). If the discrepancy is >10E-10 an error is flagged, but this does not occur for the values observed

C4. Please correct the WTP threshold (frontier) in the cost-effectiveness plane in the prevention model. This is anchored on the results for galcanezumab and not a WTP threshold of £20,000 or £30,000 per QALY.

The frontier is not intended to represent a cost-effectiveness threshold. The direct link between galcanezumab and rimegepant reflects the extended dominance of other comparators. This may not always be immediately obvious as comparators can lie only marginally above the frontier on the cost-effectiveness plane.

C5. In the acute model, please clarify why the OWSA results for "Mod/sev 24 hr per migraine, Usual care- nonresponder" and "Rimegepant discontinuation per year (0.1, 0.02, 0.22)" differ between the submitted model (upper of 17,688 and 17,790 and lower of 18,708 and 18,582) and the results presented in table 67 of the submission (upper of 17,433 and 17,863 and lower of 18,911 and 18,594).

Thank you for noting this typographical error. The model values were correct – note that the values will now be updated to reflect changes to the model made in response to EAG requests.

Addendum

Background:

The EAG have identified a key discrepancy within the company submission. Because of this, an additional priority clarification question has been identified.

This is a priority question relating to Section B (treatment efficacy).

Addendum 1. Priority question. In the table below the EAG has summarised the results included in the CS, in acute treatment, for pain relief at 2-hours. Using the data in Table 20 of the CS, the EAG considers the N in the mITT population to equal [redacted] for rimegepant and [redacted] for placebo, and not [redacted] for rimegepant and [redacted] for placebo as reported in Table 52 of the CS.

Please clarify which population has been used to inform the data reported in Table 52 and explain exactly how n/N has been derived. Please make any necessary corrections.

Source	Population	Pain relief at 2-hours	
		Rimegepant n/N (%)	Placebo n/N (%)
Table 20	"No historic use of triptans failure"	[redacted]	[redacted]
	Failed 1 triptan	263/450 (58.4)	197/460 (42.8)
	Failed ≥2 triptans	103/148 (69.5)	65/177 (36.6)
Table 52 and 'Efficacy'J35:M35	mITT	[redacted]	[redacted]

Thank you for noting this. The values for the mITT population in Table 52 and 'Efficacy'J35:M35 were left there due to an error. In addition to the other updates requested for the mITT population, these will be updated in the model to have denominators of [redacted] for rimegepant and [redacted] for placebo.

Addendum 2

The EAG does not consider monthly migraine days (MMDs) to be equal to migraine attacks per month as one migraine attack may last more than one day and up to 72 hours.

· **Please explain why migraine attacks per month are used to inform MMDs in the acute model;**

Based on this feedback from the EAG we have implemented an alternative approach; note that the base case and scenario analyses presented throughout the document are based on this updated approach. Rather than generate 0-28 MMDs per month, we generate 0-14 migraine events per month, with each event modelled over 48 hours. With this assumption, the conversion between migraine events and MMDs (e.g. for inclusion in the MMD prevention regression) was achieved using the proportion of migraine events lasting >24 hours, shown below at baseline for the pooled acute studies and BHV3000-201, respectively. E.g. for BHV3000-201, [redacted] of migraines last <1 day, and so the number of MMDs per event was estimated to be [redacted] The simplifying assumption was made that all events were capped at 2 MMDs given that pain trajectories data were only available for 48 hours per event. This assumption is conservative towards rimegepant as it limits the potential benefits for migraine improvement and/or preventive effects associated with these events beyond 48 hours for patients receiving usual care, which may be reduced with rimegepant treatment.

· **Please provide the distribution of migraine attack durations at baseline observed in the acute pooled trials (Study BHV3000-301, -302, and -303) and Study BHV3000-201 (e.g. the number of migraine attacks lasing 4 to 24 hours, 25 to 48 hours and 49 to 72 hours), as noted in clarification question A3, please provide data using the mITT population;**

Study BHV3000-301, -302, and –303 baseline migraine duration

Migraine Duration	N	%
4 to 24 hours	[redacted]	[redacted]
25 to 48 hours	[redacted]	[redacted]
49 to 72 hours	[redacted]	[redacted]
73 to 96 hours	[redacted]	[redacted]
Missing	[redacted]	[redacted]

Study BHV3000-201 baseline migraine duration

Migraine Duration	N	%
4 to 24 hours	[redacted]	[redacted]
25 to 48 hours	[redacted]	[redacted]
49 to 72 hours	[redacted]	[redacted]

· **Please comment on the impact of using 48-hour pain trajectories per migraine attack in the acute model when migraine attacks may last up to 72 hours.**

Please see response above.

This is a priority question relating to Section B (treatment efficacy).

Addendum 3

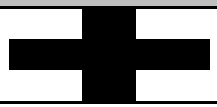
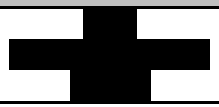
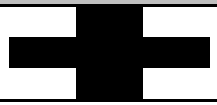
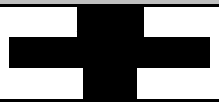
In addition, the EAG have identified 2 areas requiring confirmation:

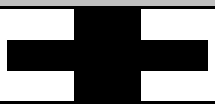
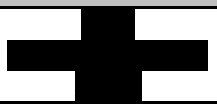
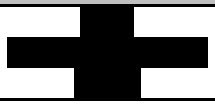
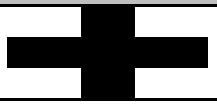
The EAG notes that the denominators used for acute subgroups in Table 35 of the CS appendices are inconsistent (for example, for the group with <4 headaches per month in study -303, n=[redacted] is the denominator for pain freedom at 2 h but a denominator of n=[redacted] if used for freedom from MBS). Please confirm that the following denominators are correct for both outcomes and that there are no errors in the number of events provided in Table 35 of the CS appendices:

a. **<4 headaches per month group:**
   i. **Study -303: n=[redacted] overall (n=[redacted] and n=[redacted] with/without prophylactic use) for rimegepant and n=[redacted] overall (n=[redacted] and n=[redacted] with/without prophylactic use) for placebo**
   ii. **Study -301: n=[redacted] overall (n=[redacted] and n=[redacted] with/without prophylactic use) for rimegepant and n=[redacted] overall (n=[redacted] and n=[redacted] with/without prophylactic use) for placebo**
b. **≥4 headaches per month group:**
   i. **Study -303: n=[redacted] overall (n=[redacted] and n=[redacted] with/without prophylactic use) for rimegepant and n=[redacted] overall (n=[redacted] and n=[redacted] with/without prophylactic use) for placebo**
   ii. **Study -301: n=[redacted] overall (n=[redacted] and n=[redacted] with/without prophylactic use) for rimegepant and n=[redacted] overall (n=[redacted] and n=[redacted] with/without prophylactic use) for placebo**

The EAG has correctly identified some transposition errors in respect of study -303 and study -301 data in Table 35 of the CS Appendices. We have re-produced a corrected version of Table 35 below.

Table 35: Co-primary endpoints: subgroup analysis by headaches per month mITT participants

	BHV3000-303[42]			BHV3000-301[43]			BHV3000-302[44]		
	Rimegepant, n/N (%)	Placebo, n/N (%)	Risk difference RIM vs PBO (95% CI); p-value	Rimegepant, n/N (%)	Placebo, n/N (%)	Risk difference RIM vs PBO (95% CI); p-value	Rimegepant, n/N (%)	Placebo, n/N (%)	Risk difference RIM vs PBO (95% CI); p-value
<4 headaches per month									
Pain freedom at 2 hours post dose									
Overall, no pain[a]									
Prophylactic medication use, no pain[b]									
No prophylactic medication use, no pain[b]									
Freedom from MBS at 2 hours post dose									
Overall[a]									
Prophylactic medication use[b]									
No prophylactic medication use[b]									

	BHV3000-303[42]			BHV3000-301[43]			BHV3000-302[44]		
	Rimegepant, n/N (%)	Placebo, n/N (%)	Risk difference RIM vs PBO (95% CI); p-value	Rimegepant, n/N (%)	Placebo, n/N (%)	Risk difference RIM vs PBO (95% CI); p-value	Rimegepant, n/N (%)	Placebo, n/N (%)	Risk difference RIM vs PBO (95% CI); p-value
≥4 headaches per month									
Pain freedom at 2 hours post dose									
Overall no pain[a]									
Prophylactic medication use, no pain[b]									
No prophylactic medication use, no pain[b]									
Freedom from MBS at 2 hours post dose									
Overall[a]									
Prophylactic medication use[b]									
No prophylactic medication use[b]									

[a] Common risk; [b] Stratum risk

In Appendix E.2 for prevention subgroup analysis, the EAG notes that the definition of the outcome is similar to that used in the NMA (proportion with at least 50% reduction in MMDs of any severity as an average across 12 weeks). However, the event rates across each subgroup do not add up to the number of events reported for the rimegepant trial in Table 36 of the CS ([redacted]/348 for rimegepant and [redacted]/347 for placebo). For example, for prophylactic medication use at randomisation, adding events in the yes and no groups only totals 134/348 for rimegepant and 92/347 for placebo.

Please clarify whether this is an error or explain the difference between definitions used for these subgroup results compared with that used in the NMA.

The number of events reported in Table 36 of the CS corresponds to the numbers of rimegepant and placebo subjects with at least 50% reduction in the mean number of **moderate or severe** migraine days per month, definition for one of the secondary endpoints. In order to conduct the NMA versus the mABs, the proportion should be indeed calculated based on the 50% reduction in MMDs of any severity.

An amendment to the NMA is provided below, the prevention model has been corrected with the revised NMA results. Please note responses to questions A18 and A24 have been updated to reflect the new results.

Updated results

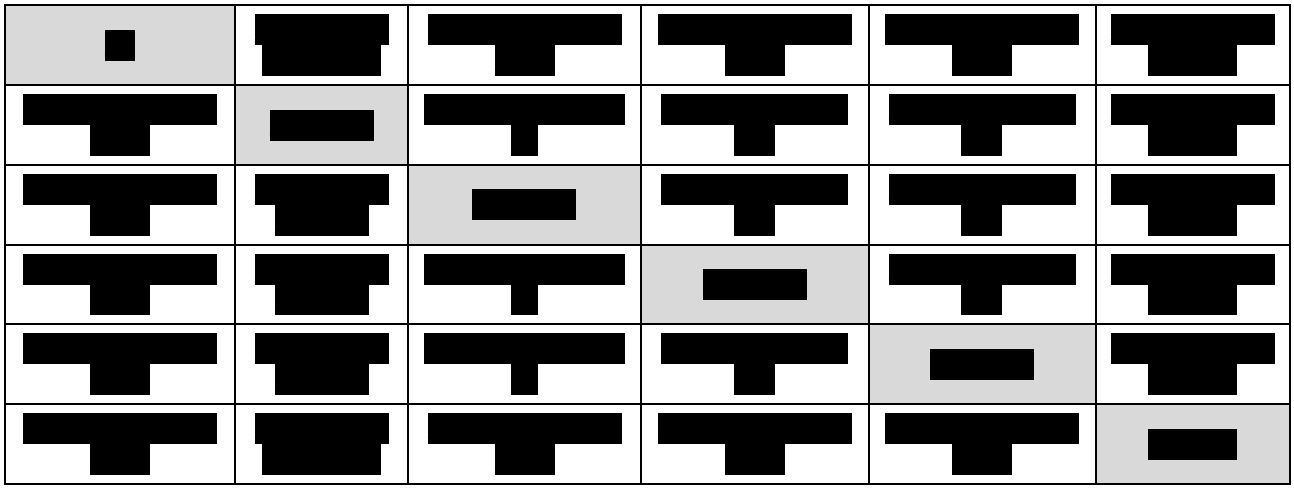
Table 8: Model fit statistics across outcomes

Model	≥50% reduction in baseline MMD		
	Dbar	pD	DIC
FE	[redacted]	[redacted]	[redacted]
RE	[redacted]	[redacted]	[redacted]
FE – Baseline adjusted	[redacted]	[redacted]	[redacted]
RE – Baseline adjusted	[redacted]	[redacted]	[redacted]

Abbreviations: Dbar = deviance; DIC = deviance information criterion; FE = fixed-effects; MMD = monthly migraine days; pD = effective number of parameters; RE = random-effects
Notes:
Bolded values indicate chosen base case model

Base case analysis

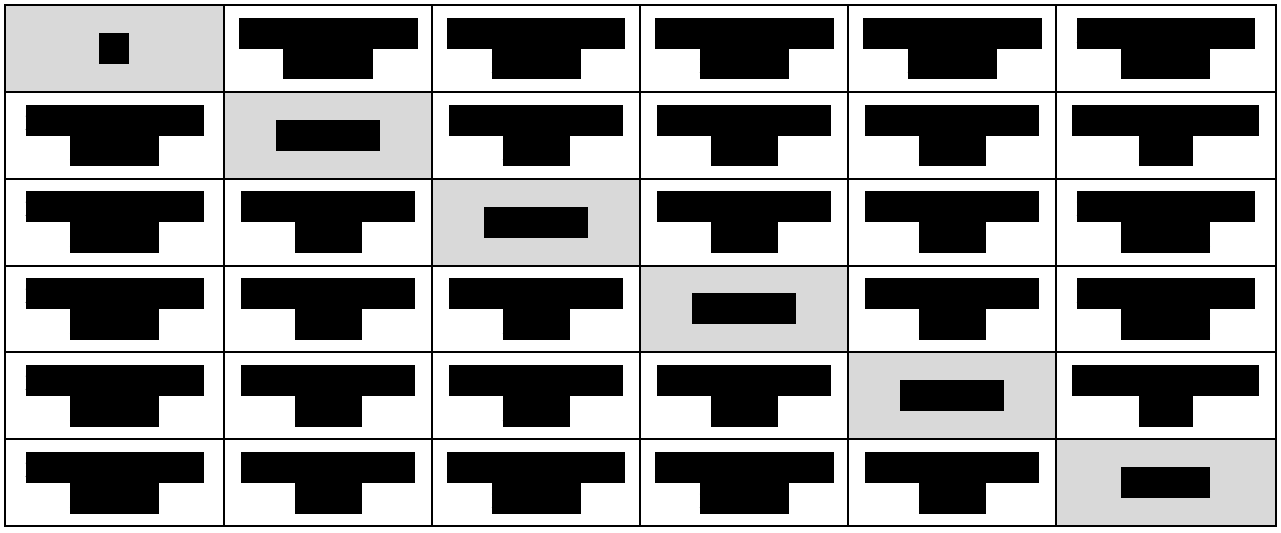
Table 9: Proportion achieving 50% reduction from baseline MMD, base case, fixed-effect baseline adjusted model (reported ORs with 95% CrIs) *selected model*



Abbreviations: CrI, credible interval; ERE, erenumab; FRE, fremanezumab; GAL, galcanezumab; PBO, placebo; RIM, Rimegepant
Notes:
Estimates are odds ratios (95% CrI). Bolded values are significant at a 5% level.

Alternate base case models

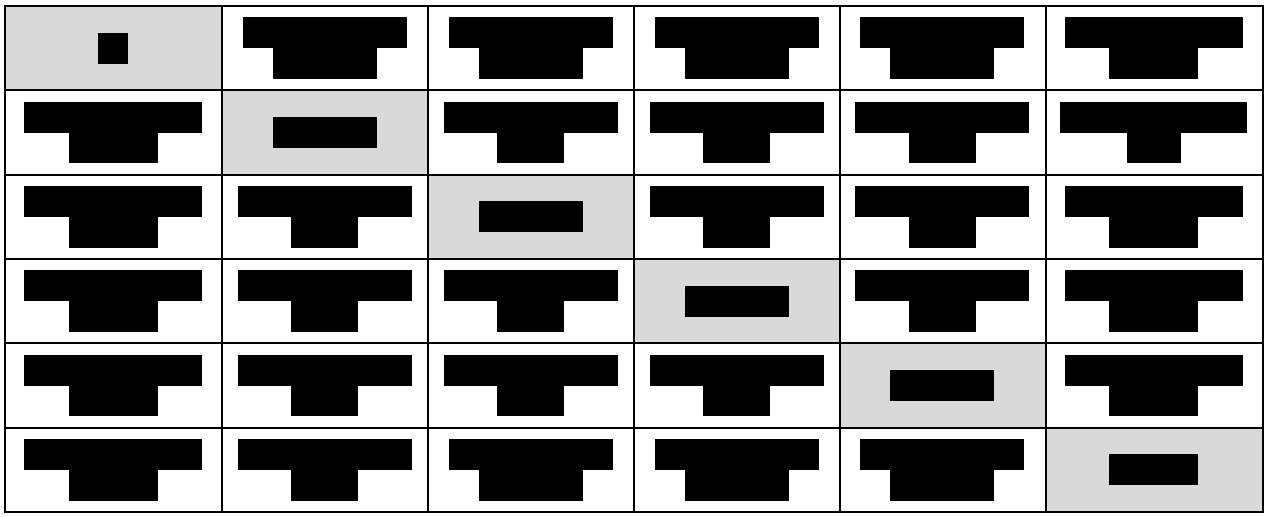
Table 10: Proportion achieving ≥50% reduction from baseline MMD, sensitivity analysis, random-effects baseline-adjusted model (reported ORs with 95% CrIs) *alternate model*



Abbreviations: CrI, credible interval; ERE, erenumab; FRE, fremanezumab; GAL, galcanezumab; PBO, placebo; RIM, Rimegepant
Notes:
Estimates are odds ratios (95% CrI). Bolded values are significant at a 5% level.

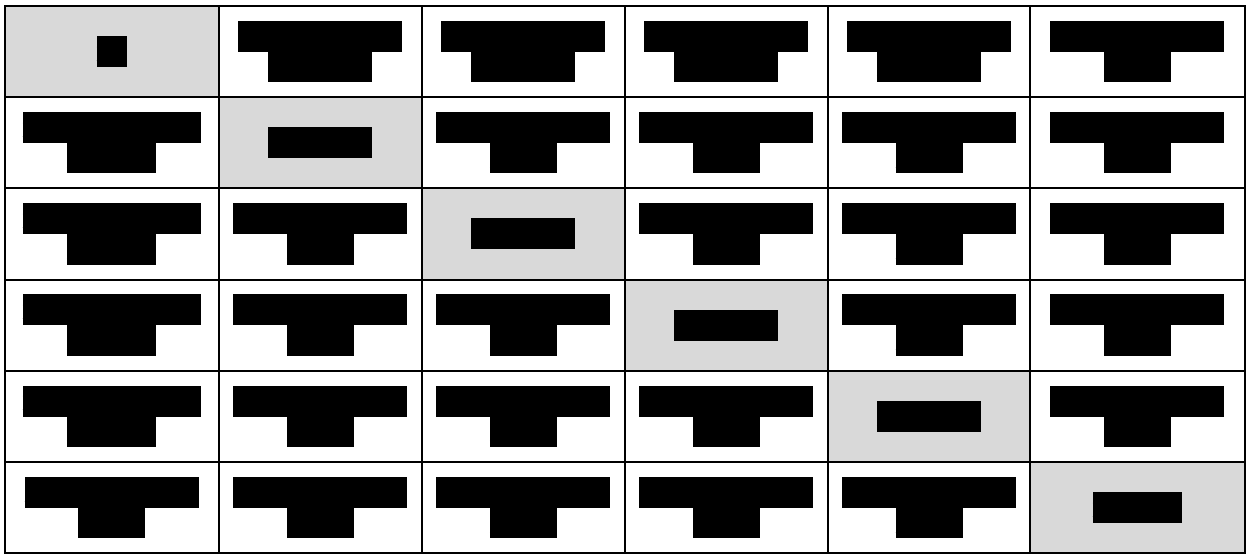
The between-trial heterogeneity parameter for this model, sd [median (95% CrI)] was: [redacted].

Table 11: Proportion achieving ≥50% reduction from baseline MMD, sensitivity analysis, fixed-effects model (reported ORs with 95% CrIs)*alternate model*



Abbreviations: CrI, credible interval; ERE, erenumab; FRE, fremanezumab; GAL, galcanezumab; PBO, placebo; RIM, Rimegepant
Notes:
Estimates are odds ratios (95% CrI). Bolded values are significant at a 5% level.

Table 12: Proportion achieving ≥50% reduction from baseline MMD, sensitivity analysis, random-effects model (reported ORs with 95% CrIs)*alternate model*

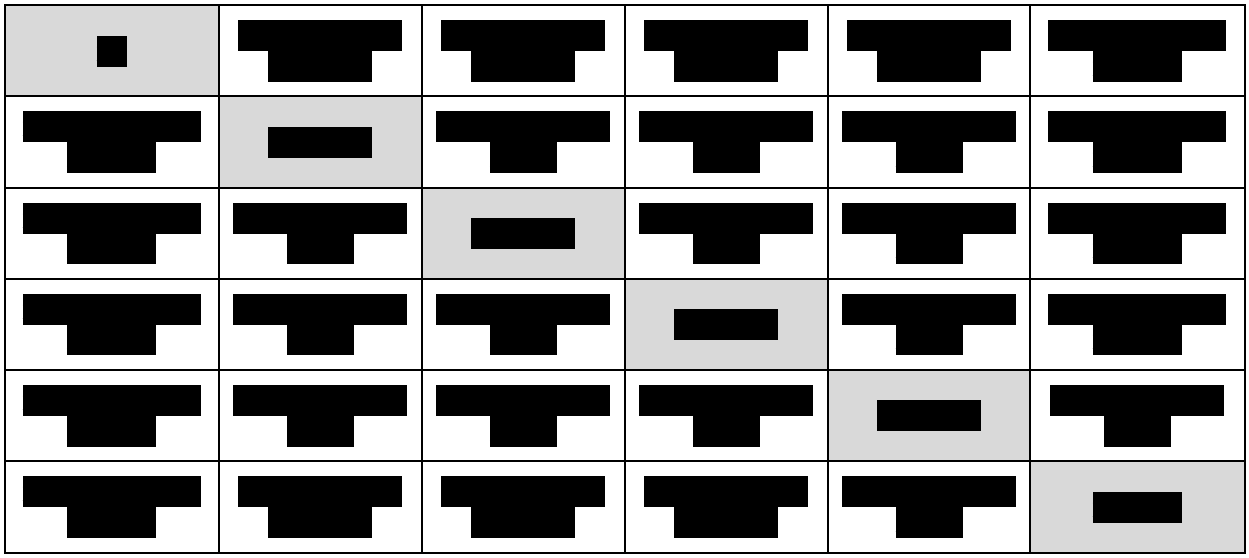


Abbreviations: CrI, credible interval; ERE, erenumab; FRE, fremanezumab; GAL, galcanezumab; PBO, placebo; RIM, Rimegepant
Notes:
Estimates are odds ratios (95% CrI). Bolded values are significant at a 5% level.

The between-trial heterogeneity parameter for this model, sd [median (95% CrI)] was: [redacted]

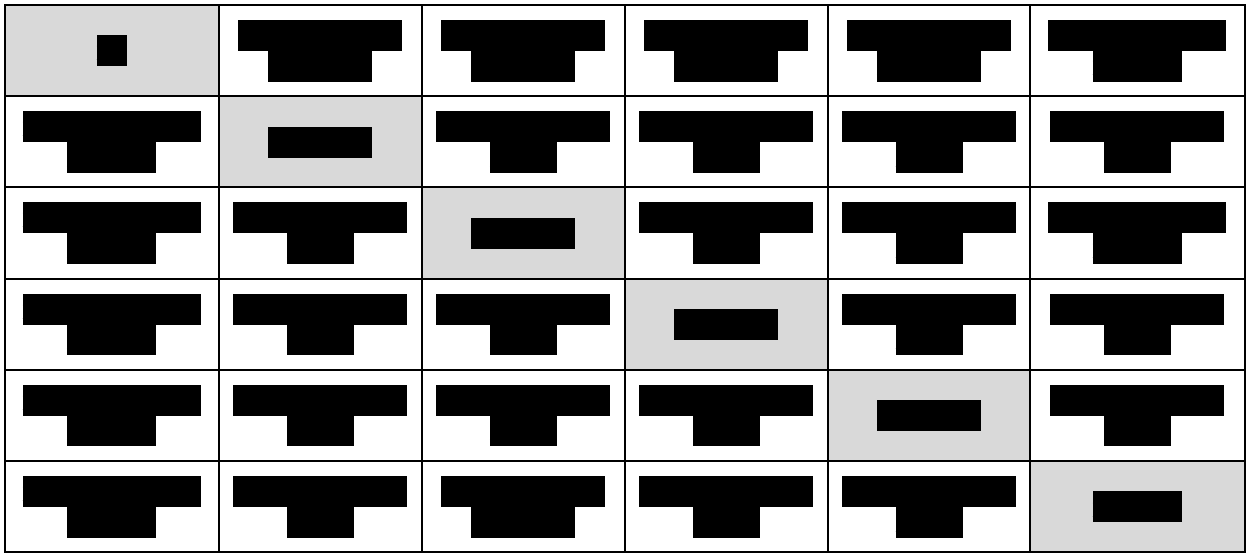
Sensitivity analysis – removing Sakai et al. 2021

Table 13: Proportion achieving 50% reduction from baseline MMD, sensitivity analysis (removing Sakai et al, 2021), fixed-effect baseline adjusted model (reported ORs with 95% CrIs) *selected model*



Abbreviations: CrI, credible interval; ERE, erenumab; FRE, fremanezumab; GAL, galcanezumab; PBO, placebo; RIM, Rimegepant
Notes:
Estimates are odds ratios (95% CrI). Bolded values are significant at a 5% level.

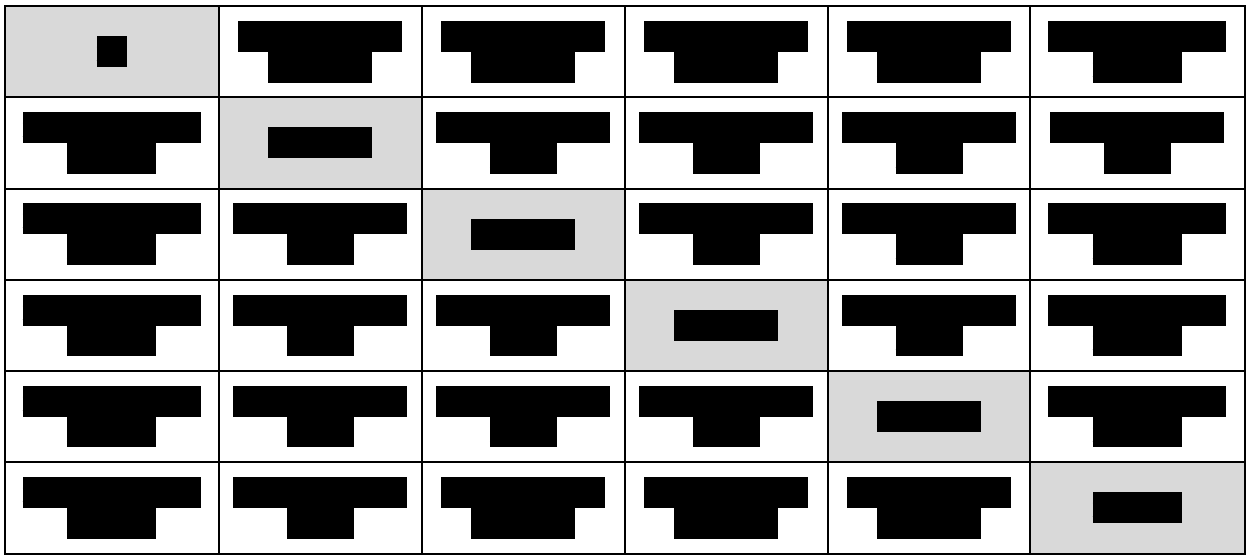
Table 14: Proportion achieving 50% reduction from baseline MMD, sensitivity analysis (removing Sakai et al, 2021), random-effect baseline adjusted model (reported ORs with 95% CrIs) *alternate model*



Abbreviations: CrI, credible interval; ERE, erenumab; FRE, fremanezumab; GAL, galcanezumab; PBO, placebo; RIM, Rimegepant
Notes:
Estimates are odds ratios (95% CrI). Bolded values are significant at a 5% level.

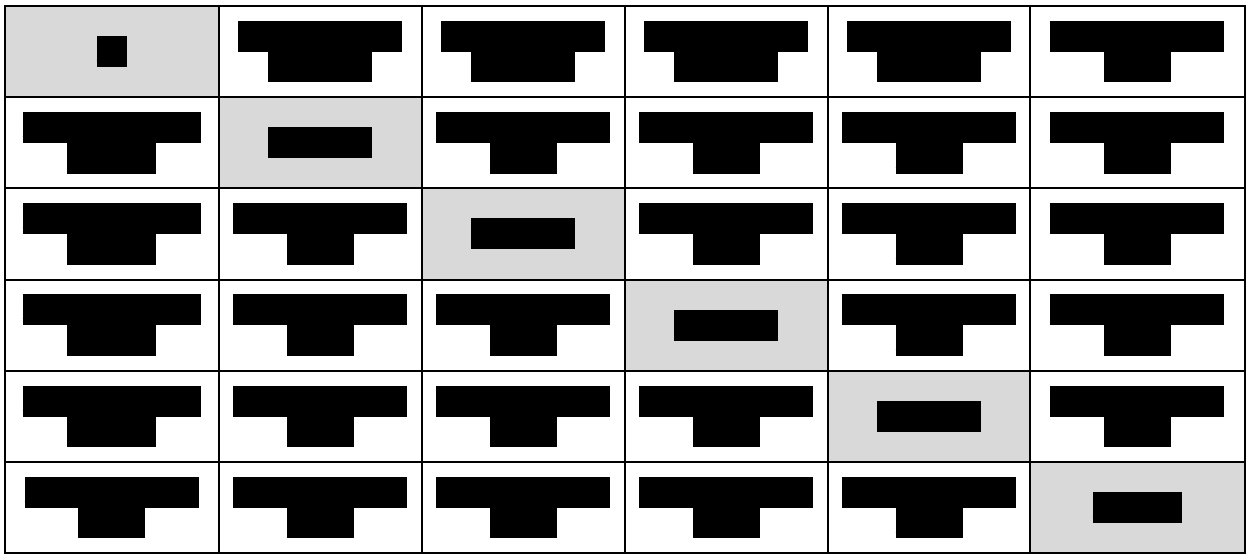
The between-trial heterogeneity parameter for this model, sd [median (95% CrI)] was: [redacted]

Table 15: Proportion achieving 50% reduction from baseline MMD, sensitivity analysis (removing Sakai et al, 2021), fixed-effects model (reported ORs with 95% CrIs) *alternate model*



Abbreviations: CrI, credible interval; ERE, erenumab; FRE, fremanezumab; GAL, galcanezumab; PBO, placebo; RIM, Rimegepant
Notes:
Estimates are odds ratios (95% CrI). Bolded values are significant at a 5% level.

Table 16: Proportion achieving 50% reduction from baseline MMD, sensitivity analysis (removing Sakai et al, 2021), random-effects model (reported ORs with 95% CrIs) *alternate model*

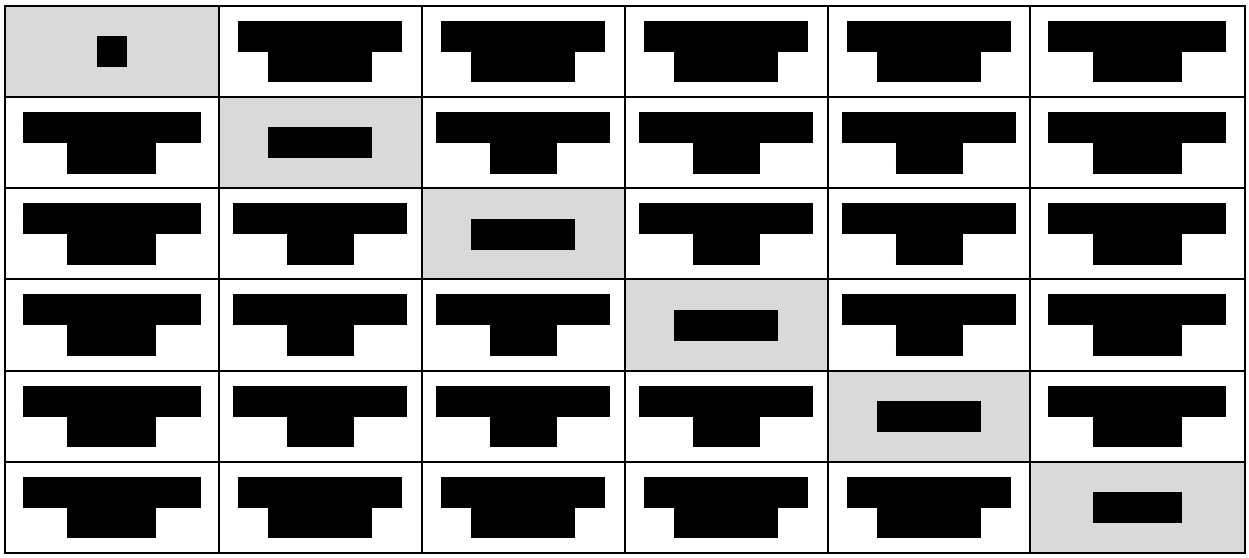


Abbreviations: CrI, credible interval; ERE, erenumab; FRE, fremanezumab; GAL, galcanezumab; PBO, placebo; RIM, Rimegepant
Notes:
Estimates are odds ratios (95% CrI). Bolded values are significant at a 5% level.

The between-trial heterogeneity parameter for this model, sd [median (95% CrI)] was: [redacted]

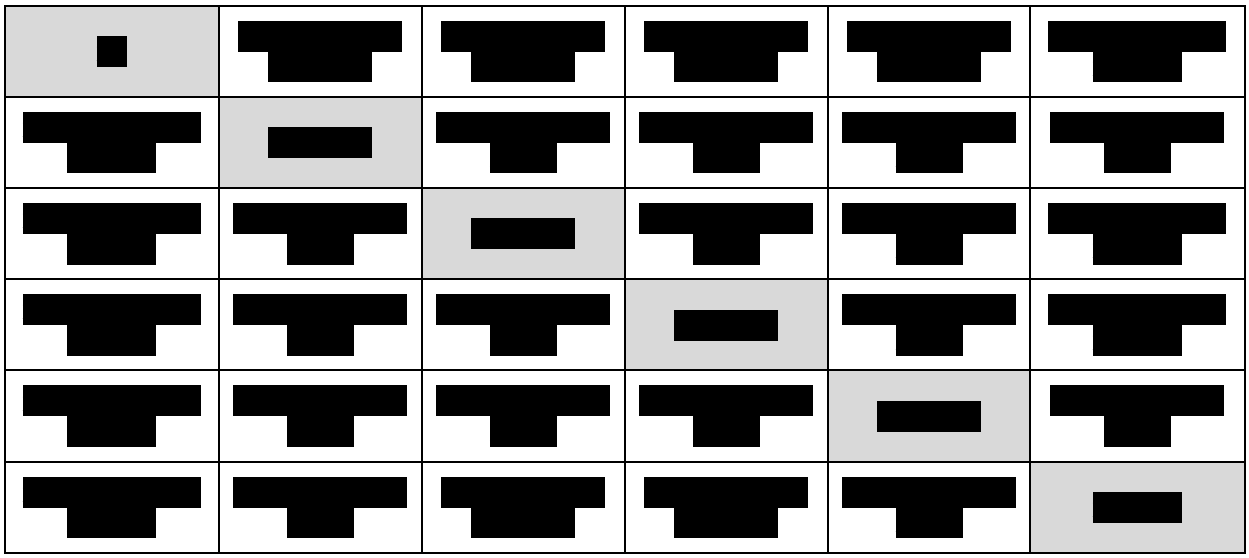
Sensitivity analysis – Phase 2 studies added

Table 17: Proportion achieving 50% reduction from baseline MMD, sensitivity analysis (Phase 2 studies), fixed-effect baseline adjusted model (reported ORs with 95% CrIs) *selected model*



Abbreviations: CrI, credible interval; ERE, erenumab; FRE, fremanezumab; GAL, galcanezumab; PBO, placebo; RIM, Rimegepant
Notes:
Estimates are odds ratios (95% CrI). Bolded values are significant at a 5% level.

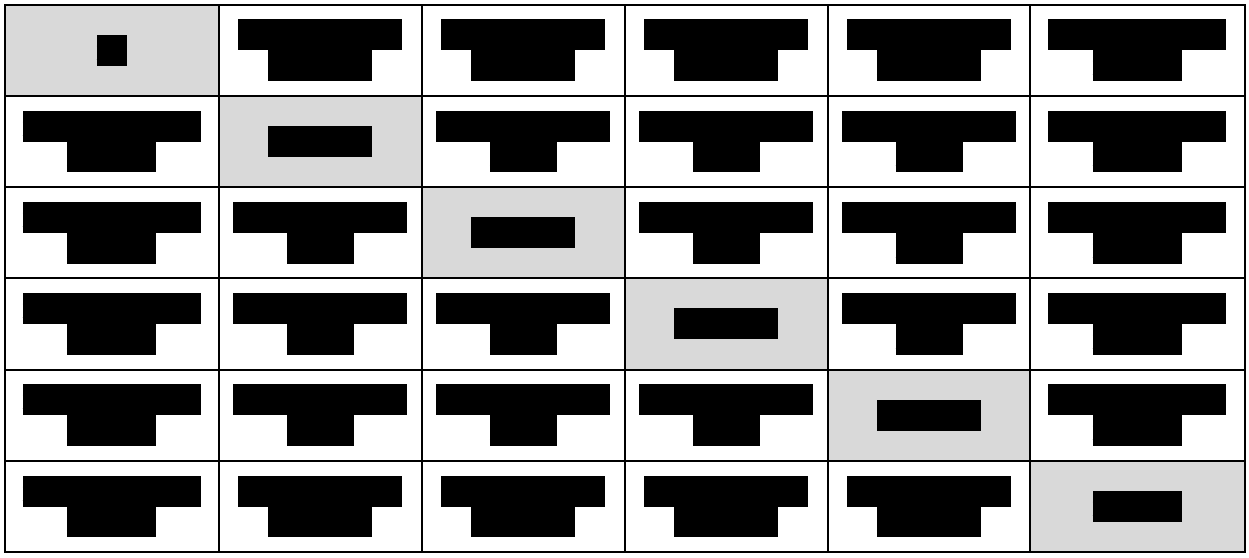
Table 18: Proportion achieving 50% reduction from baseline MMD, sensitivity analysis (Phase 2 studies), random-effect baseline adjusted model (reported ORs with 95% CrIs) *alternate model*



Abbreviations: CrI, credible interval; ERE, erenumab; FRE, fremanezumab; GAL, galcanezumab; PBO, placebo; RIM, Rimegepant
Notes:
Estimates are odds ratios (95% CrI). Bolded values are significant at a 5% level.

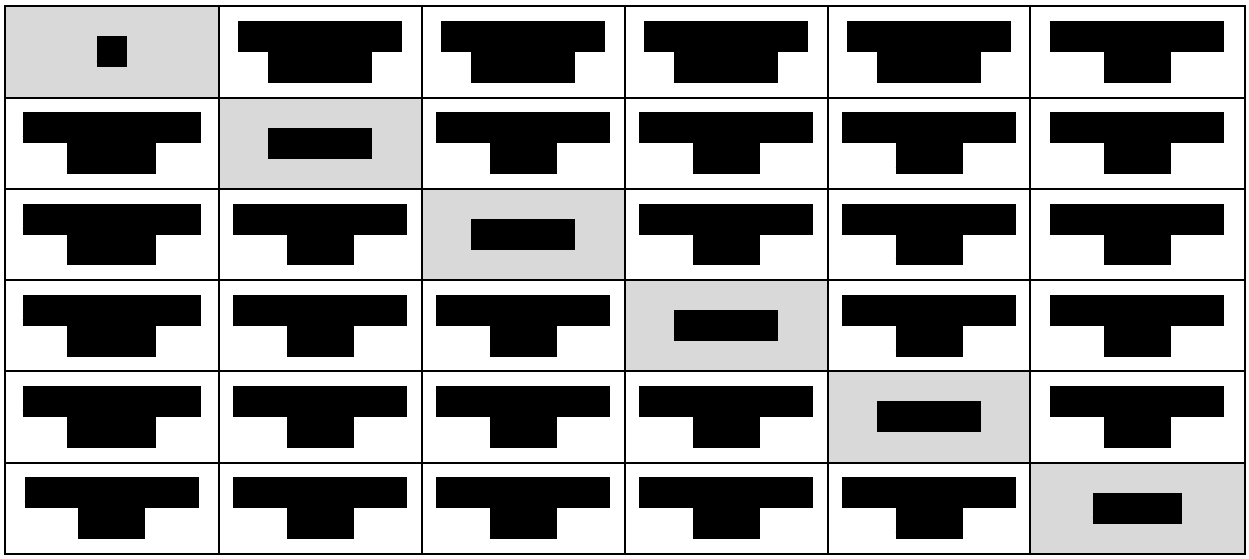
The between-trial heterogeneity parameter for this model, sd [median (95% CrI)] was: [redacted]

Table 19: Proportion achieving 50% reduction from baseline MMD, sensitivity analysis (Phase 2 studies), fixed-effects model (reported ORs with 95% CrIs) *alternate model*



Abbreviations: CrI, credible interval; ERE, erenumab; FRE, fremanezumab; GAL, galcanezumab; PBO, placebo; RIM, Rimegepant
Notes:
Estimates are odds ratios (95% CrI). Bolded values are significant at a 5% level.

Table 20: Proportion achieving 50% reduction from baseline MMD, sensitivity analysis (Phase 2 studies), random-effects model (reported ORs with 95% CrIs) *alternate model*



Abbreviations: CrI, credible interval; ERE, erenumab; FRE, fremanezumab; GAL, galcanezumab; PBO, placebo; RIM, Rimegepant
Notes:
Estimates are odds ratios (95% CrI). Bolded values are significant at a 5% level.

The between-trial heterogeneity parameter for this model, sd [median (95% CrI)] was: [redacted]

Appendix 1:

A8: Excluded Studies (see separate file)

Appendix 2:

A26d: Convergence plots for additional NMA models (see separate file)

Appendix 3:

A4: Baseline characteristics (Acute trials 301, 302, 303, & 310)

Appendix 4:

Rimegepant drop down options in CUA model

REFERENCES

[1] SUMMARY OF PRODUCT CHARACTERISTICS, VYDURA 75 mg oral lyophilisate, Section 4.1

[2] SUMMARY OF PRODUCT CHARACTERISTICS, VYDURA 75 mg oral lyophilisate, Section 4

[3] https://www.nice.org.uk/guidance/cg150/resources/headaches-in-over-12s-diagnosis-and-management-pdf-35109624582853

[4] Campbell CM, Edwards RR. Ethnic differences in pain and pain management. Pain Manag. 2012 May;2(3):219-230. doi: 10.2217/pmt.12.7. PMID: 23687518; PMCID: PMC3654683

[5] Biohaven Pharmaceuticals Inc. Data on File: Clinical study report BHV3000-301: Aphase 3, double-blind, randomized, placebo-controlled, safety and efficacy trial of BHV-3000(rimegepant) for the acute treatment of migraine. 2019.

[6] Biohaven Pharmaceuticals Inc. Data on file: Clinical study report BHV3000-302. 2020

[7] Biohaven Pharmaceuticals Inc. Data on file: Clinical study report BHV3000-303: A Phase 3, Double-blind, Randomized, Placebo-controlled, Safety and Efficacy Trial of BHV-3000 (rimegepant) Orally Disintegrating Tablet (ODT) for the Acute Treatment of Migraine.2019.

[8] Biohaven Pharmaceuticals Inc. Data on File: Clinical study report BHV3000-310: Phase 3: Double Blind, Randomized, Placebo-Controlled, Safety and Efficacy Trial of BHV 3000 (rimegepant) 75 mg for the Acute Treatment of Migraine. 2022

[9] Biohaven Pharmaceuticals Inc. Data on file: Clinical study report BHV3000-201. A Multicenter, Open-Label Long-Term Safety Study of BHV-3000 in the Acute Treatment of Migraine. 2020.

[10] Document B. Table 14.

[11] 303 TLF: 14.2.1.1.2 (pain freedom) & 14.2.1.2.2 (MBS freedom)
· 301 TLF: 14.2.1.2 (pain freedom) & 14.2.2.2 (MBS freedom)
· 302 TLF: 14.2.1.2 (pain freedom) & 14.2.2.2 (MBS freedom)
310 TLF: 14.2.1.1.1 (pain freedom) & 14.2.1.2.1 (MBS freedom)

[12] EPAR.pg109.Section 'Drug Abuse'

[13]Biohaven Pharmaceuticals Inc. Data on file PMDA tables. Table 14.1.3BE Demographics and Baseline Characteristics Episodic Migraine Treated Subjects.

[14] Biohaven Pharmaceuticals Inc. Data on file PMDA tables. Table 14.1.5BE Migraine History Episodic Migraine Treated Subjects
[15] Biohaven Pharmaceuticals Inc. Data on file PMDA tables. Table 14.1.3BE Demographics and Baseline Characteristics Episodic Migraine Treated Subjects

[16] Biohaven Pharmaceuticals Inc. Data on file PMDA tables. Table 14.2.1.1BE Migraine Days per Month Values, Changes and Percent Changes From the Observational Period Over Time on Double-Blind Treatment by Migraine Severity and Subgroups Episodic Migraine Evaluable mITT Subjects

[17] Biohaven Pharmaceuticals Inc. Data on file: Clinical study report BHV3000-305. A Phase 2/3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Rimegepant in Migraine Prevention.2020.

[18] Biohaven Pharmaceuticals Inc. Data on file: Clinical study report BHV3000-305. A Phase 2/3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Rimegepant in Migraine Prevention.2020.

[19] Serrano, D., Lipton, R.B., Scher, A.I., Reed, M.L., Stewart, W.B.F., Adams, A.M. and Buse, D.C., 2017. Fluctuations in episodic and chronic migraine status over the course of 1 year: implications for diagnosis, treatment and clinical trial design. *The journal of headache and pain*, *18*(1), pp.1-12.

[20] Aubrey Manack Adams, Michael L. Reed, Kristina M. Fanning, Dawn C. Buse, Peter J. Goadsby, Jes Olesen, David W. Dodick, Richard B. Lipton. Neurology Apr 2020, 94 (15 Supplement) 502. Exploring the Boundaries Between Episodic and Chronic Migraine: Results from the CaMEO Study (502)

[21] Chalmer MA, Hansen TF, Lebedeva ER, Dodick DW, Lipton RB, Olesen J. Proposed new diagnostic criteria for chronic migraine. Cephalalgia. 2020 Apr;40(4):399-406. doi: 10.1177/0333102419877171. Epub 2019 Sep 22. PMID: 31544467.

[22] Croop R, Lipton RB, Kudrow D, Stock DA, Kamen L, Conway CM, Stock EG, Coric V, Goadsby PJ. Oral rimegepant for preventive treatment of migraine: a phase 2/3, randomised, double-blind, placebo-controlled trial. Lancet. 2021 Jan 2;397(10268):51-60. doi: 10.1016/S0140-6736(20)32544-7. Epub 2020 Dec 15. PMID: 33338437.

[23] SUMMARY OF PRODUCT CHARACTERISTICS, VYDURA 75 mg oral lyophilisate

[24] Biohaven Pharmaceuticals Inc. Data on file: Clinical study report BHV3000-305. A Phase 2/3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Rimegepant in Migraine Prevention.2020. Section 9.3.10

[25] ibid. Table 14.3.2.3C Potential Drug Abuse Adverse Events on Double-Blind Treatment by Severity and Preferred Term Treated Subjects

[26] National Institute for Health and Clinical Excellence. Fremanezumab for preventing migraine Technology appraisal guidance (TA764) Manchester: NICE;2022 [updated 3 June 2020. Available from: https://www.nice.org.uk/guidance/ta764

[27] National Institute for Health and Clinical Excellence. Galcanezumab for preventing migraine Technology appraisal guidance (TA659) Manchester: NICE;2020 [updated 18 November 2020. Available from: https://www.nice.org.uk/guidance/ta659

[28] National Institute for Health and Clinical Excellence. Erenumab for preventing migraine Technology appraisal guidance (TA682) Manchester: NICE;2020 [updated 10 March 2021. Available from: https://www.nice.org.uk/guidance/ta682/resources/ernumab-for-preventing-migraine-pdf-82609376694469

[29] Johnston, K.M., L'Italien, G., Popoff, E., Powell, L., Croop, R., Thiry, A., Harris, L., Coric, V. and Lipton, R.B., 2021. Mapping migraine-specific quality of life to health state utilities in patients receiving rimegepant. Advances in Therapy, 38(10), pp.5209-5220.

[30] L'Italien, G., Popoff, E., Johnston, K., McGrath, D., Conway, C.M., Powell, L., Harris, L., Kowalczyk, N., Croop, R. and Coric, V., 2022. Rimegepant 75 mg for acute treatment of migraine is associated with significant reduction in monthly migraine days: Results from a long-term, open-label study. Cephalalgia Reports, 5, p.25158163221075596.

[31] Johnston, K., Harris, L., Powell, L., Popoff, E., Coric, V., L'Italien, G. and Schreiber, C.P., 2022. Monthly migraine days, tablet utilization, and quality of life associated with Rimegepant–post hoc results from an open label safety study (BHV3000–201). The journal of headache and pain, 23(1), pp.1-8.

[32] Croop, R., Lipton, R.B., Kudrow, D., Stock, D.A., Kamen, L., Conway, C.M., Stock, E.G., Coric, V. and Goadsby, P.J., 2021. Oral rimegepant for preventive treatment of migraine: a phase 2/3, randomised, double-blind, placebo-controlled trial. The Lancet, 397(10268), pp.51-60.

[33] Pfizer. Data on File: Advisory Board Meeting on Rimegepant. 2022.

[34] Pfizer. Data on File: Advisory Board Meeting on Rimegepant. 2022.

[35] Lombard L et al. J Headache Pain 2020. A global real-world assessment of the impact on health-related quality of life and work productivity of migraine in patients with insufficient versus good response to triptan medication doi: 10.1186/s10194-020-01110-9 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7189443/

[36] Doane M.J. et al. Pain Ther. 2019 Associations Between Headache-Free Days and Patient-Reported Outcomes Among Migraine Patients: A Cross-Sectional Analysis of Survey Data in Europe. doi: 10.1007/s40122-019-0133-1 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6857199/

[37] Michael J. Doane,1 Neurol Ther. 2020. The Humanistic and Economic Burden of Migraine in Europe: A Cross-Sectional Survey in Five Countries. doi: 10.1007/s40120-020-00196-2 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7606377/

[38] A M Blumenfeld. Cephalalgia 2011 Disability, HRQoL and resource use among chronic and episodic migraineurs: results from the International Burden of Migraine Study (IBMS). doi: 10.1177/0333102410381145. .https://pubmed.ncbi.nlm.nih.gov/20813784/

[39] Silberstein SD, Lee L, Gandhi K, Fitzgerald T, Bell J, Cohen JM. Health care Resource Utilization and Migraine Disability Along the Migraine Continuum Among Patients Treated for Migraine. Headache. 2018 Nov;58(10):1579-1592. doi: 10.1111/head.13421. Epub 2018 Oct 30. PMID: 30375650.

[40] Single technology appraisal:Rimegepant for treating or preventing migraine [ID1539], Document B (Company evidence submission), section B.2.12 pg131.

[41] Biohaven Pharmaceuticals Inc. Data on file: Clinical study report BHV3000-302: Clinical Study Report 2020

[42] Data on File: Study BHV3000-303 Clinical Study Report (Post-text tables 14.2.1.1.3.5, 14.2.1.2.3.5)

[43] Data on File: Study BHV3000-301 Clinical Study Report (Post-text tables 14.2.1.2.5, 14.2.2.2.5)

[44] Data on File: Study BHV3000-302 Clinical Study Report (Post-text tables 14.2.1.2.5, 14.2.2.2.5)

NICE National Institute for Health and Care Excellence

Professional organisation submission

Rimegepant for treating or preventing migraine [ID1539]

Thank you for agreeing to give us your organisation's 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.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- 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
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	Association of British Neurologists headache and pain advisory group

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ **x** an employee or representative of a healthcare professional organisation that represents clinicians? ☐ **x** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The Association of British Neurologists is the professional body that represents neurologists in the UK to 'promote excellent standards of care and champion high-quality education and world-class research in neurology'. It is funded by subscriptions from members. The advisory group members are self-nominated and selected by the elected council members, the Chair is nominated from the members by ABN council
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.]	No

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	• To reduce the impairment and improve disability caused by migraine and improve associated disease-related quality of life • Reduce the frequency and severity of headache in migraine sufferers • To provide an effective and sustained acute as well as a preventative treatment for migraine • To have a positive impact in patients' work life and in other activities of daily living • To provide an acute and preventative treatment that is well tolerated and safer than existing therapies
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	**Acute treatment:** Freedom from the most disabling migraine symptom (headache, nausea etc) within 2 hours of taking the treatment that is sustained for at least 24 hours

x cm, or a reduction in disease activity by a certain amount.)	**Preventive treatment**: In patients with **episodic** migraine (< 15 days of headaches per month) a 50% reduction either in the severity or frequency of headache is regarded as a meaningful response. In patients with **chronic** migraine (> 15 days of headache per month for at least three months) a 30% reduction either in the severity or frequency of headache is shown to have a positive impact on patients' disability. Improvement in quality of life measures such as Headache Impact Test (HIT-6), EQ5D or MIDAS often reflect considerable improvement in patients' disability particularly when headache frequency and severity is difficult to quantify in patients with poor headache record keeping.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	As a group, we strongly believe there is a very significant unmet need: • Migraine affects 15% of the general population (22% women and 8% men) and has impact similar to arthritis, diabetes and worse than asthma. Migraine along with other headache disorders have more years lived with disability worldwide than epilepsy. The condition is recognised as the seventh disabler in a recent publication by the Global Burden group. Around 1.5-4% patients have chronic migraine that is extremely disabling. The indirect cost to the economy run in billions, with 20 million lost days a year in addition to direct cost to the NHS. Still the condition is under-recognised, under-diagnosed and under-resourced. • There is a massive unmet need in both research and education on the disorder. There is a major need for education on headache disorder in primary and secondary care as well as in the general public.

	• As a result, many patients with headache disorders do not receive the right diagnosis and treatment. 50% of patients do not bother consulting as they feel their condition do not receive appropriate attention. Many continue to treat themselves with over the counter medication resulting in analgesic overuse problem. • Lack of appropriate resources to manage headache despite high cost to society, the NHS and the individual with greatest costs being indirect and largely discounted in health budget decision making. • There is a significant unmet need for a safe acute therapy for migraine. Around 30% of patients do not respond to triptans, the current gold standard acute therapy; they are also contraindicated in those with ischaemic heart disease that excludes many elderly patients
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Low frequency episodic migraine is usually self-managed in the community or through primary care. Patients with disabling or high frequency migraine are often referred to secondary care; those with refractory migraine may be are seen in specialist services which are limited in number and location Treatment is through: 1. Lifestyle, behavioural and psychological modification and education is helpful but time consuming and is often delivered by specialist headache nurses, although there are only around 50 nurses in the UK. Psychology services linked with headache clinics are rare in the UK 2. A range of acute and preventive pharmacological options: **Acute** treatments are used in a stratified approach using simple analgesics, non-steroidal anti-inflammatory agents, high dose aspirin and triptans, frequently combined with anti-emetics. Acute mediation strategies are often thwarted

	as frequent use of acute medication may cause medication overuse headache. Additionally, acute treatments are often slow to act, seldom give complete pain freedom, may not help resolve the associated symptoms of migraine such as nausea and there is often recurrence of the migraine as the effect of the medication wears off. The current choice of **preventive** treatment includes beta-blockers (contraindicated in asthma), tricyclic antidepressants (weight gain and sedation is a significant side effect), anti-convulsants such as topiramate (contraindicated in pregnancy and have significant cognitive side effects) and angiotensin-receptor blockers such as candesartan (contraindicated in pregnancy with dizziness, hypotension limits its use). Those with chronic migraine can be offered greater occipital nerve blocks, onabotulinumtoxinA: the latter is only approved by NICE following failure of three first line preventatives drugs. The CGRP-monoclonal antibodies are approved by NICE for patients with 4 or more migraine days a month but once again only following failure of at least three first line preventative drugs. There are few non-invasive neuromodulation therapies that are NICE approved but are not funded on the NHS. These include non-invasive vagal nerve stimulation (Gammacore), external trigeminal nerve stimulation (Cefaly) and single pulse transcranial magnetic stimulation. Around 10-20% patients are extremely refractory and would have exhausted all the treatment options - to be considered for invasive neuromodulation or intravenous dihydroergotamine that are expensive and are only available in few headache centres in the UK.
• Are any clinical guidelines used in the treatment of the	• NICE Clinical Guideline 150 (2012 & updates) https://www.nice.org.uk/guidance/cg150

condition, and if so, which?	• SIGN Guideline 155 - Pharmacological management of Migraine (Feb 2018) http://www.sign.ac.uk/sign-155-migraine.html • British Association of Headache (BASH) National Management System for adults 2019 https://www.bash.org.uk/guidelines/
• 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.)	Significant variations in headache care occur across the country and in part are determined by access to specialist services. In general, there is lack of expertise among many primary care healthcare professionals and many general neurologists lack detailed understanding on the disorder. Whilst guidelines exist, they are often not applied as there is a lack of expertise in making a proper diagnosis and management plan; most episodic migraineurs remain within the community or are managed by primary care.
• What impact would the technology have on the current pathway of care?	• Rimegepant would bring a novel treatment option that can be used for both acute and preventative treatment. • Rimegepant has tolerability and safety profile similar to placebo: use of many preventative medications is limited by their side effects e.g. somnolence, weight gain, depression, and use of acute treatment with triptans is contraindicated in those with cardiovascular risks. • Rimegepant is considered to have a lesser or negligible risk of producing analgesic medication overuse headache (a common cause of headache in the UK) in contrast to other currently available acute migraine therapies. • It may prevent the need for emergency care, where patients with headache represent a high proportion of patients presenting at Accident and Emergency

	• Public knowledge of a new option for migraine treatment makes it likely that patients who have previously failed other treatments will be asking their general practitioners for referrals to secondary care. This will need resources and investment both in terms of drug cost and manpower to be able to deliver the service.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	• It will be a further tool to use within the current pathway, offering the appeal of ease of use, safety and tolerability. • It can be used both as a preventive and acute therapy so may change how we recommend patients treat their migraine to a more convenient paradigm. • The much shorter half-life of Rimegepant compared with CGRP-monoclonal antibodies may offer a shorter acting safer alternative if there are cardiovascular risk concerns.
• How does healthcare resource use differ between the technology and current care?	It is likely that it will be prescribed initially in secondary care. No specific training or other set up costs are anticipated.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The treatment could be prescribed by those with special expertise in headache disorders – both in primary and secondary care.
• What investment is needed to introduce the technology? (For	A new technology for an under-funded chronic condition such as migraine may result in increased secondary care demand and additional specialist clinics may be required. There is no equipment, facilities or training involved in providing this treatment.

example, for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, especially for those patients intolerant of, or have cardiovascular contraindications to, current treatment. The new technology will provide a better option even if the responder rate remains similar to the existing treatments. This will need to be revisited once real life data is available.
• Do you expect the technology to increase length of life more than current care?	Improve quality rather than length of life.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes with far better tolerability than existing treatments. Additionally the ease of use of one orally disintegrating tablet for both acute and preventative treatment will be a great advantage for some
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Rimegepant will be most appropriate for those who are intolerant of existing medications, or in whom there are cardiovascular safety concerns preventing them from using triptans. Until robust pregnancy data is known, it would be less appropriate for women considering pregnancy

The use of the technology	
13. 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: one medication for both acute and preventative treatment will be easier for the physician to prescribe and patient to take. Rimegepant is formulated as an orally disintegrating tablet making it easier to take, even with nausea during and acute migraine attack. For preventative treatment it only needs to be taken every other day Unlike other similar technologies, there is not thought to be a risk of hepatotoxicity and no additional monitoring requirements are required
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	This will depend on the cost of the drug and estimation of Incremental Cost Effectiveness Ratio (ICER).If similar to Botulinum Toxin or CGRP monoclonal (for example) we suggest for preventative treatment it should be offered for both episodic and chronic migraine prevention as well as for the acute treatment of migraine attacks: **Acute treatment** we suggest: i) intolerance or contraindication to standard care (triptans, NSAIDs, high dose aspirin) ii) incomplete response to standard care (trial of at least 3 different triptans, including non-oral preparations, used in isolation and in conjunction with NSAIDs/aspirin and pro-kinetic antiemetic)

	iii) at least three attacks be treated and if ineffective stopped. iv) where Rimegepant would fulfil a single, effective acute and preventative monotherapy role reducing costs for alternative prescribed oral/injectable acute and preventable therapies e.g. onabotulinumtoxinA plus triptans, CGRP-monoclonal antibodies plus triptans **Preventive treatment** we suggest: in line with onabotulinumtoxinA / CGRP-monoclonal antibodies, to be offered to those failed at least three first line preventive treatments and given for a three month initial trial. **Stopping criteria:** ***'Negative':*** assessment 3 months after initiating treatment and stopping if there is lack of therapeutic response (50% in episodic and 30% in chronic migraine), ***'Positive':*** if effective in achieving the desired level of response consider discontinuing treatment after an appropriate period e.g. 6-12 months based on further clinician led assessment of the need for continued therapy.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes: **Acute treatment**: data from a phase 3 double blind RCT (n=1351) showed that Rimegepant was superior to placebo at 2 hours post dose for pain freedom (21% v 11%) (Croop *et al* Lancet 2019; 394: 737–45) **Preventive treatment**: data from a phase 2/3 double blind RCT (n=695) showed that Rimegepant was superior to placebo in reduction of mean monthly migraine days (-4.3 v -3.5) (Croop *et al* Lancet 2021; 397: 51–60)

16. 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?	Yes, it is an innovative technology, first of its class of CGRP receptor antagonist, marketed as both an acute and preventative treatment as an orally disintegrating tablet to be taken (for prevention) every other day. Its tolerability and safety are similar to placebo with no known cardiovascular risk.
• Is the technology a 'step-change' in the management of the condition?	Yes, Rimegepant is a small molecule CGRP receptor antagonist, a novel mode of action, and will be the first agent deigned for both acute and preventative treatment of migraine. It offers a therapeutic option for those in whom other classes of drugs and contraindicated or not tolerated
• eDoes the use of the technology address any particular unmet need of the patient population?	Yes, an oral acute and preventative treatment that can be used in patients with co-morbidities including cardiovascular disease
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The short term phase 3 trial (Croop *et al* Lancet 2021; 397: 51–60) reported side effect rates as similar to placebo: excellent tolerability is likely to improve compliance and improve quality of life compared to existing treatments with poorer side effect profile

Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Not entirely: the Phase 3 trial for preventative treatment excluded patients with more than 18 migraine days per month, whereas in UK practice those with chronic migraine (>15 headache days per month) are those most likely to require preventative treatment. The preventive study also excluded those who failed at least two preventive treatments. If NICE was to recommend this treatment following failure of three preventive treatment options, this study does not have the patient population for this recommendation. Likewise, for acute treatment the study population did not exclude those who had an adequate response to standard acute treatments (NSAIDs and triptans)
• If not, how could the results be extrapolated to the UK setting?	The trial results are likely still to be applicable although treatment response may be reduced as in UK practise as Rimegepant would probably be used in patients refractory to standard preventIve treatments (at least three) dependent on the cost of the drug.
• What, in your view, are the most important outcomes, and were they measured in the trials?	**Acute treatment** the most important outcomes are: 1. freedom from pain at 2 hours post-dose. 2. freedom from the most bothersome symptom at 2 hours post-dose. 3. 2-24 hour sustained pain freedom.

	The phase 3 trial considered all 3 of these although the latter only as a secondary endpoint. **Preventive treatment** the most important outcomes are: 1. Reduction in frequency and severity of headache by 50% in episodic and 30% in chronic migraine. 2. Percentage of patients with sustained headache response over time with these outcomes. 3. % of patients with 75% and 100% response rate. 4. Significant reported change in patient quality of life measures e.g. HIT6, MIDAS, EQ5D, MSQ (validated quality of life measure in migraine). The phase 3 trial considered reduction in monthly migraine days as the primary end point, and at least a 50% reduction in the mean number of moderate or severe migraine days and change in MSQ as secondary end points.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	n/a
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to our knowledge.

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Real life data and long term treatment efficacy and safety profile is awaited.
20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance for erenumab [TA682], galcanezumab [TA659] and fremanezumab [TA631] for preventing migraine or since the publication of NICE technology appraisal guidance for botulinum toxin type A for the prevention of headaches in adults with chronic migraine [TA260]?	No

21. How do data on real-world experience compare with the trial data?	No peer reviewed published literature with real world data yet available.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Migraine is more common in women (22%) compared to men (8%).
22b. Consider whether these issues are different from issues with current care and why.	No
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your submission.

- There is an unmet need for patients with episodic and chronic migraine, conditions that result in very high levels of disability across the UK patient population
- A novel new paradigm for treatment of migraine that has evidence for use as both an acute and preventative therapy unlike any other similar therapy currently available with a novel and pathophysiology relevant mode of action targeting a known pathogenic mechanism in migraine.
- The treatment is an orodispersible tablet used as both an acute and an alternate day preventive treatment
- Better compliance than existing treatment because of better tolerability and ease of use
- Side effects of Rimegepant are similar to placebo and are much less than with many other current acute and preventative treatments

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

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

Professional organisation submission

Rimegepant for treating or preventing migraine [ID1539]

Thank you for agreeing to give us your organisation's 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.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- 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
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**British Association for the Study of Headache**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	**x** an employee or representative of a healthcare professional organisation that represents clinicians? **x** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**The British Association for the Study of Headache is the national society of headache specialists and neurologists with interest in headache. BASH is a member of the International Headache Society and is mainly funded by its members through annual membership fee. It also receives educational grants from industry partners for organising on-line or face to face educational meetings for the healthcare professionals in the United Kingdom.**
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.]	**In the last one year, BASH has received educational grants from Lundbeck, Allergan, TEVA and Elli Lily towards organisation of webinars that run monthly as a headache education programme for the healthcare professionals in primary and secondary care. BASH received £ 4000 from each industry partner.**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	• Migraine is the most prevalent neurological condition that affects 15% of the general population. Around 2-5% are affected on more than 15 days a month (chronic migraine) that causes considerable disability among sufferers affecting their daily routine and work related activity. Migraine is most common in the productive years of life between age 18-45 and is three times more common in women. The aim of treatment is to provide: • Effective and sustained relief of headache and associated symptoms in an acute migraine episode. • Reduce the frequency and severity of headaches in migraine suffers. • Improvement in quality of life related to work and activities of daily living. • Treatment that is well tolerated, safe and has no or few side effects.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	• Acute Treatment: Freedom from headache and associated symptoms (nausea, vomiting, sensitivity to light sound, smell and aggravation of symptoms on physical exertion) within 2 hours of taking the abortive treatment with no recurrence in 24 hours of treatment. Preventive Treatment:

x cm, or a reduction in disease activity by a certain amount.)	• A 50% reduction in either severity or frequency of headache/migraine episodes in those with episodic form of disorder (Episodic Migraine is defined as one with < 15 days of headaches per month) • A 30% reduction in either severity or frequency of headache/migraine episodes in those with chronic form of disorder (Chronic Migraine is defined as one with > 15 days of headaches per month). • An objective improvement in quality of life measured with validated tests e.g., Headache Impact Test-6 (HIT-6), Migraine Disability Assessment Tests (MIDAS) or EuroQoL scores in 5 dimensions of health (EQ-5D)
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	• Migraine is recognised as a seventh most disabling condition by WHO affiliated group 'Lifting the burden' (LTB). Its impact on quality of life is more than diabetes, asthma and epilepsy put together. The condition cost billions in healthcare and indirectly to the economy in general. The condition is under-recognised and under-resourced resulting in delays in reaching the right diagnosis. The headache services in the UK are patchy and restricted to major neurological centres causing long waiting times and travel to be seen by trained headache specialists. • Most of the available treatments have tolerability issues or restricted use due to co-morbid conditions. Most if not all are unsafe in pregnancy. The responder rate is no more than 50-60% for most treatments. As a result many patients resort to regular painkillers that adds to the problem of analgesic overuse. • Around 30% patients do not respond to Triptan, the current gold standard acute therapy; it is also contraindicated in those with ischaemic heart disease that excludes many elderly patients. • Therefore, there is unmet need in both service provision and choice of therapies available for both acute and preventive treatments.
What is the expected place of the technology in current practice?	

9. How is the condition currently treated in the NHS?	• In the UK we have 1 Neurologist per 100,000 population that is significantly lower than our European Colleagues (Italy has 1 in 10,000). Due to lack of specialists many patients choose not to consult a primary care physician and rely on over the counter painkillers. • There is currently a lack of expertise on headache within primary care with only a handful of primary care physicians feel comfortable in the diagnosis and treatment of migraine. There is also lack of expertise among Neurologists with only 70 out of 900 have special interest in headache disorders. • Advice on lifestyle, triggers and disease education to the patients can be offered by headache specialist nurses, although we only have 50 such nurses in the UK. Cognitive and behaviour therapy that can be offered by psychologist is extremely rare in NHS. Acute Treatments: • Many patients resort to over the counter painkillers of which many have codeine (opiates) with a significant risk of analgesic overuse headaches. • Simple painkillers and Non-steroidal anti-inflammatory drugs (NSAIS) are the mainstay of acute therapy frequently combined with anti-emetics. Those with gastric irritation cannot take NSAID. The only other option is triptan which is ineffective in 30% and those with ischaemic heart disease and other vascular disorders cannot be given triptans. Preventive Treatments: • The current choice of preventive therapy includes beta-blockers (contraindicated in asthma), tricyclic antidepressants (weight gain and sedation is a significant side effect), anti-convulsants such as topiramate (contraindicated in pregnancy and have significant cognitive side effects) and angiotensin-receptor blockers such as candesartan (contraindicated in pregnancy with dizziness, hypotension limits its use). • Those with chronic migraine can be offered greater occipital nerve blocks, OnabotulinumtoxinA or CGRP monoclonal antibodies but are only approved following failure of three first line drugs.

	Some of the CGRP monoclonal antibodies can be given in frequent episodic migraines but once again following failure of at least three first line drugs. • There are few non-invasive neuromodulation therapies that are NICE approved but are not funded on the NHS. These include vagal nerve stimulation, cefaly, single pulse transcranial magnetic stimulation. • Around 10-20% patients are extremely refractory and would have exhausted all the treatment options- to be considered for invasive neuromodulation or intravenous dihydroergotamine that are expensive and are only available in few headache centres in the UK.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	• NICE Guidelines CG150 (2012 and 2015) https://www.nice.org.uk/guidance/cg150 • SIGN Guidelines 155 (2018) https://www.sign.ac.uk/sign-155-migraine.html • BASH National Headache Management System for adults https://www.bashorg.uk/guidelines/
• 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.)	• The pathway is totally dependent on the availability of service and the specialist in headache disorder which varies from very good to extremely poor. • Currently the comprehensive headache services are limited to no more than 15 headache centres in the UK. Other centres have neurologist with limited expertise in dealing with headache disorders.

• What impact would the technology have on the current pathway of care?	• Rimegepant is the first ever of its kind that is effective for both acute and preventive treatment. It is well tolerated and has a safety profile similar to placebo. The risk of analgesic overuse headache is minimal. • An effective abortive and preventive option would reduce visits to primary care physicians as well as emergency care.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	• Rimegepant will provide the only option to work both as abortive and preventive treatment option. • Patients with contraindications to current treatment options or tolerance issues or lack of efficacy would be considered for this treatment.
• How does healthcare resource use differ between the technology and current care?	• Being a new treatment, its use may initially be restricted to secondary care and subjected to NICE guidelines restrictions. The treatment is oral and hence no training is required and there is no cost involved in setting up a service.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	• The treatment could be prescribed by those with special expertise in headache disorders – both in primary and secondary care.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	• The funding is mainly the cost of the drug. There are no equipments, facilities or training involved in providing this treatment.

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	• The treatment will be well suited for those intolerant of current treatment options, although real life data may provide evidence for this to be a better option to currently available treatments.
• Do you expect the technology to increase length of life more than current care?	• Reduced disability and improved quality of life
• Do you expect the technology to increase health-related quality of life more than current care?	• As the treatment has a safety profile similar to placebo, it will provide a better quality of life than existing therapies. In addition as the treatment is suited for both acute and preventive options, it will obviate the need for two treatments.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	• First line treatment for those with contraindications and tolerability issues with current treatment options • Additional options for those with lack of efficacy to current treatments.
The use of the technology	

13. 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.)	• Prescribing Rimegepant will be similar to prescribing other drugs. Safety profile similar to placebo. No monitoring is required.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	• This will depend on the cost of the drug and estimation of Incremental Cost Effectiveness Ratio (ICER). • If the cost is comparable to OnabotulinumtoxinA / CGRP Monoclonal antibodies – the stopping rules will have to be similar • Acute Treatment – be offered to those unable to take simple painkillers and / or triptans due to contraindications or tolerability or lack of efficacy. At least three attacks be treated and if ineffective stopped. • Preventive Treatment – be offered to those failed at least three first line preventive treatments and given for three months. Treatment is considered effective if there is improvement in either severity or frequency of headache (30% for chronic and 50% for episodic migraine). The

	treatment is stopped after three months if ineffective or continued for 12 months if proven effective.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes The Acute treatment RCT showed superiority of Rimegepant to placebo at 2 hours (21% v 11%). Croop etal Lancet 2019;394:737-45 The Preventive treatment RCT showed that Rimegepant was superior to placebo in reducing monthly migraine days (-4.3 v -3.5). Croop et al Lancet 2021;397:51-60
16. 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?	• The treatment is first of its kind that is effective both as abortive and preventive treatment. It is oral formulation and has a safety profile similar to placebo.
• Is the technology a 'step-change' in the	• Rimegepant is a CGRP receptor antagonist – this is the first of its kind to be available as a therapeutic option of both abortive and preventive treatment.;

management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	• Patients with contraindication to use of NSAID (gastro-esophageal disease) and triptans (ischaemic heart disease) would be the most to benefit from Rimegepant as an effective abortive treatment.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	• The safety profile of Rimegepant is similar to placebo. Hence the drug is better tolerated and will be a better option in improving quality of life.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	• The preventive study (Croop et al 2021) included patients with 4-18 days of headaches per month. Those with more than 18 days of headache were excluded. However, vast majority of chronic migraine sufferers have daily headaches and excluding those with more than 18 days of headache would have excluded a big chunk of chronic migraine patients seen in clinical practice. • The preventive study also excluded those who failed at least two preventive treatments. If NICE was to recommend this treatment following failure of three preventive treatment options, this study does not have the patient population for this recommendation. • The acute study (Croop et al 2019) did not exclude those with inadequate response to triptans and NSAID, the population that could be considered for first line treatment with Rimegepant

• If not, how could the results be extrapolated to the UK setting?	• A high cost drug will not be considered as a first line preventive treatment in the UK. However, there is lack of data on patients that have failed three drugs in the study by Croop et al, 2021. A health economic assessment would deem necessary if the treatment is to be considered as fourth treatment option. Similarly for acute treatment option, cost effectiveness estimation should include patients outcome who have failed to respond or not tolerating the first line options of NSAID and triptans.
• What, in your view, are the most important outcomes, and were they measured in the trials?	PREVENTIVE TREATMENT • A 50% reduction in either severity or frequency for episodic and a 30% reduction in those with chronic migraine is meaningful. • Reduction in the use of rescue medication. • Improvement in quality of life measured through HIT-6 MIDAS and EQ-5D The trial used primary efficacy endpoint as change of mean monthly migraine days. The secondary efficacy endpoints were 50% reduction in moderate to severe headache pain intensity, mean monthly migraine days, mean days of rescue medication and assessment of quality of life through MSQ and MIDAS ACUTE TREATMENT • Pain freedom at two hours • Freedom from associated symptoms (nausea, vomiting, photophobia, phonophobia, osmophobia, aggravation with physical activity) at two hours. • No recurrence at 2-24 hours

	The trial did address all these efficacy measures.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	There is no real life data available
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	The evidence is based on two trials mentioned above. No real life data is available.
20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance for erenumab [TA682],	No

galcanezumab [TA659] and fremanezumab [TA631] for preventing migraine or since the publication of NICE technology appraisal guidance for botulinum toxin type A for the prevention of headaches in adults with chronic migraine [TA260]?	
21. How do data on real-world experience compare with the trial data?	No real life data available.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Migraine is three times more common in women as well as it is highly prevalent in productive years 18-45.

22b. Consider whether these issues are different from issues with current care and why.	

Key messages

- 23. In up to 5 bullet points, please summarise the key messages of your submission.

- Rimegepant is the first ever CGRP receptor antagonist that works both as abortive and preventive treatment option. There is no such treatment available that works effectively for acute therapy and preventive option.
- Rimegepant has a safety profile similar to placebo.
- Rimegepant is less likely to cause analgesic overuse headache.
- Rimegepant is an orodispersible tablet with good tolerability that will improve patient compliance.
- Rimegepant provides an effective abortive treatment option in those with contraindications to NSAID and triptans.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

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

Patient organisation submission

Rimegepant for treating or preventing migraine [ID1539]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- 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
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	**The Migraine Trust**
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The Migraine Trust is dedicated to helping people affected by migraine. We are the only UK migraine charity providing information and support, campaigning for awareness and change, and funding and promoting research. One in seven people in the UK live with migraine, and this complex and debilitating neurological disorder significantly affects their lives. We have been leading and bringing the migraine community together to change this since 1965. Every year over two million people visit our website and thousands contact our helplines for information and support on all aspects of migraine and for help in managing it at work, in education, and in accessing healthcare. We campaign for increased awareness and understanding of migraine, and national policy change to improve the lives of people who get it. We have funded over 140 medical research projects and hold an international symposium every two years to bring together the world's leading experts on migraine. We are funded through legacies, individual donations, community and event fundraising, corporate partnerships, trusts and foundations, and industry. We are not a membership organisation, but we do have over 26,000 people signed up to receive our monthly e-bulletin.
4b. Has the organisation received any funding from the manufacturer(s) of the	We have received the following funding in 2020/21: • £15,000 from Abbvie for the State of the Migraine Nation work. • £40,000 from Lundbeck - £20,000 for our new website and £20,000 for our support services. • £3,725 from TEVA which was a general educational grant.

technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] If so, please state the name of manufacturer, amount, and purpose of funding.	So far in 2021/22 we have received £20,000 from Abbvie to develop new resources on migraine in children and young people.
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We ran a survey for people affected by migraine to obtain information on their experience of the impact of migraine and treatments on their symptoms and ability to function. This was not specifically in relation to the use of Rimegepant which is not available in the UK but with other CGRP mAbs. We feel there are parallels that can be drawn from this data. We ran two surveys (one in May 2020 and one in November 2020) reviewing the impact of the COVID-19 pandemic on migraine. We have also recently launched our 2021 'Dismissed for too long' report into migraine care across the UK, this included a nationally representative commissioned censuswide poll in July 2021 and FOI requests to NHS Trusts across the UK in May 2021. These have provided context and information for this response.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	**What is migraine?** Migraine is a complex brain disease that greatly impacts individuals, their families, and society as a whole. It is the third most common disease in the world, affecting around 1 in 7 of the global population. According to NHS England, in the UK there are around 10 million people (aged 15-69) living with migraine. Migraine has a huge impact on an individual's health and wellbeing, and can impact all aspects of life. It is a highly individualised condition and people's experiences will vary greatly. There are different types of migraine which can feature different symptoms. The most common symptom associated with migraine is the 'headache' – usually a severe throbbing pain on one side of the head, made worse by movement. Other symptoms include aura (such as visual disturbances, weakness on one-side, speech and cognitive difficulties), sensitivity to light, sound and smells, nausea and dizziness. If you have migraine you are likely to get regular migraine attacks. More than three quarters of people living with migraine experience at least one attack each month, but the number can vary considerably. Attacks can last from a few hours to several days. Migraine is defined as episodic or chronic (defined as 15 headache days a month with at least eight having migraine features). The World Health Organization (WHO) categorises chronic migraine as causing the same level of disability as dementia and quadriplegia. Migraine is three times more common in women (22%) than men (8%). We don't know why people get migraine, but for most people it is a genetic condition. Although currently there are a range of acute and preventive treatments for migraine, they have (in the majority of cases) been repurposed from other conditions and often have a range of side-effects which can impact tolerability. There is currently no cure for migraine. **What is it like to live with the condition?**

	Migraine exacts a large personal toll on people's lives. People with migraine most commonly report that migraine has significantly impacted the following aspects of their life: work and career, family relationships, social life, and mental health and wellbeing. **a. Work and career** – Migraine is the leading cause of disability for people aged 15-49 and the second most disabling medical condition in the world. Our Migraine Community Survey (2019) found that nearly half (47%) of respondees consider themselves to have a disability as defined by the Equality Act 2020 because of their migraine. This can create challenges in the workplace as people with migraine try to access the support they need to stay in work, develop, and progress. Our Migraine Community Survey found that 41% of eligible respondees 'definitely agree' that migraine has significantly impacted their career. People with migraine told us: "I lost my job because of migraine." "The lack of understanding of what migraine is…means that I was recently threatened with a level 3 disciplinary. I may lose my job despite 35 years of experience. It made me feel undervalued and discriminated against." **b. Family relationships** Over half (54%) of respondees to our CGRP Patient Experience Survey (2019) strongly agree that migraine has had a significant impact on their relationship with their partner or spouse and one-third (35%) strongly agree that migraine has significantly impacted their relationship with their children. People with migraine told us: "My family have suffered in helplessness for decades, unable to ease my pain…While they have lived their lives together I have been alone in a dark room isolated by my disease."

	"Migraine has stolen years of my life. I have missed so many events and missed out on so much of my son's life because of it." **c. Social life** Migraine can be a very isolating condition, with 83% of respondees to our CGRP Patient Experience Survey (2019) strongly agreeing that migraine has significantly impacted their social life. The unpredictable nature of migraine, both episodic and chronic, can prevent people from being able to make plans or commit fully to family or leisure activities. People with migraine told us: "My friends have disappeared. This condition has ruined my existence." "My whole life revolves around migraine. I never see my friends or make any plans because migraine rules everything." **d. Mental health and wellbeing** People with migraine are three times more likely than people without migraine to have depression. 70% of respondees to our CGRP Patient Experience Survey strongly agree that migraine has significantly impacted their mental health and wellbeing. Our more recent surveys support these findings: ○ A Censuswide survey that we ran this summer found that almost a third (32%) of those with migraine said that their migraine negatively affected their mental health and almost a third (32%) said that their migraine negatively affected their overall health ○ Three in ten (30%) of those with migraine said that their migraine negatively affected their working life. ○ A quarter (25%) of those with migraine said that their migraine negatively affected their family life and 27% said it negatively affected their social life.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	While migraine cannot be cured, there are numerous acute and preventive treatments currently available to patients on the NHS in England and Wales to help them work with their clinician to manage this condition. Our Migraine Community Survey found that patients are most likely to be using the following types of treatments to help them manage their migraine: triptans (58%), lifestyle modifications (56%), over the counter painkillers (51%), and preventives (39%). However, it is important to emphasise that patients often have to try numerous different medicines before they find something that may work for them. Current treatments available for migraine on the NHS in England and Wales are grouped into two categories – acute treatments and preventive treatments. Patient's are also expected to use 'best supportive care' which includes reviewing and managing lifestyle factors (e.g. routine, sleep, hydration etc) to help manage migraine. **Acute treatments** Acute treatments are usually the first line of treatment and include simple analgesics (e.g. paracetamol, ibuprofen, aspirin), migraine specific treatments (triptans) and anti-emetic medication. These are used to treat an attack when it comes on, and can be helpful. Although for a proportion of people these treatments are ineffective or unsuitable. With analgesic and triptans people need to be cautious of taking them on too many days per month (15 and 10 respectively) as it increases the likelihood of medication overuse headache. This is a condition that causes a daily headache with migraine symptoms, and can cause the chronification of migraine. It is also difficult to treat as patients need to stop taking the treatment for a period of time. This is challenging and has a huge impact on their wellbeing and mental health. People with migraine can experience other adverse side effects from acute treatments, including fatigue, nausea, confusion and anxiety. For many, this limits the number of treatment options available to them.

	Preventive treatments For the prevention of migraine, NICE clinical guideline 150 recommends a suite of different drugs that can be considered by patients and their clinician, including anticonvulsants, tricyclic antidepressants and betablockers. However, many of these were developed for other conditions and have been repurposed for migraine. They often have severe and unwanted side-effects. For some people they are ineffective. For example, topiramate is very poorly tolerated in greater than 50% of patients and the Medicines and Healthcare products Regulatory Agency (MHRA) warns that sodium valproate causes learning disability in approximately 40% of babies born to mothers using it. Our CGRP Patient Experience Survey found that 90% of respondees had experienced adverse side-effects from migraine preventives, excluding CGRP. They told us: ““Propranolol side-effects were so bad that I had to take a month off of work.” “Low blood pressure from beta blockers and horrendous brain fog from Topamax. It was so intense that I had to come off the drug.” “I tried Botox and had a reaction to it. My throat swelled and I had a hard time breathing.” “Some preventives have caused me to have brain fog, taste changes, musculoskeletal pain, and sleepiness during the day.” Regardless of these side-effects, it is also important to stress that these ‘first line’ preventives also don’t work for everyone with migraine or they can stop working relatively quickly. Our CGRP Patient Experience Survey shows that 78% of respondees had tried more than five different preventives and 70% had also failed to respond to more than five different preventives. Patients told us:

	"No preventives have been successful, apart from topiramate which works for a couple of months and then stops completely." "I have tried everything there is to try! Anti-depressants, anti-convulsants, HRT, etc. I experienced unpleasant side-effects to a greater or lesser extent from everything and no relief from migraine at all." After trying a range of oral preventive treatments patients should have access to further preventive treatment options, including other medications (e.g. flunarizine), Greater Occipital Nerve (GON) blocks, Botox (for chronic migraine), new CGRP mAbs (e.g. fremanezumab, erenumab and galcanezumab) and devices. However, access to these is patchy and not everyone who is eligible can access them. There are also issues around side effects and suitability. **Best supportive care** For many patients it's not always clear what this means, and they often feel left to 'get on with it' by themselves, with little input from healthcare professionals. Generally, migraine patients are disappointed by the care and treatment they receive on the NHS. In our 2019 community survey just 15% believed the NHS was able to manage migraine well (compared to 56% who thought it was not).
8. Is there an unmet need for patients with this condition?	There is an unmet need for patients with migraine, particularly those who: • are unable to tolerate existing treatments. • don't meet eligibility criteria for treatments. • are unable to access specialist clinics (made worse during the COVID-19 pandemic). • have other health conditions. As highlighted above there is unmet need for both acute and preventive treatment options for migraine.

	Acute Current acute treatments (specifically triptans) aren't suitable for everyone, including those with cardiovascular risk factors. For those that can take analgesics or migraine specific treatments (triptans), they are at risk of medication overuse headache if they take them on too many days per month, which can lead to patients not treating migraine effectively as they are afraid to take too many, or worsening their symptoms through overuse. Patients who are unable to find a suitable preventive treatment may also come to rely on triptans and risk medication overuse headache by taking them too often. They can also have unpleasant side effects such as nausea, dizziness, tightness or irritation in the throat and some people report feeling 'out of it' after taking a triptan. **Preventive** There is also unmet need for patients in need of preventive treatment, specifically those who fail to respond to current preventive treatments. Many patients struggle to find an effective preventive treatment, or fail to access appropriate preventive treatments. Although there are good treatment options (for both chronic migraine and episodic migraine) such as Botox and CGRP mAbs. We know many people struggle to access these, and there are gaps for those that either don't meet the eligibility criteria or don't respond to these treatments. The COVID-19 pandemic has compounded access issues to migraine treatment and led to an increase in unmet need. For example, one in eight (12%) people accessing support for their migraine said they had been unable to access treatment and / or medication for their migraine over the last year, according to our survey run in July 2021. The censuswide survey found that over half of people (55%) said that the changes to the healthcare system since the beginning of the pandemic had affected the management of their migraine.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Although patients have not had the opportunity to use this treatment (unless part of a clinical trial), we know that many patients are unable to take the currently available acute treatments such as triptans. This is due to cardiovascular comorbidities, lack of efficacy or problems with side effects or medication overuse. For these patients a suitable treatment option is required as best supportive care is their alternative and preventives are not adequately effective for many. In terms of other (presumed) advantages to Rimegepant, patients are keen for an oral treatment that can be used as both an acute and preventive treatment option. Although the CGRP mAbs have revolutionised treatment for a lot of people, issues with access and the nature of administration (subcutaneous injection) mean that patients are keen for a more convenient treatment. Rimegepant as an oral tablet is likely to be more suitable for certain patient groups (e.g. those who are unable to inject themselves). There also seem to be fewer side-effects with the gepants when compared to other treatments including triptans, and the oral preventive treatments.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Again, we have limited information as patients are unable to access these currently. However, based on what we know there seems to be few disadvantages to the treatment. One potential disadvantage is whether they are as effective as some other treatments, particularly triptans when used as an acute treatment. For people who are unable to take oral treatment, Rimegepant is unlikely to be a suitable option.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	As an acute treatment, it offers a treatment option for patients who cannot have triptans due to lack of efficacy, complications with medication overuse and rebound effects, side effects or those with contraindications such as cardiovascular disease and brainstem aura. An acute treatment option for this subset of patients is needed.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	It should be made available to everyone who meet the treatment criteria regardless of their age, gender, disability, ethnicity, religion or geographical location.

Other issues	
13. Are there any other issues that you would like the committee to consider?	Access to appropriate treatment for patients with migraine is an issue. Alongside the gepants, there are other new migraine treatments that have recently been approved (CGRP mAbs). However, there are significant issues with access to these treatments. For example, despite the CGRP mAbs being approved we know many people who are eligible for these treatments are unable to access them. Either because they are unable to access a specialist who can prescribe them, or because there is no provision or funding in place to provide them. When reviewing Rimegepant the committee should consider how people will be able to access these treatments if approved. As part of our dismissed for too long report we submitted an FOI to NHS Trusts in all four nations asking for more information around how migraine is managed and access to headache specialists, and appropriate treatment. In England, just 16% (n=15) of all NHS Trusts responding to the FOI said eligible patients could access CGRP mAb treatment, while another 15 explicitly said they could not.
Key messages	
14. In up to 5 bullet points, please summarise the key messages of your submission: • Migraine is a complex brain disease that greatly impacts the day-to-day lives of people who live with the condition. In particular, it impacts people's wellbeing, relationships, education and employment.	

- While there are a range of acute and preventive treatments for migraine available on the NHS, many people find these unsuitable due to side-effects, contraindications and lack of efficacy in managing symptoms. Rimegepant is a migraine specific acute and preventive treatment, which is easily administered.
- There are potential benefits to Rimegepant (and other gepants) in terms of not causing medication overuse headache, which can be a significant issue for many people affected by migraine.
- An oral treatment that can be used as both an acute and preventive treatment is likely to be beneficial and acceptable to a range of people with migraine, and can potentially reduce the need for multiple medications. Many people would prefer the ease of taking one tablet to manage their migraine.
- Consideration should be given to how people with migraine would access these treatments if approved. Otherwise many people will not benefit from the treatment.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

.....

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.

.....

BMJ TAG

Rimegepant for treating or preventing migraine

STA Report

Source of funding

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

Title:	Rimegepant for treating or preventing migraine
Produced by:	BMJ Technology Assessment Group (BMJ TAG)
Authors:	Steve Edwards, Director of Health Technology Assessment, BMJ-TAG, London Nicole Downes, Senior Clinical Evidence Analyst, BMJ-TAG, London Gemma Marceniuk, Senior Health Economist, BMJ-TAG, London Charlotta Karner, Clinical Evidence Manager, BMJ-TAG, London Alexander Allen, Senior Clinical Evidence Analyst, BMJ-TAG, London Isaac Mackenzie, Health Economist, BMJ-TAG, London
Correspondence to:	Steve Edwards, BMJ TAG, BMJ, BMA House, Tavistock Square, London, WC1H 9JR.
Date completed:	30/08/2022
Source of funding:	This report was commissioned by the NIHR Evidence Synthesis Programme as project number 13/54/16.
Declared competing interests of the authors	No competing interests were declared which affect the impartiality of this report. BMJ Technology Assessment Group (BMJ-TAG) and the editorial team of The BMJ work independently to one another. The views and opinions expressed in this report are those of the BMJ-TAG.
Acknowledgments:	The EAG would like to thank Dr Anna Cohen, Consultant Neurologist at Luton and Dunstable University Hospital and Royal Free Hospital London, and Dr Nicola Giffin, Consultant Neurologist at Royal United Hospital Bath, for providing clinical advice throughout the project, and for providing feedback on the clinical sections of the report.
Rider on responsibility for report:	The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.
Report reference:	Edwards SJ, Downes N, Marceniuk G, Karner C, Allen A, Mackenzie I. Rimegepant for treating or preventing migraine: A Single Technology Appraisal. BMJ Technology Assessment Group, 2022.

Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Nicole Downes	Critical appraisal of the company's submission and the clinical evidence; drafted and reviewed the clinical sections of the report
Charlotta Karner	Critical appraisal of the company's submission and the clinical evidence; critiqued the company's literature reviews and drafted the critique of the methods review sections
Alexander Allen	Cross-checking and validation of clinical results sections within the EAG report against the company's submission and clarification responses
Gemma Marceniuk	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Isaac Mackenzie	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

All authors read and commented on draft versions of the EAG report.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

AE	Adverse event
AIC	Akaike Information Criterion
AUC	Area under the curve
BASH	British Association for the Study of Headache
BL	Baseline
BMI	Body Mass Index
BNF	British National Formulary
BSC	Best Supportive Care
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CFB	Change from baseline
CGRP	Calcitonin gene-related peptide
CI	Confidence interval
CM	Chronic migraine
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company submission
CSR	Clinical study report
CT	Computer tomography
CUA	Cost utility analysis
CV	Cardiovascular
DBT	Double-blind treatment
DIC	Deviance Information Criterion
DSU	Decision Support Unit
EAG	External Assessment Group
ED	Emergency department
eDiary	Electronic diary
EE	Economic evaluation
EF	Emotional function
EM	Episodic migraine
EMA	European Medicines Agency
EOD	Every other day
ERE	Erenumab
FDA	Food and Drug Administration
FRE	Fremanezumab
GAL	Galcanezumab
GB	Great Britain
GLMEM	Generalised linear mixed effects model
GP	General practitioner

GPwSI	General practitioner with a special interest
HCRU	Healthcare resource use
HRG	Healthcare resource group
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ICHD-III	International Classification of Headache Disorders, third edition
IHS	International Headache Society
IQR	Interquartile range
ITT	Intention to treat
IWRS	Interactive web response system
KM	Kaplan-Meier
LSM	Least squares mean
mAb	Monoclonal antibody
MBS	Most bothersome symptom
MFIQ	Migraine Functional Impact Questionnaire
MHDs	Monthly headache days
MHRA	Medicines and Healthcare products Regulatory Authority
MIDAS	Migraine Disability Assessment Test
mITT	Modified intent to treat
MMDs	Monthly migraine days
MOH	Medication overuse headache
MQoLQ	Migraine Quality of Life Questionnaire
MRI	Magnetic resonance imaging
MSQv2	Migraine-Specific Questionnaire Version 2
MSQv2.1	Migraine-Specific Questionnaire Version 2.1
MSQoL	Migraine Specific Quality of Life Questionnaire
MWPLQ	Migraine Work and Productivity Loss Questionnaire
N/A	Not applicable
NB	Negative binomial
NBRM	Negative binomial regression model
NCT	National Clinical Trial
NHS	National Health Service
NHWS	National Health and Wellbeing Survey
NICE	National Institute of Health and Care Excellence
NMA	Network meta-analysis
NMB	Net monetary benefit
NR	Not reported
NSAIDs	Non-steroidal anti-inflammatory drugs
ODT	Orally dispersible tablet
OLE	Open-label extension

ONS	Office for National Statistics
OR	Odds ratio
OTC	Over the counter
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PBO	Placebo
PICOS	population, intervention, comparator, outcomes, study design
PoM	Preference of Medication
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PRN	*Pro re nata* (“as needed”)
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PT	Preferred Term
QALHs	Quality Adjusted Life Hours
QALYs	Quality Adjusted Life Years
RCT	Randomised Controlled trial
RFP	Role function preventive
RFR	Role function restrictive
RIM	Rimegepant
RWE	Real-world evidence
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SM	Satisfaction with Medication
SmPC	Summary of Product Characteristics
STA	Single technology appraisal
TA	Technology appraisal
UK	United Kingdom
USA	United States of America
USD	United States Dollars
UTI	Urinary tract infection
WPAI	Work Productivity and Activity Impairment
WTP	Willingness to pay
YLDs	Years of life lived with disability
ZINB	Zero-inflated negative binomial

1 Executive summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Section 1.3 explains the key issues in more detail and other issues are described in Section 1.4. A summary of the EAG's preferred assumptions and resulting ICERs is provided in Section 1.5. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1. Summary of key issues (acute migraine treatment and migraine prevention)

Issue	Summary of issue	Report sections
Acute migraine		
1	Exclusion of CM patients from acute RCTs and extrapolating evidence from EM patients	1.3.1, 2.3.1.1, 3.1.4
2	Cost-effectiveness results based on the ODT formulation trials	1.3.1, 4.2.3.1.1
3	Using response to the first migraine attack to inform response to subsequent migraine attacks	1.3.1, 4.2.4.1
4	Baseline distribution of MMDs	1.3.1, 4.2.6.1
5	Assuming rimegepant PRN can result in reductions in MMDs	1.3.1, 4.2.7.1.4
Migraine prevention		
6	Discrepancy between the population described in the marketing authorisation[1] and the decision problem described by the company (at least four migraine attacks per month vs at least four MMDs)	1.3.2, 2.3.2.1, 3.2.5
7	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)	1.3.2, 2.3.2.1, 3.2.5
8	Uncertainty concerning the efficacy of rimegepant vs mAbs due to a lack of direct evidence and limitations of the NMA	1.3.2, 2.3.2.3, 3.2.4, 3.2.5
9	Gradual vs immediate reversion to baseline MMD during the assessment period and after the assessment period	1.3.2, 4.2.4.2
10	Response probability for rimegepant	1.3.2, 4.2.7.2
11	Applying the NMA results from Cycle 1 vs Cycle 3	1.3.2, 4.2.7.2

12	Comparator treatment acquisition costs	1.3.2, 4.2.12.2.4

Abbreviations: CM, chronic migraine; EM, episodic migraine; mAbs, monoclonal antibodies; MMDs, monthly migraine days; NMA, network meta-analysis; ODT, orally dispersible tablet; PRN, *pro re nata*; RCTs, randomised controlled trials.

1.2 Overview of key model outcomes

1.2.1 Acute migraine treatment

Overall, the technology is modelled to affect quality-adjusted life years (QALYs) by:

- reducing the number of migraine days per month (MMDs) compared to best supportive care (BSC);
- reducing the severity of migraines (pain relief) compared to BSC.

Overall, the technology is modelled to affect costs by:

- its higher unit price compared to BSC;
- reducing the number of severe migraines that incur healthcare costs compared to BSC.

The modelling assumptions that have the greatest effect on the ICER are:

- adopting a societal perspective (including lost productivity costs);
- assuming rimegepant *pre re nata* (PRN) can result in reductions in MMDs;
- the time horizon;
- the quality-adjusted life hour (QALH) outcomes;
- the baseline number of MMDs.

1.2.2 Migraine prevention

Overall, the technology is modelled to affect QALYs by:

- Reducing the number of MMDs (the monoclonal antibodies [mAbs] are better at reducing MMDs than rimegepant [the mAbs show higher a proportion of patients achieving > 50% MMD reduction, with statistical significance for galcanezumab 120 mg and fremanezumab 225 mg] and therefore rimegepant results in lower QALYs than the mAbs).

Overall, the technology is modelled to affect costs by:

- Reducing the number of MMDs which reduces the number of healthcare costs (the mAbs are better at reducing MMDs than rimegepant [the mAbs show a higher proportion of patients achieving > 50% MMD reduction, with statistical significance for galcanezumab 120 mg and

fremanezumab 225 mg] and therefore rimegepant results in higher healthcare costs than the mAbs);

- Its lower unit price compared to the mAbs;
- Bring given as a tablet, rather than intravenously (incurring one-off training costs on how to self-administer treatment and ongoing administration costs for patients who cannot self-administer treatment).

The modelling assumptions that have the greatest effect on the ICER are:

- Response at 12-weeks;
- Long-term discontinuation rates;
- The utility values according to MMD and treatment.

1.3 Summary of the EAG's key issues

1.3.1 Acute migraine treatment

Table 2. Issue 1: Exclusion of CM patients from acute RCTs and extrapolating evidence from EM patients

Report section	2.3.1.1, 3.1.4
Description of issue and why the EAG has identified it as important	The RCTs included to support rimegepant use in acute migraine treatment (EM or CM patients) exclude those with CM by only including those with <15 monthly headache days, meaning it is unclear whether similar efficacy would apply to those with CM. While the EAG's clinical experts do not expect there to be a difference in the efficacy of an acute treatment between EM and CM patients, they highlight the lack of evidence investigating this potential difference and the fact that MOH may be a bigger issue for CM patients, which can perpetuate headaches.
What alternative approach has the EAG suggested?	As the CM group was excluded, there is nothing that can be done within the trials to assess whether results for the CM group would differ to the EM group covered in the trials. Other evidence assessing the difference between the efficacy of acute migraine treatments in EM and CM would be useful to inform the discussion.
What is the expected effect on the cost-effectiveness estimates?	It is possible that CM patients may be more difficult to treat than the EM group covered by the trials due to the increased risk of MOH with more frequent medication use, which might mean a higher ICER for this group.
What additional evidence or analyses might help to resolve this key issue?	Evidence comparing the effectiveness of acute migraine treatments in EM and CM patients may help to determine whether it is appropriate to extrapolate evidence from the included acute RCTs to the CM population.

Abbreviations: CM, chronic migraine; EAG, External Assessment Group; EM, episodic migraine; ICER, incremental cost-effectiveness ratio; MOH, medication overuse headache; RCTs, randomised controlled trials.

Table 3. Issue 2: Cost-effectiveness results based on the ODT formulation trials

Report section	4.2.3.1.1
Description of issue and why the EAG has identified it as important	Although the marketing authorisation and submission is focused on the ODT formulation, three of the four trials informing the company's economic analysis (studies BHV3000 -301, -302 and -201) are based on a tablet formulation. The company also excluded a second study using the ODT formulation of rimegepant from their base case analysis (study BHV3000-310). During the clarification stage the company provided pooled results from trials using the ODT formulation only (studies BHV3000-303 and 310) and found that the ODT formulation may have contributed to a slightly higher percentage of patients receiving pain relief at 2 hours than compared to the combined tablet and ODT formulation pooled analysis, which would suggest the pooled estimate is generating a conservative ICER. However, when treatment effectiveness data from the ODT formulation trials were applied in the economic analysis, the ICER in the mITT population (only including studies BHV3000-303 and 310) was £22,645, which is higher than the ICER in the mITT population including trials of both formulations (£19,285).
What alternative approach has the EAG suggested?	The EAG requests that the company explains what is driving the change in the ICER.
What is the expected effect on the cost-effectiveness estimates?	The ICER is above a WTP threshold of £20,000 per QALY when the economic analysis is informed by the ODT formulation trials.
What additional evidence or analyses might help to resolve this key issue?	Given that the results are at face value counterintuitive, the EAG is concerned about the robustness of the model. If the company can explain what is driving the change in the ICER, this may increase the EAG's confidence in the model and in using the pooled formulations to inform the analysis.

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; mITT, modified intention to treat; ODT, orally dispersible tablet; QALY, quality-adjusted life year; WTP, willingness-to-pay.

Table 4. Issue 3: Using response to the first migraine to inform response to subsequent migraine attacks

Report section	4.2.4.1
Description of issue and why the EAG has identified it as important	The single attack design of the rimegepant acute RCTs (BHV3000-301, -302, -303 and -310) meant that there are no clinical data indicating how many patients would respond after taking rimegepant to treat a second or third migraine, who did not respond during their first episode. The economic model therefore assumes that patients who do not respond to the first treatment (based on pain relief at two hours) would not respond to a subsequent treatment. Clinical experts to the company and EAG agree that in the treatment of acute migraine, it is generally recommended to try a particular treatment on two or three episodes before abandoning it. In the context of a single attack design, the response rate after the first attempt is unknown, but it is conceivable that some of the initial non-responders would respond on the second attack. The EAG also notes that no stopping rule is included in the SmPC for rimegepant or economic model for the ICER evidence report on acute treatments in migraine (rimegepant, lasmiditan and ubrogepant).
What alternative approach has the EAG suggested?	The EAG is unaware of any data on the effectiveness of rimegepant on subsequent migraine attacks after an initial failure that could inform an alternative approach.
What is the expected effect on the cost-effectiveness estimates?	The impact on the cost-effectiveness results could be large as patients who respond to treatment and stay on treatment accrue more QALYs, more treatment costs and fewer healthcare resources.
What additional evidence or analyses might help to resolve this key issue?	There is currently no long-term data to inform how response to a single attack may predict response on future migraine episodes. The EAG therefore considers this to be an unresolvable area of uncertainty.

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years; RCT, randomised controlled trial; SmPC, summary of product characteristics.

Table 5. Issue 4: Baseline distribution of MMDs

Report section	4.2.6.1
Description of issue and why the EAG has identified it as important	According to the company's OWSA, the baseline MMD is a key model driver, with a higher baseline MMD leading to a lower ICER for rimegepant vs BSC. The EAG does not consider study BHV3000-201, which included patients with 2 to 14 migraine attacks per month, to be the most appropriate source to inform the baseline distribution of MMDs. As noted in Issue 1, the EAG is unsure whether efficacy would be the same for CM and EM as the RCTs included to support rimegepant use in acute migraine treatment (EM or CM patients) exclude those with CM. The EAG's clinical experts also advised that the severity of migraines (pain trajectories) could be influenced if a patient is experiencing more than 9 migraine attacks per month. For these reasons, the EAG would prefer baseline MMDs (and all baseline patient characteristics) to be informed by the acute pooled RCTs to ensure consistency between sources used for pain relief, pain trajectories and baseline MMDs. The EAG also notes that the ICER evidence report on acute treatments in

	migraine used a mean of 4.8 MMDs at baseline which is closer to the MMDs estimated from the acute pooled RCTs than study BHV3000-201.
What alternative approach has the EAG suggested?	During the clarification stage company was requested to provide a scenario using the acute pooled RCTs to inform the distribution of MMD at baseline. The company did not provide the requested scenario as they did not think it was an appropriate distribution to consider. The EAG would urge the company to reconsider this.
What is the expected effect on the cost-effectiveness estimates?	When the EAG explored a scenario using the mean number of migraine attacks from the acute pooled RCTs (using the mean-based approach as opposed to the distribution-based approach) the company's ICER increased from £17,160 to £21,520 in the subgroup of patients with at least 2 triptan failures and from £19,743 to £25,015 in the corrected mITT population including study BHV3000-310.
What additional evidence or analyses might help to resolve this key issue?	Additional clinical expert would be helpful to understand the distribution of MMDs that would be seen in clinical practice in the company's positioning.

Abbreviations: BSC, best supportive care; CM, chronic migraine; EAG, External Assessment Group; EM, episodic migraine; ICER, incremental cost-effectiveness ratio; mITT, modified intention to treat; MMD, monthly migraine day; OWSA, one-way sensitivity analysis; RCT, randomised controlled trial.

Table 6. Issue 5: Assuming rimegepant PRN can result in reductions in MMDs

Report section	4.2.7.1.4
Description of issue and why the EAG has identified it as important	The EAG considers the long-term reductions in MMD with PRN rimegepant to be highly uncertain as this is based on a *post-hoc* analysis of the long-term safety study which may suffer from confounding (including but not limited to a possible placebo effect). Also, compared to the model time horizon (20 years), the long-term reductions in MMD with PRN rimegepant are based on a relatively short follow-up period (1 year), and small numbers at risk during the last few weeks of follow-up.
What alternative approach has the EAG suggested?	In the absence of long-term comparative evidence, the EAG considers it more appropriate to remove reductions in MMD by PRN rimegepant from the base case analysis and include them in scenario analysis.
What is the expected effect on the cost-effectiveness estimates?	Removing reductions in MMD by PRN rimegepant increased the company's ICER from £17,160 to £22,529 in the subgroup of patients with at least 2 triptan failures and from £19,743 to £28,728 in the corrected mITT population including study BHV3000-310.
What additional evidence or analyses might help to resolve this key issue?	During the clarification stage, the company was asked to identify comparative evidence to inform a more robust estimate of treatment effectiveness. In their response, the company said it was not possible to collect this data and acknowledged that the lack of a comparator arm in the study design of 201 is a limitation. Additional clinical expert input would be helpful to validate the company's assumption.

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; MMD, monthly migraine day; PRN, *pro re nata*.

1.3.2 *Migraine prevention*

Table 7. Issue 6 Discrepancy between the population described in the marketing authorisation and the decision problem described by the company

Report section	2.3.2.1, 3.2.5
Description of issue and why the EAG has identified it as important	For migraine prevention, the company specifies a population in the decision problem that is narrower than the NICE final scope, restricting it to patients with EM, ≥4 MMDs and who have failed on at least three prior oral preventive treatments. However, the marketing authorisation for rimegepant in migraine prevention is specifically for those with EM and ≥4 migraine attacks per month (any severity). As migraine attacks can last >24 h (accepted by the company in their response to Addendum 2 of the clarification questions), the population specified in the decision problem may therefore be slightly broader than the marketing authorisation in terms of migraine burden.
What alternative approach has the EAG suggested?	The EAG requests that the company clarifies this discrepancy at Technical Engagement and confirms whether the decision problem should specify at least four 'migraine attacks' per month rather than at least four 'MMDs', in line with the marketing authorisation.
What is the expected effect on the cost-effectiveness estimates?	N/A.
What additional evidence or analyses might help to resolve this key issue?	N/A.

Abbreviations: EAG, External Assessment Group; EM, episodic migraine; MMDs, monthly migraine days; N/A, not applicable; NICE, The National Institute of Health and Care Excellence.

Table 8. Issue 7: 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)

Report section	2.3.2.1, 3.2.5
Description of issue and why the EAG has identified it as important	Despite the decision problem described by the company focusing on a subset of EM patients that have failed three prior preventive drug treatments, those with non-response to more than two classes of preventive medications are excluded from the BHV3000-305 trial. The EAG's clinical experts note that higher numbers of prior treatment failures may indicate more refractory migraines that may be more difficult to treat even with new drug classes. While the company suggests that, [redacted], the rimegepant trial may provide a conservative estimate of efficacy in the refractory population, the EAG considers that there is insufficient evidence to support this conclusion.
What alternative approach has the EAG suggested?	This issue is thought to be unresolvable as the company state that data were not collected to allow any assessment of how prior treatment failures may affect rimegepant efficacy in the BHV3000-305 trial (i.e., comparing groups with one, two or no prior treatment class failures).
What is the expected effect on the cost-effectiveness estimates?	If the excluded population does represent a group that is harder to treat and has a reduced response rate in the economic model (≥50% reduction in MMDs over 12 weeks) compared to those included in the trial, this may mean an increased ICER if data for this group of patients were included in the trial. The magnitude of this possible increase is unclear.

What additional evidence or analyses might help to resolve this key issue?	N/A.

Abbreviations: EAG, External Assessment Group; EM, episodic migraine; ICER, incremental cost-effectiveness ratio; mAb, monoclonal antibody; MMDs, monthly migraine days; N/A, not applicable.

Table 9. Issue 8: Uncertainty concerning the efficacy of rimegepant vs mAbs due to a lack of direct evidence and limitations of the NMA

Report section	2.3.2.3, 3.2.4, 3.2.5
Description of issue and why the EAG has identified it as important	While the EAG acknowledges approaches taken by the company to limit uncertainty in the NMA, including adjustment for baseline risk and alignment of outcome definitions across studies, limitations such as differing treatment failure histories, inclusion of CM patients in some studies and differences in analysis populations and missing data handling remain. Based on these remaining limitations, the EAG prefers NMA results from random effects models adjusted for baseline risk.
What alternative approach has the EAG suggested?	The EAG notes that efforts to reduce the heterogeneity and uncertainty within the NMA have been made by the company and considers outstanding limitations to be unresolvable, particularly given the limitations of the rimegepant trial itself (for example, limiting the inclusion of comparator mAb trials to those in refractory populations that had failed on a certain number of treatments would not be appropriate considering the rimegepant trial excludes more refractory patients), overlapping issues (for example, to resolve concerns about inclusion of CM patients in the FOCUS trial for fremanezumab, the EAG considered whether excluding this trial may be an option, but given it is the only trial in the refractory population for this treatment this was not thought to be appropriate) and availability of data for comparator mAb trials.
What is the expected effect on the cost-effectiveness estimates?	The limitations discussed mean there is uncertainty in terms of the clinical effectiveness of rimegepant vs mAbs and the effect on the cost-effectiveness is unclear.
What additional evidence or analyses might help to resolve this key issue?	In the absence of direct evidence from an RCT comparing rimegepant and mAbs, the EAG considers the random effects NMAs with adjustment for baseline risk to provide the most appropriate estimate of the efficacy for rimegepant vs mAbs for use in the cost-effectiveness analyses.

Abbreviations: CM, chronic migraine; EAG, External Assessment Group; mAbs, monoclonal antibodies; NMA, network meta-analysis; RCT, randomised controlled trial.

Table 10. Issue 9: Gradual vs immediate reversion to baseline MMD during the assessment period and after the assessment period

Report section	4.2.4.2
Description of issue and why the EAG has identified it as important	The company's assumptions regarding reversions to baseline MMD, are inconsistent. During the assessment period, the reversion to baseline takes 12 months, but after the assessment period, the reversion to baseline is immediate. This approach favours the least effective treatment (rimegepant) as these patients will maintain benefits for longer after discontinuation than patients who initially respond then discontinue.
What alternative approach has the EAG suggested?	The company provided a scenario assuming an immediate reversion to baseline in both periods. An alternative approach would be to assume the reversion to baseline takes 12 months in both periods.
What is the expected effect on the cost-effectiveness estimates?	As shown in the company's scenario analysis, assuming an immediate reversion to baseline in both periods reduce the ICERs for each mAb vs rimegepant by around £10,000, favouring the mAbs.
What additional evidence or analyses might help to resolve this key issue?	Due to time constraints, the EAG has been unable to explore a scenario where the reversion to baseline takes 12 months for both periods. The EAG would consider this scenario to be more plausible than assuming an immediate reversion to baseline MMD and would therefore ask the company to explore this.

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; mAb, monoclonal antibody; MMD, monthly migraine day.

Table 11. Issue 10: Response probability for rimegepant

Report section	4.2.7.2
Description of issue and why the EAG has identified it as important	The EAG considers the rimegepant response probability (49.1%) to be inconsistent with the outcome included in the NMA for two reasons. Firstly, the rimegepant response probability is based on the outcome "at 12-weeks" while the NMA is based on the "average over 12-weeks". Secondly, the rimegepant response probability is based on patients with moderate-to-severe migraine attacks while the NMA is based on mild-to-severe attacks.
What alternative approach has the EAG suggested?	The company should employ a rimegepant response probability based on the "average over 12-weeks" and in patients with mild-to-severe migraine attacks (38.5%).
What is the expected effect on the cost-effectiveness estimates?	The company provided a scenario using a rimegepant response probability of 38.5% at the clarification stage and the impact on the cost-effectiveness results was large; the ICERs for the mAbs vs rimegepant reduced by around £12,000, favouring the mAbs.
What additional evidence or analyses might help to resolve this key issue?	The company should implement the alternative approach the EAG has suggested.

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; mAb, monoclonal antibody; NMA, network meta-analysis.

Table 12. Issue 11: Applying the NMA results from Cycle 1 vs Cycle 3

Report section	4.2.7.2
Description of issue and why the EAG has identified it as important	Given that response in the NMA was assessed as the "average over 12-weeks" and not "at 12-weeks", the EAG considers that the results from the NMA should be implemented in the economic analysis from Cycle 1 (Weeks 1 to 4) rather than Cycle 3 (Weeks 9 to 12). The company's current approach is favouring the least effective treatment (rimegepant).
What alternative approach has the EAG suggested?	The EAG would suggest applying the NMA results from Cycle 1 whilst also maintaining patients on treatment until the end of the assessment period (Week 12). Based on study BHV3000-305 and the comparator trials, patients achieve a significant reduction in MMDs in the first few weeks of treatment and therefore the EAG would not consider it unreasonable for the company to apply Week 12 MMD distributions according to response from Cycle 1. An alternative would be to derive Week 4 and Week 8 MMD distributions from study BHV3000-305 according to response.
What is the expected effect on the cost-effectiveness estimates?	The EAG would expect the cost-effectiveness of rimegepant compared to the mAbs to reduce if the NMA results were applied from Cycle 1.
What additional evidence or analyses might help to resolve this key issue?	The company should implement the alternative approach the EAG has suggested.

Abbreviations: EAG, External Assessment Group; mAb, monoclonal antibody; MMD, monthly migraine distribution; NMA, network meta-analysis.

Table 13. Issue 12: Comparator treatment acquisition costs

Report section	4.2.12.2.4
Description of issue and why the EAG has identified it as important	The EAG has two issues with the acquisition costs assumed for the comparators (mAbs). Firstly, for the mAbs, the company applied different acquisition costs in the initial 28-day cycle and subsequent 28-day cycles. For rimegepant, the acquisition cost in the initial 28-day cycle is the same as subsequent 28-day cycles. This issue is important because the company is inflating the initial 28-day cycle cost applied to the mAbs, without justification. The EAG also found that the monthly regimen assumed for erenumab (offered every 30.4 days) does not match the regimen included in the BNF and marketing authorisation (offered every 28 days).
What alternative approach has the EAG suggested?	The EAG considers that initial 28-day treatment acquisition cost should equal the ongoing 28-day treatment acquisition cost for all treatments (while the exception of the loading dose for galcanezumab). The EAG is also of the opinion that the regimen for erenumab should match the regimen reported in the BNF and marketing authorisation.
What is the expected effect on the cost-effectiveness estimates?	As shown in the EAG's scenario analysis, removing the additional cost in the initial 28-day cycle reduces the ICER by around £800, favouring the comparators, and amending the frequency of erenumab administration increases the ICER by around £25,000, favouring rimegepant.
What additional evidence or analyses might help to resolve this key issue?	The company should implement the alternative approaches the EAG has suggested or provide further justification for their approach.

Abbreviations: BNF, British National Formulary; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; mAb, monoclonal antibody.

1.4 Other key issues: summary of the EAG's view

The EAG also had a number of other issues with the company's modelling assumptions, these are summarised in Table 14.

Table 14. Other key issues

Item	Section
Acute migraine	
It is more plausible for rimegepant responders at 2 hours who discontinue treatment in the long-term to follow the trajectories of BSC all-comers rather than BSC responders	4.2.4.1
The BL_severity coefficient in the QALH regression appears to be applied to the wrong proportion of migraine attacks in the economic analysis	4.2.11.1.4
There is an unexplainable discrepancy in the long-term discontinuation rates reported in the CS and provided in response to clarification	4.2.8.1
The company should include drug wastage costs	4.2.12.1.5
The control group in Vo *et al*. 2018 should be used to estimate HCRU and the company should update the MMDs used to calculate the weighted average of the frequency groups to reflect the selected population	4.2.12.1.5
The company should provide a scenario using HSUVs from Xu *et al.* 2011	5.1.3
Migraine prevention	
The distribution of baseline MMD should reflect the marketing authorisation (EM)	4.2.6.2
There is an unexplainable discrepancy in the long-term discontinuation rates reported in the CS and provided in response to clarification	4.2.8.2
The company should provide the baseline EQ-5D from the rimegepant and placebo arms of study BHV3000-305	4.2.11.2.1

Abbreviations: BSC, best supportive care; CS, company submission; EM, episodic migraine; HCRU, healthcare resource use; HSUV, health state utility value; MMD, monthly migraine day; QALH, quality-adjusted life hour.

1.5 Summary of EAG's preferred assumptions and resulting ICER

1.5.1 Acute migraine treatment

Table 15 summarises the EAG's preferred assumptions for the acute model and the cumulative impact these assumptions have on the ICER.

Table 15. EAG's preferred model assumptions and cumulative results (acute treatment)

Preferred assumption	Section in EAG report	Cumulative ICER (£/QALY)
Company base case in the subgroup of patients with at least 2 triptan failures	5.1.1	£17,160
Corrected company base case in the subgroup of patients with at least 2 triptan failures	6.1	£17,521
Company's corrected scenario in the mITT population including study BHV3000-310 (efficacy)	4.2.2.1 and 6.1	£19,743
Baseline patient characteristics from the mITT population including study BHV3000-310*	4.2.6.1	£26,348

Patients who discontinue rimegepant follow BSC all-comer pain trajectories	4.2.4.1**Error! Reference source not found.**	£28,063
One-off cost for a specialist to prescribe rimegepant	4.2.12.1.5	£29,609
No reductions in MMD frequency	4.2.7.1.4	£31,179
2-year time horizon	4.2.5.1	£50,054

Abbreviations: BSC, best supportive care; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; mITT, modified intention-to-treat; MMD, monthly migraine day; QALY, quality adjusted life year

*Assumption requires the model to switch from the distribution-based approach to the mean-based approach

Modelling errors identified and corrected by the EAG are described in Section 6.1. For further details of the exploratory and sensitivity analyses done by the EAG, see Section 6.2.1.

The key differences between the company's preferred assumptions and the EAG's preferred assumptions include using the full trial population, using the acute pooled randomised controlled trials (RCTs) to inform baseline characteristics, assuming a mix of responders and non-responders to BSC when responders to rimegepant discontinue rimegepant and receive BSC, adding the cost of a specialist to prescribe rimegepant, and removing the reductions in MMD frequency by PRN rimegepant. The latter assumption also justified a shorter time horizon.

1.5.2 Migraine prevention

Table 16 summarises the EAG's preferred assumptions for the prevention model and the cumulative impact these assumptions have on the ICER. All ICERs in Table 16 are south-west quadrant ICERs (rimegepant is cheaper and less effective than the comparators). Based on willingness-to-pay (WTP) thresholds of £20,000 or £30,000 per QALY, rimegepant could be considered cost-effective compared to each mAb as the EAG's preferred base case ICERs are above these WTP thresholds.

Table 16. Summary of EAG's preferred model assumptions and cumulative results (migraine prevention)

Preferred assumption	Section in EAG report	Cumulative ICER (£/QALY) rimegepant vs mAb		
		Ere	Gal	Fre
Company base case	5.2.1	£92,671	£115,211	£118,883
Poisson distribution for MMD at baseline	4.2.6.2	£96,311	£119,721	£123,535
Random-effects baseline risk adjusted NMA including the phase II studies	4.2.7.2	£93,948	£120,839	£113,566
Rimegepant response probability in mild-to-severe patients assessed as the "average over 12-weeks"	4.2.7.2	£84,188	£108,021	£100,489
Reversions to baseline MMD, once treatment is discontinued are immediate in the assessment period and post-assessment period	4.2.4.2	£82,547	£105,929	£98,540

The initial 28-day treatment acquisition costs are equal to the ongoing 28-day treatment acquisition costs, and erenumab is administered as per the dose in the BNF (every 28 days)	4.2.12.2.4	£102,881	£105,929	£97,812
Truncating the distribution of MMDs to EM	4.2.6.2	£107,748	£110,934	£102,449

Abbreviations: BNF, British National Formulary; EAG, External Assessment Group; Ere, erenumab; Fre, fremanezumab; Gal, galcanezumab; ICER, incremental cost-effectiveness ratio; mAb, monoclonal antibody; MMD, monthly migraine day; NMA, network meta-analysis; QALY, quality adjusted life year.

The key differences between the company's preferred assumptions and the EAG's preferred assumptions include using an alternative network meta-analysis (NMA), an alternative rimegepant response probability, assuming reversions to baseline MMD are immediate in the assessment period and post-assessment period, changing how comparator acquisition costs are modelled, and truncating the distribution of MMDs to reflect the marketing authorisation (episodic migraine [EM]). For further details of the exploratory and sensitivity analyses done by the EAG, see Section 6.3.2.

2 Introduction and background

2.1 Introduction

Herein is a critique of the evidence submitted to the Single Technology Appraisal (STA) in support of the clinical and cost-effectiveness of rimegepant orally dispersible tablets (ODT [VYDURA®; Pfizer, Inc.]) in the treatment or prevention of migraine.

2.2 Background

Within Section B.1 of the company submission (CS), the company provides an overview of:

- rimegepant ODT, including its mechanism of action, dose and method of administration (CS, Section B.1.2);
- migraine, including diagnosis and classification, clinical presentation, epidemiology, disease burden and disease management (CS, Section B.1.3).

Based on advice from the External Assessment Group (EAG)'s clinical experts, the CS presents an accurate overview of migraine diagnosis and classification, clinical presentation, epidemiology and disease burden and management. However, although the EAG's clinical experts agree that migraine frequency may reduce after the menopause, they do not agree that increasing age is necessarily associated with reduced frequency of migraine in an individual and note that 40 years of age, which the company suggest in Section B.1.3.1 of the CS is the threshold above which migraine prevalence is lower, is not a meaningful cut-off.

Migraine is a common neurologic disease that can be disabling, with attacks consisting of head pain (typically unilateral), throbbing and other symptoms such as photophobia, phonophobia, nausea and vomiting.[2-4] Intense pain and other symptoms can lead to patients being unable to perform daily activities, with studies reporting that ~80% of patients are unable to work or function normally during attacks.[5, 6] Attacks can vary in duration and may last for days if untreated and patients are also affected in between attacks in terms of concern about when the next attack will be.[7, 8]

Migraine is diagnosed based on a patient's medical history and physical examination findings,[9] as outlined in The International Classification of Headache Disorders (ICHD) Diagnostic Criteria for migraine[2] (see Table 3 in the CS), and there are no confirmatory diagnostic tests available.[10] It is important that migraine is differentiated from other types of primary headache (for example, cluster and tension headaches, which can be diagnosed using headache diaries and trigger trackers), trigeminal neuralgia (a disorder of severe facial pain)[11] and secondary headaches.

Prevalence of migraine is higher in women, who tend to experience more frequent migraine attacks that are more severe, last longer and are more challenging to treat overall. Migraine can occur with or without aura (a preceding sensation such as flashing lights, blurred vision, weakness, numbness or ringing in the ears),[2] with approximately one third of patients experiencing aura,[4] and are also classified as episodic migraine (EM) or chronic migraine (CM) based on the frequency of migraines or headaches.[2] EM is the focus of the CS for migraine prevention and is defined as headache occurring on <15 days per month for the last three months, which on some days is migraine. The submission for rimegepant use in acute migraine includes CM and EM, with CM including those with ≥15 headache days per month, presenting on ≥8 days with typical migraine features.[12] The EAG's clinical experts note that CM can be more difficult to treat.

Migraine is among the most frequent neurological diseases and its burden may be underestimated due to its transient nature.[13] Based on an estimate from a previous National Institute for Health and Care Excellence (NICE) technology appraisal for botulinum toxin type A in migraine (TA260), there are ~190,000 migraine attacks every day in England, with six million people having migraine in the UK.[14] Based on data from 2018/2019, ~2.5 million primary care appointments are linked to headaches and migraines in the UK, of which ~100,000 are referred to hospital.[15] NHS RightCare has reported an addressable issue of inappropriate referral of migraine patients to secondary care,[16] which the company argues could be partially addressed by the introduction of new treatment options into the primary care setting. However, the EAG's clinical experts note that, if recommended, they would expect rimegepant to be prescribed by specialists at least initially, possibly moving to primary care over time.

2.2.1 Positioning of Rimegepant in the UK treatment pathway

The CS provides a reasonable overview of current service provision for the management of migraine.

The company proposes two positions for rimegepant, which is a small molecule calcitonin gene-related peptide (CGRP) receptor antagonist, in the UK treatment pathway, including acute treatment (regardless of whether the person has EM or CM) and the prevention of EM. Currently, there is no single medication recommended by NICE for both the acute and preventive treatment of migraine. Treatment pathways for each of these indications are discussed in separate sections below.

2.2.1.1 Treatment of acute migraine

Current treatment options in acute migraine are summarised in Section B.1.3.3.1 of the CS based on the NICE clinical guideline (CG150: Headaches in over 12s: diagnosis and management)[17] and include

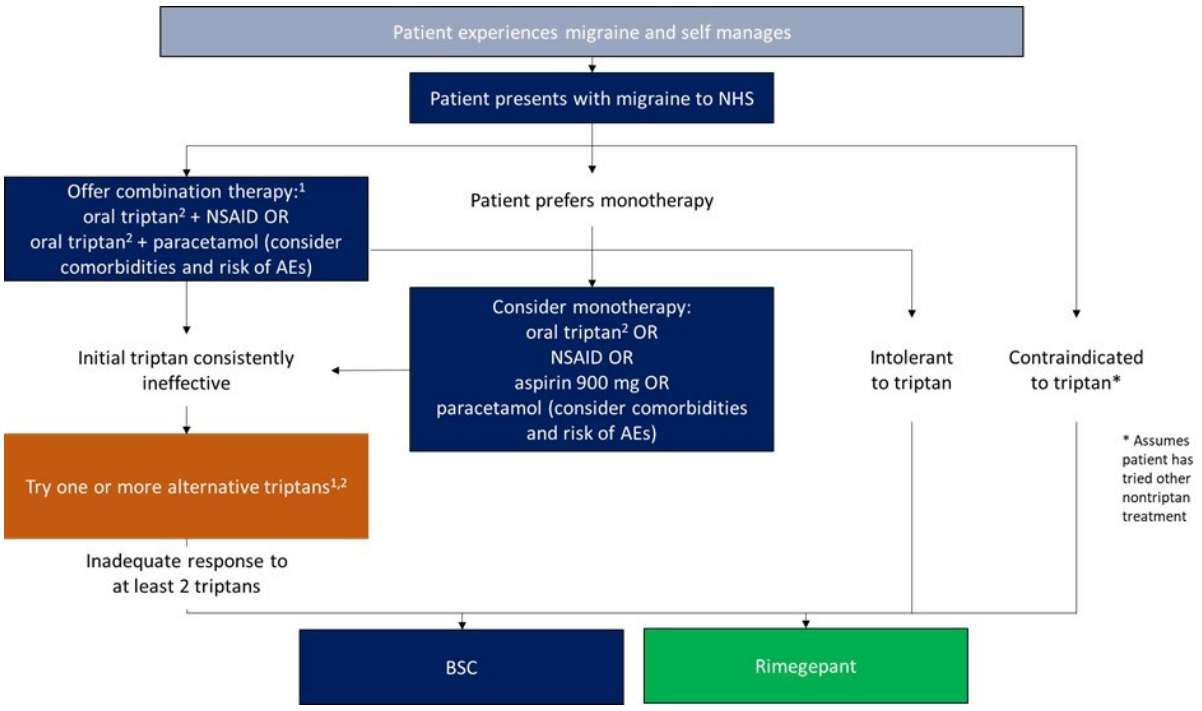
analgesics (ibuprofen, aspirin or paracetamol) and triptans either alone or in combination with paracetamol or a non-steroidal anti-inflammatory drug (NSAID). Anti-emetics can also be prescribed regardless of whether vomiting occurs. Oral triptans are usually used unless vomiting restricts treatment. The EAG's clinical experts note that some patients will have tried over the counter (OTC) medications such as paracetamol and NSAIDs before seeking help for their migraines, meaning triptans would be the next option, but that all options would be explored based on patient history and comorbidities when presenting to the National Health Service (NHS), usually in primary care.

The company describes lack of efficacy, safety and tolerability concerns and medication overuse headache (MOH) as limitations of currently available treatments for acute migraine, , with discontinuation being common. The EAG's clinical experts agree with the limitations highlighted by the company. There are safety concerns about using triptans in those with a history of vascular disease, multiple risk factors for vascular diseases and during pregnancy,[18] and common alternatives to triptans (for example, NSAIDs) have been associated with an increased risk of serious gastrointestinal safety and renal toxicity events.[19-21] Estimates suggest that 15% to 25% of patients using acute migraine treatments may have inadequate symptom control and may benefit from access to new treatments.[18] Suboptimal treatment of acute migraines for those with EM may increase the risk of progression to CM (which is associated with an increased disease burden), with very poor acute treatment efficacy reported to lead to more than a three-fold increased risk of progression.[22] Poor efficacy can also contribute to medication overuse leading to MOH, which is a concern for many of the acute treatments currently used for migraine[23] (see Section B.1.3.2.2 of the CS).

The company, therefore, positions rimegepant acute migraine treatment (with or without aura, with EM or CM) in patients who have had inadequate symptom relief after taking at least two triptans or in whom triptans are contraindicated or not tolerated, and where there is inadequate pain relief with NSAIDs and paracetamol (Figure 1, reproduced from Figure 1 of the CS). The company positions rimegepant for use after at least two triptan failures as they highlight a lack of studies supporting use of a third triptan after two have failed.[24] The EAG's clinical experts note that in practice, the same triptan would be tried for two or three acute attacks before concluding it is ineffective and moving on to a second triptan. They highlight that further triptans are an option in practice but only a small proportion would try a third triptan, with very few trying more than this. The decision to try a third or further triptan may depend on the reason the prior treatment had to be stopped; if it was due to an adverse event rather than a lack of efficacy, trying a third triptan may be more likely.

The EAG's clinical experts agree with the company's positioning of rimegepant in the acute migraine treatment pathway, though they note that given it is a new technology it is likely to be a drug that is initially prescribed by a specialist and may move to primary care over time.

Figure 1. Proposed positioning of rimegepant for the treatment of acute migraine (reproduced from Figure 1 of the CS)



Abbreviations: AEs, adverse events; BSC, best supportive care; NHS, National Health Service; NSAID, non-steroidal anti-inflammatory drug. Pathway based on NICE CG150 guideline[17].

[1]Consider an anti-emetic in addition to other acute treatment for migraine even in the absence of nausea and vomiting

[2]When prescribing a triptan, start with the one with the lowest acquisition cost

2.2.1.2 Prevention of episodic migraine

Current treatment options for EM prevention are summarised in Section B.1.3.3.2 of the CS based on NICE guidance (NICE clinical guideline [CG150][17] and technology appraisals for erenumab [TA682],[25] fremanezumab [TA764/TA631][26] and galcanezumab [TA659][27]), which include three oral drugs used as first- to third-line treatment options (topiramate, propranolol and amitriptyline) and three injectable monoclonal antibodies (mAbs) that are currently recommended by NICE for use in patients with ≥4 migraine days per month and where at least three prior preventive drug treatments have failed or are not tolerated. Although the aim is to reduce monthly migraine days (MMDs), it is unlikely that migraines will be eliminated completely and patients usually manage attacks that do

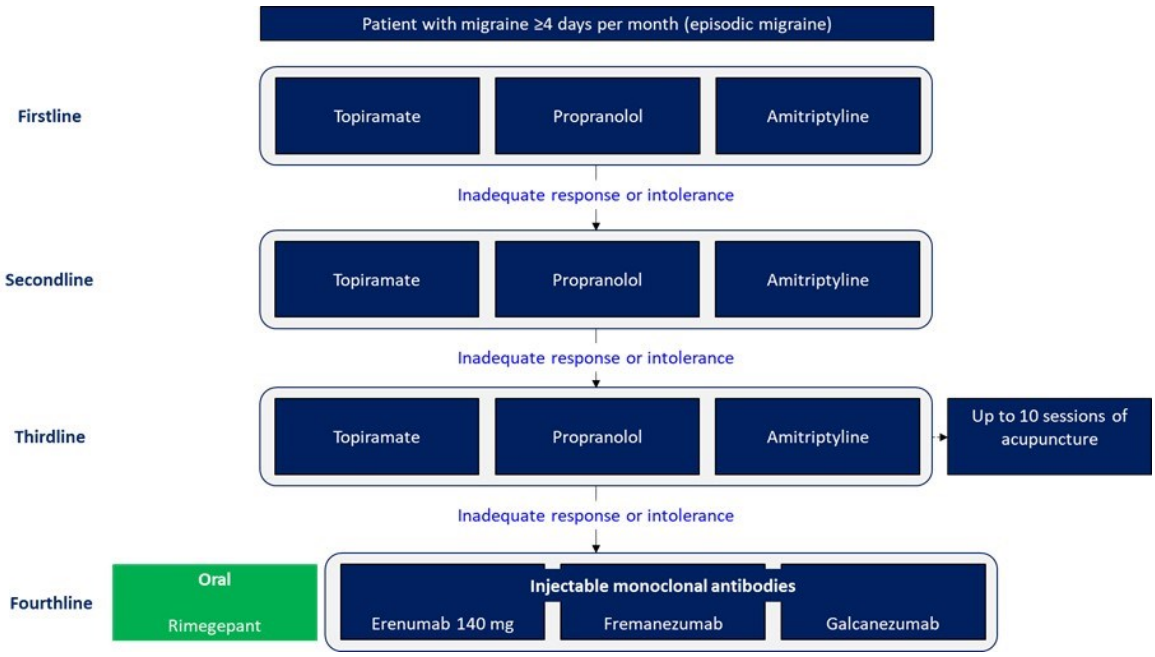
occur with acute treatments for symptom relief (for example, triptans) and rescue medications if those fail (such as NSAIDs).[28-30]

The EAG's clinical experts agree with the company's summary of current treatments; however, they note that in practice, limited resources and difficulty accessing specialists means that most people currently receiving mAbs are those with CM and only a small proportion (~10% estimated by one expert) EM patients that are eligible for mAbs may be receiving them in their practice. They also note that candesartan is another common oral option that may be tried before considering mAbs, particularly if contraindications rule out other options. Non-pharmacological treatments such as acupuncture may be considered but do not currently have a large role in migraine prevention; where used, this is likely to on top of preventive pharmacological treatments.

The company highlights challenges relating to the preventive migraine treatments that are currently available. None of the first-line oral treatments were designed specifically for migraine and many are associated with suboptimal outcomes and high rates of adverse events, poor tolerability and contraindications or interactions,[4, 31-35] contributing to poor adherence.[36] Anti-CGRP mAbs approved by NICE have some advantages over traditional oral preventive treatments. However, challenges exist, such as longer half-lives requiring months for the drug to be eliminated before treatment can be changed (for example, an issue in planning or managing a pregnancy),[37-39] requirement for self-injection after training (as it is thought that patients generally prefer oral medication over injections[37-41] and the initial training requires healthcare resource) and high rates of certain side effects (such as constipation with erenumab)[42-45] resulting in discontinuations in clinical practice.[46-48]

For EM prevention, the company positions rimegepant as an alternative to the anti-CGRP mAbs currently recommended by NICE; specifically, for people with EM (<15 headache days per month) with ≥4 migraine days per month and in whom at least three prior preventive drug treatments have failed (see Figure 2, reproduced from Figure 2 of the CS). The company suggests that oral rimegepant may allow patients to receive the treatment more quickly compared to mAbs and in the primary care setting rather than requiring secondary care referral; however, although the EAG's clinical experts highlight that rimegepant being an oral drug makes it an attractive option, they note that, as a new technology, it is likely that rimegepant would be prescribed by a specialist initially and may move to primary care over time. The EAG's clinical experts agree overall with the company's positioning of rimegepant for migraine prevention in those with EM but note that given its oral formulation, it is possible that it may become an attractive option earlier in the pathway, though this would be a commissioning decision.

Figure 2. Proposed positioning of rimegepant for the prevention of migraine in people with episodic migraine and ≥4 migraine days per month (reproduced from Figure 2 of the CS)



Abbreviations: CS, company submission; NICE, The National Institute of Health and Care Excellence; TA, technology appraisal. Pathway based on NICE CG150 guideline[17] and NICE TA659[27], TA682[25] and TA764/631[26].

2.3 Critique of the company's definition of the decision problem

A summary of the final scope issued by NICE,[49] together with the company's rationale for any deviation from this, is provided. Separate tables are presented for acute migraine (Table 17) and migraine prevention (Table 18). Key differences between the decision problem addressed in the CS and the scope are discussed in greater detail in the sections that follow each table, but the EAG notes that the population in the CS is narrower than that specified by NICE for acute treatment and migraine prevention, which in both cases means some of the comparators listed in the NICE final scope are not relevant.

2.3.1 *Acute migraine treatment*

Table 17. Summary of decision problem – acute migraine

	Final scope issued by NICE[49]	Decision problem addressed in the submission	Rationale if different from the scope	EAG comment
Population	Adults with migraine	For patients who have had inadequate symptom relief after taking at least two triptans or in whom triptans are contraindicated or not tolerated.	Rimegepant would not be used in patients in whom triptans are a suitable option. The unmet need for a new therapy is greatest in patients with inadequate response to or safety or tolerability issues with triptans. Experts acknowledge there is no clear evidence that using the third triptan after two triptan treatment failures was beneficial[50] and remains uncommon in clinical practice.[51] No RCTs have investigated how many patients would benefit from a third triptan after failure to	Overall, the EAG considers the narrower population in the decision problem to be reasonable. In addition to inadequate symptom relief after taking at least two triptans (or intolerance or contraindication), the CS also specifies that the indicated population should have had inadequate response to other acute treatment options (such as NSAIDs and paracetamol). The key RCTs included in the CS for acute migraine treatment are not specific to those failing at least two triptans (or where they are contraindicated or not tolerated), but data were provided for this specific subgroup. This was similar for the long-term open-label study, which differed to the RCTs in terms of number of moderate to severe attacks per month required for inclusion. Included RCTs only cover those with EM as those meeting criteria for CM were excluded. RCTs are also specific to those with 2 to 8 moderate to severe migraine attacks per month, while the SmPC does not specify severity or frequency of attacks.[1] At clarification, the company confirmed that they anticipate rimegepant would be used for moderate to severe attacks.

			respond to an initial two triptans.[24]	See Section 2.3.1.1 below for further discussion.
Intervention	Rimegepant	Rimegepant ODT: 75 mg as needed	As per scope.	The intervention specified in the CS is rimegepant, matching the final scope. Based on the SmPC,[1] rimegepant (ODT formulation) is indicated for the acute treatment of migraine with or without aura in adults at a dose of 75 mg daily, as needed. The EAG notes that, although the marketing authorisation and submission is focused on the ODT formulation, some of the included trials are based on a tablet formulation. See Section 2.3.1.2 below for further discussion.
Comparators	Paracetamol, with or without an anti-emetic An NSAID (such as aspirin, ibuprofen, diclofenac or naproxen), with or without an anti-emetic An oral or non-oral triptan (such as sumatriptan, zolmitriptan, rizatriptan, almotriptan or eletriptan), with or without an anti-emetic Paracetamol with an oral or non-oral triptan, with or without an anti-emetic An NSAID with a triptan, with or without an anti-emetic BSC	BSC (placebo)	As noted above, the target population for rimegepant is in those who have exhausted all available acute treatment options (triptans, NSAIDs, paracetamol, and combinations thereof), thus leaving BSC as the only relevant comparator. Placebo in Study BHV3000-303 is considered to approximate BSC. While RWE indicated a small proportion of these patients may try	As the company positions rimegepant (in the acute setting) for those that have failed (or are intolerant of or contraindicated to) at least two triptans and where all other acute treatment options have been exhausted, the EAG agrees that BSC is the only relevant comparator. Based on input from the EAG's clinical experts, the EAG considers the placebo arms of the included RCTs to be reflective of BSC. See Section 2.3.1.3 below for further discussion.

			a third triptan or a mix of suboptimal treatment, there is no clear evidence that using those suboptimal treatments is of benefit.	

Outcomes	• Reduction in headache pain (including freedom from pain) • Speed of onset • Freedom from MBS • Reduction in nausea and vomiting • Reduction in hypersensitivity (e.g., light, sound, smell) • Regain of normal functioning • Prevention of recurrence • Use of rescue medication • Adverse effects of treatment • Health-related quality of life	• Pain freedom at 2 h and 8h • Sustained pain freedom from 2 to 24 h and 2 to 48 h • Pain relief at 2 h, at 8h • Sustained pain relief from 2 to 24 h, from 2 to 48 h • Assessment of migraine pain and symptoms and severity • Freedom from MBS at 2 h • Freedom from nausea at 2 h • Freedom from photophobia at 2 h • Freedom from phonophobia at 2 h • Functional disability at 2h • Prevention of recurrence • Rescue medication within 24 h • Adverse events • Health-related quality of life	As per scope.	The EAG agrees that all outcomes described in the NICE final scope have been covered in some form in the CS. The EAG's clinical experts agree that focusing on pain relief at 2 h to inform efficacy in the economic model was appropriate. See Section 2.3.1.4 below for further discussion.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost	As per the NICE reference case the cost-effectiveness of rimegepant is expressed in terms of incremental costs per QALY and costs have been considered from the perspective of the NHS and Personal Social Services.	As per scope. Two separate cost-utility models to address the acute migraine and migraine prevention indications.	The EAG agrees that the economic analysis is generally in line with the NICE final scope. The company used a 20-year time horizon for the base case. The EAG considers the company's long-term modelling assumptions regarding reductions in MMDs to be too uncertain to accurately capture the costs and consequences over a 20-year time horizon. Shorter time horizons (2 years) have been adopted in other economic

	effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.			evaluations for the treatment of acute migraines.[52-54] Health effects were expressed in QALYs. Study BHV3000-201 obtained MSQv2 responses from patients which the company mapped to the EQ-5D. HSUVs according to the pain intensity level of a migraine were obtained from the literature and patients completed the EQ-5D in these studies. The base case perspective on costs was the NHS and PSS and a sensitivity analysis was conducted from the societal perspective, in which costs associated with lost productivity were included. The cost-effectiveness results in the CS reflect list prices as no PASs are in place for rimegepant or the comparator (BSC).
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • Subgroups defined by migraine severity • People currently having treatment for the prevention of migraine • People with or at risk of developing medication overuse headache • People for whom triptans are contraindicated or not tolerated	• People currently having treatment for the prevention of migraine • Subgroup analysis by number of previous triptan failures • People for whom triptans are contraindicated due to CV risk • Number of headaches days per month (<4 vs ≥4 days) • Other pre-specified subgroup analyses: age, race, sex and migraine aura	Subgroup analyses by migraine severity were not provided as these were not prespecified in the trials. Subgroup analyses based on risk of developing MOH could not be performed as this data was not collected in the trials.	Most subgroups mentioned in the NICE final scope are covered in the CS, as well as some additional subgroups not specified by NICE. The only factor that was stratified for at randomisation was use of preventive migraine treatment. The EAG prefers the use of the overall mITT population for analyses rather than any of the subgroups. See Section 2.3.1.5 below for further discussion.

	• Subgroups defined by number of headache days per month			
Special considerations, including issues related to equity or equality	N/A	• Frequent and severe migraine is classified as a disability under the 2010 Equality Act • Migraine is about three times more common among women than men, which raises potential equity issues Please refer to Section B.1.4 of the CS for a discussion of equality considerations.	N/A	N/A
Other issues	N/A	N/A	N/A	The EAG's clinical experts consider that given it is a new technology, it is likely rimegepant would initially be prescribed by a specialist and possibly move to primary care in time, which would differ to other acute treatments for migraine that can be accessed from primary care.

Abbreviations: BSC, best supportive care; CS, company submission; CV, cardiovascular; EAG, External Assessment Group; HSUV, health state utility value; MBS, most bothersome symptom; mITT, modified intention to treat; MMDs, monthly migraine days; MOH, medication overuse headache; MSQv2, Migraine-Specific Questionnaire Version 2; N/A, not applicable; NHS, National Health Service; NICE, The National Institute for Health and Care Excellence; NSAIDs, non-steroidal anti-inflammatory drugs; ODT, orally dispersible tablet; PAS, Patient Access Scheme; PPS, Personal Social Services; QALY, Quality-Adjusted Life Year; RCTs, randomised controlled trials; RWE, real-world evidence; SmPC, summary of product characteristics.

2.3.1.1 Population

As described in Section 3.1.2, in the EAG's preferred analysis, four randomised controlled trials (RCTs [BHV3000-301, -302,-303 and -310]) inform the clinical effectiveness of rimegepant for acute migraine treatment and are used to inform parameters in the economic model, alongside a long-term open-label study (BHV3000-201). The EAG notes that in response to clarification question A4, the company prefers only three of these RCTs (BHV3000-301, -302 and -303) to be included. The EAG's preference for pooled results from all four RCTs is based on reasons described in Section 3.1.2. Inclusion criteria for the four RCTs were identical (adults aged ≥18 years with at least a 1-year history of migraine, two to eight moderate to severe migraine attacks per month and <15 monthly headache days per month in the preceding three months; see Table 7 in the CS and Table 80 of the CS appendices for further inclusion criteria). The long-term open-label study is similar to the RCTs in terms of inclusion criteria but there was one notable difference; patients with a higher number of moderate to severe migraine attacks per month could be included (two to fourteen rather than two to eight) and CM patients (≥15 headache days per month) were not excluded. The EAG notes that while the RCTs are specific to those with two to eight moderate to severe migraine attacks per month, the Summary of Product Characteristics (SmPC) and the population described by the company in the decision problem does not specify severity or frequency of attacks.[1] However, the company confirm that they anticipate rimegepant would be used to treat moderate to severe migraine attacks (response to clarification question A2).

For the treatment of acute migraine (including those with EM and CM), the population specified by the company in the decision problem is narrower than the NICE final scope,[49] as it is restricted to patients with inadequate symptom relief with at least two triptans (or in whom triptans are contraindicated or not tolerated) and where other acute options (such as paracetamol and NSAIDs) have been exhausted. Overall, although it may also have been a useful option if placed earlier in the treatment pathway, the EAG and the EAG's clinical experts consider the narrower population to be reasonable, particularly as it is a group with high unmet need as other treatment options have been exhausted and that it is likely to be prescribed by a specialist initially given it is a new technology.

Despite the company's positioning of rimegepant for this specific population, the EAG notes that the population in the main trials focused on in the submission (RCTs and long-term open-label study) is not specific to those with at least two triptan failures (only 9.3% of those in the three pooled RCTs had discontinued at least two triptans) or where other acute options such as NSAIDs and

paracetamol have been inadequate; however, data were reported for the specific subgroup with at least two triptan discontinuations for three of the four RCTs (BHV3000-301, -302 and -303).

Furthermore, although the appraisal for rimegepant for acute migraine treatment aims to include patients with EM and CM, all four RCTs exclude those with CM (<15 monthly headache days an inclusion criterion). The EAG's clinical experts note that they would not expect there to be a difference in the efficacy of an acute treatment between EM and CM patients and that there is a lack of evidence investigating a potential difference, but note that if conventional analgesics and triptans are taken on more than ten days per month they can cause MOH and perpetuate the headache, which may be more likely in those with CM as they have a higher number of headache days. The company argue that rimegepant is not thought to be associated with the same risk of MOH and highlights evidence based on real-world data of rimegepant patients in the USA that suggests that the prevalence of MOH is reduced after rimegepant prescription.[55] Based on the evidence included in the submission, the EAG notes the following:

- it is unclear how thorough the identification of possible MOH events was in the longer term evidence, but there [redacted] of MOH in the long-term (up to 52 weeks) study (BHV3000-201) used to support rimegepant in the acute setting (see company response to clarification question A15) and no cases in the long-term phase (up to 52 weeks) of BHV3000-305 used to support rimegepant in the prevention setting (where every other day [EOD] dosing meant there was a median average exposure of [redacted] tablets per month).
- both of these long-term studies allowed inclusion of CM as well as EM patients, though the proportion with CM is unclear
- using the acute RCTs involving treatment of single attacks only, it would not have been possible to assess MOH in this setting.

Although clinical expert feedback and [redacted] MOH [redacted] across longer term clinical evidence covering CM and EM patients suggest it may be reasonable to extrapolate data from the acute trials in EM to the CM population, the EAG considers that there is uncertainty about this and it would be preferable to also have data for acute efficacy in CM patients or evidence to support the idea that efficacy of acute migraine treatments does not differ between EM and CM patients. This is highlighted as a key issue in Section 1.3.1 (Table 2).

Even after clarification (response to clarification question A3), in the economic model, the company prefer to use outcome data from the acute RCTs that is specific to the subgroup with at least two triptan failures (9.3% of the modified intention to treat [mITT] population, only available for BHV3000-301, -302 and -303 trials). Pooled results for the mITT population for comparison were provided as requested by the EAG (response to clarification questions A3, A4 and A12). The EAG considers the full trial population to be more appropriate for the following reasons:

- although it was a pre-specified subgroup analysis, the definition used in the trials was amended *post-hoc* for use in the appraisal, and 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;
- although most baseline characteristics within the subgroup with at least two prior triptan discontinuations (due to lack of efficacy or intolerance) were balanced between the two arms (Table 19 of the CS), a higher proportion in the placebo group had aura (a symptom that the EAG's clinical experts note may affect how difficult migraines are to treat). Similarly, as discussed in Section 4.2.7.1.2, a [redacted] proportion in the rimegepant group compared to placebo had severe migraine at baseline ([redacted] vs [redacted]%). [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 there is [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 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]).

Other than excluding CM patients, the EAG's clinical experts note that most of the baseline characteristics of the included trials (for the mITT population) are reflective of patients seen in UK clinical practice. Comparing the baseline characteristics between the mITT population and subgroup with history of at least two triptan discontinuations (Table 19 of the CS and response to clarification question A4), some characteristics differ slightly ([redacted] age, [redacted] proportion of males, [redacted] proportion of white race and [redacted] duration in hours when attacks are untreated); however, as the mITT population was considered to be reflective of UK practice and given the limitations of the subgroup analysis discussed above, the EAG favours the use of this larger population in analyses. The EAG notes that the characteristics of the long-term open-label safety study differ compared to the RCTs for some characteristics, which is likely due to the wider inclusion criteria for this trial.

In summary, the EAG considers the company's proposed positioning and target population for rimegepant in the treatment of acute migraine to be reasonable given it is a group where other acute treatment options have been exhausted and that the data from the key included trials are relevant to the UK population. Despite some concerns about the generalisability of the full trial populations (mITT) to the population specified by the company in the decision problem, there are [redacted] in results for most outcomes between subgroups based on triptan discontinuation and the mITT analyses are preferred by the EAG due to limitations of the triptan discontinuation subgroup. Exclusion of CM patients from all four RCTs means there is a lack of evidence for the use of rimegepant to treat acute migraine in this group; although based on clinical expert feedback and events in the included long-term clinical evidence it may be reasonable to extrapolate to the CM population, there is uncertainty about this and evidence to support the idea that the efficacy of acute migraine treatments does not differ between EM and CM patients would be useful.

2.3.1.2 Intervention

The intervention covered in the CS is rimegepant (brand name VYDURA®), matching the NICE final scope.[49] The CS focuses on the ODT formulation of rimegepant, which is the formulation included in the marketing authorisation.[1] A summary of rimegepant is provided in Table 2 of the CS. The

European Medicines Agency (EMA)'s Committee for Medicinal Products for Human Use adopted a positive opinion on 24 February 2022 and Great Britain (GB) marketing authorisation was received from the Medicines and Healthcare Products Regulatory Agency (MHRA) on 10 June 2022, with approved indications identical for both.

Rimegepant's approved indications includes use as an acute treatment of migraine (with or without aura) in adults, where a dose of 75 mg daily (one ODT) is to be taken "as needed"/*pro re nata* (PRN; maximum dose 75 mg daily). It is taken by placing the ODT on or under the tongue and can be taken without liquid and with or without meals.

Treatment regimens in the included trials were in line with those described in the SmPC[1] in terms of dose (75 mg), including the RCTs and the long-term open-label safety study (although the latter also contained a group that took rimegepant PRN in addition to EOD, discontinuation data for the groups using only PRN rimegepant was included in the economic model). However, a limitation of the RCTs was that they only assessed response after one dose, whereas in practice further doses may be taken on subsequent days if the migraine continues; as the primary aim of these trials was to assess the acute efficacy of rimegepant (within 2 h), this was not thought to be a major limitation. A limitation of the RCTs in terms of modelling is that the studies are only single attack, whereas in practice an acute treatment would be trialled for multiple attacks before decisions about non-response are made (Section 4.2.4.1).

Although the marketing authorisation[1] is for the ODT formulation and the focus of this appraisal, two of the four RCTs (BHV3000-301 and -302) and the long-term open-label safety study used a tablet formulation (non-ODT) of rimegepant. The company notes that evidence suggests that the two formulations are bioequivalent;[56] however, the EAG's clinical experts note that formulation may have an impact on efficacy, particularly at acute time-points (for example, 2 h). As requested by the EAG at clarification, the company explored this by comparing results when only studies using the ODT formulation were included to results when all studies regardless of formulation were included (response to clarification questions A11 and A12). The EAG agrees that results are [redacted], though slightly [redacted] when focusing on the studies using the ODT formulation, and that including studies using either of the two rimegepant formulations is appropriate. However, the EAG notes that in Section 4.2.3.1.1 the difference in cost-effectiveness results is counterintuitive when comparing analyses using pooled results from ODT only RCTs to pooled results when both rimegepant formulations are included and the EAG requests that this is explained (Section 1.3.1, Table 3).

2.3.1.3 Comparators

The EAG agrees that given the population focused on in the CS is narrower than that in the NICE final scope,[49] specifically those with failures on at least two triptans (or who are intolerant of or contraindicated to triptans) and for whom all other acute options have been exhausted, best supportive care (BSC) is the only relevant comparator.

The EAG's clinical experts note that in practice, BSC where triptans had been inadequate, contraindicated or not tolerated would be use of medications such as paracetamol and NSAIDs as needed; however, the decision problem addressed includes those where these options have also been exhausted. In this situation, the EAG's clinical experts highlight that it is unlikely these medications would be used if they do not work and that a preventive medication may be considered if migraine frequency demanded it. Overall, the EAG agrees that the placebo arm of the included RCTs is reflective of BSC; the placebo arms consisted of a single matching placebo dose and rescue medication after 2 h if needed, and patients in both arms of the trials were also allowed to continue preventive medication if it had been stable for at least three months.

2.3.1.4 Outcomes

The EAG notes that the number of outcomes included in the CS from the RCTs is extensive, covering all of those listed in the NICE final scope[49] in some form. Relevant outcomes from the long-term open-label safety study were also used to inform some parameters in the economic model.

The EAG's clinical experts agree that appropriate outcomes at suitable time-points were measured in the trials. They note that focusing on pain relief at 2 h in the economic model was more appropriate than pain freedom at 2 h given that a degree of pain relief is important to patients, and that the 2 h time-point is more appropriate than the 8 h time-point, as by 8 h it is difficult to distinguish treatment efficacy from spontaneous recovery (Section 4.2.7.1.1).

2.3.1.5 Subgroups

Most subgroups mentioned in the NICE final scope[49] are covered in the CS in some form, as well as some additional ones that were not specified by NICE. Those not covered include those at risk of developing MOH and subgrouping based on the severity of migraine. The EAG is not concerned about their omission as data was not collected and/or the subgroup would have been associated with similar limitations described in Section 2.3.1.1 for the triptan discontinuation subgroup as it was

not stratified for at randomisation. The EAG notes that the only factor that the acute RCTs were stratified for at randomisation was use of preventive migraine treatment.

Despite outcomes being reported for the subgroup with a history of at least two triptan discontinuations (in the three RCTs where this data could be obtained), the EAG prefers the use of the overall mITT population for analyses rather than any of the subgroups, for reasons described in Section 2.3.1.1.

2.3.2 *Migraine prevention*

Table 18. Summary of decision problem – migraine prevention

	Final scope issued by NICE[49]	Decision problem addressed in the submission	Rationale if different from the scope	EAG comment
Population	Adults with migraine	Patients with episodic migraine who have ≥4 migraine days a month but <15 headache days a month and have failed at least three preventive drug therapies	In the preventive setting, rimegepant is expected to be used in patients who have failed at least three oral preventive therapies (i.e., in the same position as currently used injectable preventive mAbs).	Overall, the EAG considers the narrower population specified in the decision problem to be reasonable. However, the SmPC specifies at least 4 migraine attacks per month[1] rather than at least 4 migraine days outlined in the decision problem. As individual attacks can last >24 h, the population being addressed may therefore be slightly broader than the marketing authorisation. The key RCT included in the CS for rimegepant in migraine prevention is not specific to those with episodic migraine and excluded those that had a history of non-response to more than two prior preventive treatments (despite rimegepant being positioned for use in the group with at least three prior preventive drug failures). See Section 2.3.2.1 below for further discussion.
Intervention	Rimegepant	Rimegepant ODT: 75 mg every other day (EOD)	As per scope.	The intervention specified in the CS is rimegepant, matching the final scope. Based on the SmPC,[1] in the prevention setting, rimegepant (ODT

				formulation) is indicated for the prevention of episodic migraine in adults with ≥4 migraine attacks per month (75 mg taken EOD). The EAG notes that although the marketing authorisation and submission is focused on the ODT formulation, the only included trial for the preventive setting is based on a tablet formulation. See Section 2.3.2.2 below for further discussion.
Comparators	• Oral preventive treatments (such as topiramate, propranolol, amitriptyline) • Erenumab (≥4 migraine days per month and after ≥3 preventive drug treatments have failed) • Galcanezumab (≥4 migraine days per month and after ≥3 preventive drug treatments have failed) • Fremanezumab (in chronic migraine and after ≥3 preventive drug treatments have failed) • Botulinum toxin type A (in chronic migraine that has not responded to ≥3 prior	• Erenumab (≥4 migraine days per month and after at least three preventive drug treatments have failed) • Galcanezumab (≥4 migraine days per month and after at least three preventive drug treatments have failed) • Fremanezumab (≥4 migraine days per month and after at least three preventive drug treatments have failed)	As noted above, rimegepant would be used in patients in whom conventional oral therapies have failed. The mAb comparators included in this submission are used in a similar population to that expected for rimegepant: patients with ≥4 MMDs and for whom at least three preventive treatments have failed. It is noted that the fremanezumab NICE recommendation was updated subsequent to the issuance of the final scope for this appraisal. In a rapid review of fremanezumab (TA764/TA631[26] [published February 2022]), the recommendation for fremanezumab was aligned with the recommendation for erenumab[25] and galcanezumab[27] (i.e. ≥4 MMDs and after at least three preventive drug treatments have failed).	The EAG agrees that the marketing authorisation for rimegepant rules out oral preventive treatments and botulinum toxin type A as comparators. The EAG's clinical experts note that although recommended, current use of mAbs in eligible episodic migraine patients is limited. This is based on resources and not because they are ineligible for the mAbs. There is not a large group within the specified population that would be ineligible for mAbs but eligible for rimegepant. The EAG, therefore, agrees that BSC is not a relevant comparator for the appraisal and if recommended, rimegepant is an option only where mAbs would also be considered.

	pharmacological prophylaxis therapies) • BSC		Botulinum toxin type A is excluded as a comparator, as the NICE recommendation is limited to chronic migraine (TA260).[14] BSC is not deemed an appropriate comparator as the target population would be eligible to receive one of the injectable mAbs, which have been recommended by NICE for more than a year now.	The EAG notes that the only evidence for the comparison between rimegepant and the mAbs is based on indirect estimates from an NMA, which is associated with limitations. See Section 2.3.2.3 below for further discussion.
Outcomes	• Frequency of headache days per month • Frequency of migraine days per month • Severity of headaches and migraines • Number of cumulative hours of headache or migraine on headache or migraine days • Reduction in acute pharmacological medication • Health-related quality of life • Adverse effects of treatment	• Change from baseline in MMD at 12 weeks • Proportion of patients with ≥50% reduction in MMD from baseline at 12 weeks • Number of triptan or ergotamine days per month • Change from baseline in MIDAS at 12 weeks • Change from baseline in MSQv2 at 12 weeks • Adverse events	As per scope.	The EAG notes that although most outcomes described in the NICE final scope have been covered in some form in the CS, others have not. However, based on feedback from its clinical experts, the EAG agrees that those key to decision-making have been covered and outcomes informing the economic model are appropriate. See Section 2.3.2.4 below for further discussion.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for	As per the NICE reference case the cost-effectiveness of rimegepant is expressed in terms of incremental costs per QALY and costs have been considered from the perspective of the NHS and PSS.	As per scope. Two separate cost-utility models to address the acute migraine and migraine prevention indications.	The EAG agrees that the economic analysis is in line with the NICE final scope. The company used a 20-year time horizon for the base case. Costs were considered from an NHS and PSS perspective.

	estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.			Health effects were expressed in QALYs. Study BHV3000-305 obtained MSQv2 responses from patients which the company mapped to the EQ-5D. PAS discounts are in place for the comparators and cost-effectiveness results including these discounts can be found in the confidential appendix. The cost-effectiveness results in the CS are based on list prices.
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • People with chronic or episodic migraine • Subgroups defined by the number of previous preventive treatments • Subgroups defined by the frequency of episodic migraine	• Prophylactic migraine medication use at randomisation • Headaches per month (<6 vs. ≥6; <8 vs. ≥8; <12 vs. ≥12; and <15 vs. ≥15) • Other pre-specified subgroup analyses: age, race, sex, ethnicity, BMI, migraine aura, historical chronic migraine, MMD in observation period, CV risk contraindicating triptans	The licence for rimegepant is for episodic migraine[1] and, as such, no data are presented for chronic migraine in the submission. It was not possible to analyse according to the number of previous preventive treatments as these data were not collected in the trial. Real-world data available from the USA, where rimegepant was approved by the FDA for the prevention of migraine in May 2021, show that over [redacted]% of prescriptions are in patients who have previously been on at least one alternative prevention agent.	The EAG notes that a lack of data on the number of previous preventive treatments means subgroups based on this cannot be provided. Other subgroups from the NICE final scope are covered in some form. The only factor that was stratified for at randomisation was use of an additional preventive migraine treatment at baseline. The EAG agrees with the decision to focus on the overall population in the trial rather than the subgroup with episodic migraine.

				See Section 2.3.2.5 below for further discussion.
Special considerations, including issues related to equity or equality	N/A	• Frequent and severe migraine is classified as a disability under the 2010 Equality Act • Migraine is about three times more common among women than men, which raises potential equity issues Please refer to Section B.1.4 of the CS for a discussion of equality considerations.	N/A	N/A
Other issues	N/A	N/A	N/A	The EAG's clinical experts consider that, as a new technology, it is likely rimegepant (if recommended) would initially be prescribed by a specialist and possibly move to primary care in time. Initially, this would be in line with where the proposed comparators (mAbs) are prescribed but would differ if moved to primary care. If moved to primary care, rimegepant may become easier to access compared to mAbs, as the EAG's clinical experts highlight long waiting lists for specialists.

Abbreviations: BMI, body mass index; BSC, best supportive care; CS, company submission; CV, cardiovascular; EAG, External Assessment Group; EOD, every other day; FDA, Food and Drug Administration; mAbs, monoclonal antibodies; MIDAS, Migraine Disability Assessment Test; MMDs, monthly migraine days; MSQv2, Migraine-Specific Questionnaire Version 2; NHS, National Health Service; NICE, The National Institute for Health and Care Excellence; NMA, network meta-analysis; ODT, orally dispersible tablet; PAS, Patient Access Scheme; PSS, Personal Social Services; QALY, Quality-Adjusted Life Year; RCT, randomised controlled trial; SmPC, summary of product characteristics.

2.3.2.1 Population

One USA-based RCT (BHV3000-305), and a long-term open-label extension (OLE) phase of this trial, were the focus for assessing the clinical effectiveness of rimegepant in EM prevention. Results from BHV3000-305 were used to inform parameters in the economic model, alongside the network meta-analysis (NMA) described in Section 3.2.4.

Age ≥18 years, at least a 1-year history of migraine and between 4 and 18 migraine attacks of moderate to severe severity, lasting 4 to 72 h if untreated, were some of the inclusion criteria for the RCT (see Table 8 of the CS for further inclusion criteria). At the end of the double-blind treatment (DBT) phase, participants from either group could enter a long-term OLE phase (up to 52 weeks) with rimegepant as long as they still met the inclusion criteria described for the RCT phase.

For migraine prevention, the decision problem in the CS is narrower than the NICE final scope[49] as it is restricted to patients with EM, ≥4 MMDs and who have failed on at least three prior oral preventive treatments. The EAG notes that the marketing authorisation[1] for rimegepant in migraine prevention is specifically for those with EM and ≥4 migraine attacks per month (any severity). As migraine attacks can last >24 h, the population specified in the decision problem may therefore be slightly broader than the marketing authorisation. This is highlighted as a key issue in Section 1.3.2 (Table 7).

In terms of further limiting its use to those with at least three prior failures on preventive drugs, although the fact it is an oral treatment specifically developed for migraine makes it an attractive option if it were to be placed earlier in the pathway, the EAG and its clinical experts consider the narrower population to be reasonable, given it is a group where existing oral treatments have been exhausted and other treatments recommended for this group are all injectables.

The included RCT is not specific to EM as it includes 23% with CM, which may affect the generalisability of the trial results to the population specified in the decision problem. The EAG's clinical experts note that the inclusion of CM may affect results, as CM may be more difficult to treat due to secondary sensitisation and medication overuse. While the EAG agrees that as randomisation did not stratify for EM vs CM, bias may be introduced by focusing on the EM subgroup, the EAG requested at clarification that further assessment of the within-trial differences between these two groups be performed and commented on to inform the critique. Although limited by a [redacted] CM group, [redacted] outcomes was

detected. Results for [redacted] in the CM vs EM group, which is [redacted] if CM is considered more difficult to treat (company response to clarification question A22). The EAG notes that response in the EM subgroup is [redacted] but [redacted] to that of the [redacted], respectively). Baseline characteristics between the EM subgroup and overall population were [redacted]. Based on these factors, the EAG agrees that focusing on the overall population of this trial is appropriate. Further discussion about CM and the NMA is provided in Section 3.2.4.2.

Although the EAG's clinical experts agree that baseline characteristics of the included RCT are generally reflective of those described in the decision problem that would be seen in clinical practice, they note that the inclusion of some patients with CM means MMDs in the observation period and number of moderate to severe attacks per month are higher than what would be seen for EM patients in UK practice. They highlight that the number of moderate to severe attacks per month would be closer to four rather than eight (see Table 25 of the CS), which may mean the trial represents a population with a higher migraine burden compared to EM patients. As discussed in the previous paragraph, this was assessed at clarification by comparing results in the EM subgroup to the CM subgroup and overall mITT group.

Applicability of the trial to the group with failure on at least three prior oral preventive drugs is also questionable, given the trial excluded those with failures on more than two drug categories of migraine preventive treatment, as described in Table 22 of the CS. The EAG's clinical experts note that patients with migraines not responding to multiple classes of preventive drugs may indicate refractory migraine, which may be more difficult to treat even when trying a new drug class, such as rimegepant. The company suggests in Section B.2.9.8 of the CS that,

[redacted] the company considers that results from the BHV3000-305 trial for rimegepant may provide a conservative estimate of treatment effect for a refractory population. The EAG considers this to be based on the point estimates provided for [redacted]. However, the EAG does not consider these differences to be substantial and the [redacted], when calculated by the EAG, [redacted] within each comparison. Based on this and the expectation (based on feedback from

the EAG's clinical experts) that it would be more difficult to achieve a response in those that have a history of non-response to a higher number of treatments, the EAG does not agree with the company's conclusion. This is highlighted as a key issue in Section 1.3.2 (Table 8). Differences between treatment history of included studies is also highlighted as a limitation of the NMA in the CS (Section B.2.9.8.P), which is critiqued in Section 3.2.4 below.

In summary, the EAG considers the company's proposed positioning and target population for rimegepant in the prevention of EM to be reasonable given it is a group where the only options currently are injectable mAbs and where an oral alternative would be useful. There are, however, some concerns about the use of ≥4 MMDs in the decision problem compared to ≥4 migraine attacks per month in the SmPC[1] in specifying the population rimegepant is to be used in for prevention and the applicability of the single RCT included for this indication, as a proportion with CM are included and a group with more treatment failures and most relevant to the decision problem (those failing at least three prior oral preventives) have been excluded from the trial. Given that randomisation was not stratified by EM vs CM with [redacted] identified between these two subgroups and [redacted] for the [redacted], the EAG agrees that focusing on the overall population (rather than the EM subgroup) is the most appropriate option. Given there are no data available within the trial to assess how history of prior treatment failures may affect response to rimegepant, and that the key group in the decision problem was excluded from the trial, the EAG notes this as a limitation of the evidence for rimegepant in the prevention of EM.

2.3.2.2 Intervention

The intervention covered in the CS is rimegepant (brand name VYDURA®), matching the NICE final scope.[49] The CS focuses on the ODT formulation of rimegepant, which is the formulation included in the marketing authorisation.[1] A summary of rimegepant is provided in Table 2 of the CS. The EMA's Committee for Medicinal Products for Human Use adopted a positive opinion on 24 February 2022 and GB marketing authorisation was received from the MHRA on 10 June 2022, with approved indications identical for both.

Rimegepant's approved indications includes use as a preventive treatment for people with EM and ≥4 migraine attacks per month in adults, where a dose of 75 mg daily (one ODT) is to be taken EOD.

It is taken by placing the ODT on or under the tongue and can be taken without liquid and with or without meals.

The treatment regimen in the DBT phase of the included trial was in line with those described in the SmPC[1] in terms of dose (75 mg EOD); however, the long-term OLE phase also allowed PRN use of rimegepant as an acute treatment if a migraine occurred on a day that they were not due to take a preventive dose of rimegepant. In addition, this trial only involved use of a non-ODT tablet formulation, differing from the intervention covered by the marketing authorisation[1] and described in the decision problem. The company notes that evidence suggests that the two formulations are bioequivalent.[56] Although the EAG's clinical experts raised this as a possible issue in terms of assessing efficacy for the acute treatment setting (where efficacy was measured at a time-point of 2 h), there was less concern about the effect on outcomes in the preventive setting given outcomes are measured over a longer time-period in this setting to determine efficacy.

The EAG's clinical experts highlight that some of the medications used in the trial to treat acute events if they occurred, such as baclofen, would not be used in UK practice. However, it is unclear how many patients received acute medication with drugs that would not be used in UK practice and therefore the degree to which this impacts the applicability of the trial to the UK setting is unclear.

2.3.2.3 Comparators

The EAG agrees that given the marketing authorisation for rimegepant[1] in migraine prevention is specifically for those with EM and ≥4 migraine attacks per month, and that the company position rimegepant for use in EM patients that have failed three prior oral preventives, existing oral preventives (such as topiramate and propranolol) and botulinum toxin type A are not appropriate comparators for this appraisal.

Although the EAG's clinical experts highlight that in practice only ~10% of those with EM having failed at least three prior oral preventive drugs get access to the anti-CGRP mAbs, they note that this is because of a lack of resources and difficulty accessing specialists (who currently prescribe these treatments) rather than them not being eligible or clinically suitable for mAbs. They note that if there were more clinics then more patients within this group would receive mAbs and that they are not aware of a large group of patients that would be contraindicated to mAbs but where rimegepant would be an option if recommended, other than patients that may prefer an oral treatment to

injections. Therefore, the EAG agrees that BSC is not an appropriate comparator for rimegepant in this appraisal and, if recommended, rimegepant would be positioned for use only in patients where anti-CGRP mAbs are considered an option. The EAG's clinical experts note that as it is a new technology, rimegepant for use in migraine prevention is likely to be prescribed by a specialist initially, possibly moving to primary care over time. They highlight that the fact it is an oral option may make it an attractive option for earlier in the pathway, but that this would be a commissioning decision.

The EAG's clinical experts note that although mAbs and rimegepant target the CGRP pathway, they have different mechanisms of action meaning rimegepant use in patients that had to discontinue mAbs would not be ruled out and vice versa for mAb use in those discontinuing rimegepant. In current clinical practice, patients failing on a mAb would be treated with BSC. If rimegepant were to be considered suitable for use in patients that have failed on a mAb, the company would need to demonstrate that it is a cost-effective treatment option compared to BSC in the population failing a mAb. The EAG is not aware that the clinical data required to perform this analysis is available to the company.

The EAG notes that there is no direct evidence for the comparison between rimegepant and the mAbs; evidence for this comparison relies on indirect estimates from an NMA, which is associated with limitations and is described in further detail in Section 3.2.4 below

2.3.2.4 Outcomes

The EAG notes that most outcomes highlighted in the NICE scope[49] are reported in the included trial and provided in the CS. However, outcomes of migraine severity, frequency of headaches (rather than specifically migraines) and cumulative hours of headaches or migraines were not reported. Based on feedback from clinical experts, outcomes key to decision-making have been covered by the RCT and outcomes informing the economic model are appropriate. Migraine severity was however an exploratory outcome as part of the long-term OLE phase of the study. The OLE phase of the study was used to inform discontinuation in the economic model.

The EAG's clinical experts agree that appropriate outcomes at suitable time-points were measured in the trials. They note that the 50% reduction in MMDs used as the threshold for determining response in the economic model was appropriate for EM and that a time-point of 12 weeks was

suitable. See Section 4.2.6.2 for a discussion of the MMD distributions from study BHV3000-305 applied in the economic model and Section 4.2.7.2 on how the treatment effect is modelled.

2.3.2.5 Subgroups

The EAG acknowledges that data to inform subgroups based on number of previous preventive treatments were not collected in the trial. Results for subgroups based on whether or not other migraine preventive medications were being taken at randomisation (rather than prior use) have, however, been provided.

Other subgroups mentioned in the NICE final scope[49] (EM vs CM and different frequencies of EM) have been covered in the CS in some form based on headache frequencies (<15 days vs ≥15 days, with <15 days usually the threshold for EM, and various other cut-offs explored). However, the EAG asked for further assessment of the difference between outcomes for those with EM and CM at the clarification stage, which were provided (response to clarification question A22). Results for other subgroups not specified in the NICE final scope but pre-specified in the trial are also provided in the CS. The EAG notes that the only factor that was stratified for at randomisation was use of preventive migraine treatment at randomisation.

As discussed in Section 2.3.2.1, the EAG agrees with the decision by the company to focus on the overall population in the trial rather than the subgroup with EM.

Reporting of outcomes for the subgroups was limited to the 50% reduction in MMD outcome, which was thought to be reasonable given this is the outcome included in the economic model and that results for all subgroups other than preventive migraine treatment at randomisation may be limited given they were not stratified for at randomisation.

3 Clinical effectiveness

3.1 Acute migraine treatment

3.1.1 Critique of the methods review

The company conducted a systematic literature review (SLR) to identify randomised controlled trials (RCTs) of rimegepant and relevant comparators. The SLR was conducted according to best practice guidance provided by Cochrane and reported according to the guidance provided by The National

Institute of Health and Care Excellence (NICE) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[60] The company present the methods and results of the SLR in Appendix D of the company submission (CS), and the External Assessment Group's (EAG's) critique is presented in Table 19 below.

For the SLR in the acute migraine setting, an original search of electronic databases was conducted in November 2021, which was updated in March 2022. In total, four RCTs (25 publications) were included, with three of these trials providing direct clinical evidence for the efficacy and safety of rimegepant (BHV3000-301, -302 and -303) in the company's original submission.[61-63] The fourth trial (CN170-003, NCT01430442) was excluded from the submission as it was a small dose-finding study in which 75 patients received rimegepant 75 mg tablets.[64] The EAG does not consider a phase II design or a smaller sample size to be sufficient reasons to exclude a trial. At the clarification stage, the company provided further rationale for this study's exclusion (including the fact that it used an earlier rimegepant formulation that has not been demonstrated to be bioequivalent to the formulations used in the other trials), which the EAG agrees is reasonable (response to clarification question A4).

In addition to the three initially included RCTs, a long-term safety study (BHV3000-201) was included in the submission.[65] This was not identified in the SLR as it is a single arm study and the SLR was limited to RCTs, but it did support the company's marketing authorisation application. Patients from the three acute migraine RCTs (BHV3000-301, -302 and -303) were eligible for inclusion in the long-term safety study. Further details and a critique of included studies are provided in Section 3.1.2 of this report.

In the submission, the company mentions another completed clinical trial of rimegepant in the treatment of acute migraine that was excluded in the SLR; BHV3000-310 (NCT04574362), a phase III, double-blind, randomised, placebo-controlled trial of rimegepant 75 mg conducted in China and Korea.[66] The trial was identified in the search of clinical trial registries but was excluded as it did not support the marketing authorisation application and was conducted in an Asian population, which the company states, has limited generalisability to the UK clinical practice. The EAG's clinical experts do not consider geographical location or race likely to affect the results or the generalisability to UK practice. The EAG, therefore, requested that the company explore the impact of including the trial on the results. The results of this are presented in Sections 3.1.3.1, 3.1.3.6 and 8.1 of this report,

where inclusion of this trial in the modified intention to treat (mITT) population is the EAG's preferred analysis.

Table 19. Summary of EAG's critique of the methods implemented by the company to identify evidence relevant to the acute migraine setting

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods
Data sources	Appendix D.1	**The EAG considers the sources and dates searched to be comprehensive.** Databases searched: • Embase; MEDLINE; Embase; the Cochrane Library (CENTRAL). Registries: • WHO ICTRP; ClinicalTrials.gov Conference proceedings: • EAN; EHF; IHS; MTIS; WCN Congress Other Grey Literature: • Reference list searches of relevant SLRs, The original database search was conducted in November 2021, which were updated in March 2022. Conferences were searched between 2019 and 2021.
Search strategies	Appendix D.1.1	**The EAG is satisfied that the company's searches have identified all evidence relevant to the decision problem.** The search strategies for the literature review used free-text keywords, medical subject headings (MeSH) and EMTREE terms for the population and interventions of interest, along with study design filters adapted from NICE guidelines for developing literature search strategies.[67]
Inclusion criteria	Appendix D.1.2.3 (Table 8)	**The EAG considers it unlikely that relevant evidence was excluded based on the eligibility criteria used.** The eligibility criteria matched the target population, intervention, comparators, outcomes defined by NICE in the final scope. Records were limited to English language studies. Studies were excluded at the title/abstract screening stage if they did not report on the outcomes mentioned in the PICOS criteria, which may have led to some relevant studies being excluded. A reference list of all records excluded at full text review was provided at the clarification stage for the SLR of acute migraine.
Screening	Appendix D.1.2	**The EAG considers the reporting of methods for screening to be adequate.** Records were dual screened at both the abstract and full text review stage.
Data extraction	Appendix D.1.2.3	Data extraction was conducted on the four studies included in the SLR. Data extraction was conducted by two researchers, (one primary extractor and a second quality check reviewer). Journal websites were checked for supplementary data and errata. Data was stored and managed in Microsoft Excel.
Tool for quality	Appendix D.1.2.3 and	**The EAG agrees with the company's choice of quality assessment tool of RCTs.**

assessment of included study or studies	D.5 (Table 13)	The company used an appropriate method to assess the quality of the included RCTs and provided justification for each of the quality assessment answers. At the clarification stage the company provided a quality assessment of the single arm safety study BHV3000-201 using the NICE assessment tool. The EAG considers an alternative assessment tool such as the Cochrane ROBINS-I tool would have been more appropriate. The EAG's assessments of the included studies are presented in Section 3.1.2.

Abbreviations: CENTRAL, Cochrane Controlled Register of Trials; EAG: External Assessment Group; EAN, European Academy of Neurology; EHF, European Headache Federation; IHS, International Headache Society; MTIS, Migraine Trust International Symposium; NICE, National Institute for Health and Care Excellence; PICOS, population intervention comparator outcome study design; RCT, randomised controlled trial; SLR, systematic literature review; WCN, World Congress of Neurology; WHO ICTRP: World Health Organisation International Clinical Trials Registry Platform

3.1.2 Critique of trials of the technology of interest

Originally, only three RCTs (BHV3000-301, -302 and -303) were included and pooled for the acute treatment of migraine in the CS and the company maintains this preference after clarification (response to clarification question A4). However, the fourth RCT (BHV3000-310) is included in the EAG's preferred analysis as, based on feedback from the EAG's clinical experts, the EAG did not agree that it being in an Asian population was a reason for exclusion, particularly as studies solely in an Asian population had been included for the migraine prevention network meta-analysis (NMA). While [redacted] for the BHV3000-310 trial [redacted] (see company response to clarification question A5), [redacted] (see company response to clarification questions A4 and A12); although the proportion with response in the rimegepant arm of the BHV3000-310 trial is [redacted] for outcomes such as pain relief at 2 h compared to [redacted], placebo response rates are [redacted] for [redacted].

Similarly, the EAG prefers the analysis in the mITT population, while the company prefers to focus on the subgroup with at least two triptan failures, which is further discussed in Sections 2.3.1.1 and 3.1.3.

The EAG also queried at clarification whether results between studies using the orally dispersible tablet (ODT) and non-ODT formulation of rimegepant were similar, as the ODT formulation is the focus of this appraisal; the results provided in the company's response to clarification questions A11

and A12 [redacted] for the outcomes requested (pain relief at 2 h and pain freedom at 2 h, as well as adverse events) and inclusion of all four trials is appropriate. However, counterintuitive cost-effectiveness results (Section 4.2.3.1.1) were observed.

Details of the methods employed in these four RCTs are provided in Section B.2.3. A of the CS and Section L.1 of the CS appendices. The EAG provides a critique of the internal validity of the four included RCTs in Table 20 below, including the design, conduct and analysis. The EAG agrees mostly with the company's risk of bias assessment provided in Table 12 of the CS and the company's response to clarification question A10. However, the EAG notes some concerns about whether use of the mITT population may introduce bias and the strong assumption for those with missing data (assumed to be non-responders), particularly as the proportion of patients this assumption was made for, and whether it was comparable between arms, is unclear. The EAG, therefore, notes there is a potential risk of bias associated with the trials, but this is unclear due to insufficient information.

The EAG notes that a long-term open-label study (BHV3000-201) was used to inform some longer-term parameters in the economic model. In BHV3000-201, everyone received rimegepant and participants from the acute BHV3000-301, -302 and -303 trials could be enrolled regardless of prior response to rimegepant or placebo. Participants that had not been involved in any of these three RCTs could also be enrolled in BHV3000-201.

The long-term study consisted of long-term (up to 52 weeks) use of 75 mg rimegepant oral tablet (non-ODT formulation), where the primary aim was to assess the safety and tolerability of rimegepant. The lack of a comparator group is a limitation, as is the fact that patients were assigned to groups based on baseline monthly migraine days (MMDs). However, the EAG agrees it is useful for informing long-term safety with rimegepant use. A total of [redacted] participants across the three acute RCTs were enrolled in the long-term study, which also allowed inclusion of a broader group of patients compared to the acute RCTs; the acute RCTs limited enrolment to those with <15 headache days and two to eight moderate to severe migraine attacks per month, whereas anyone with two to fourteen moderate to severe migraine attacks could be included in the long-term study, regardless of the number of headache days per month. The broader inclusion criteria of the long-term study are more relevant to the decision problem than the acute RCTs as the decision problem includes episodic migraine (EM) and chronic migraine (CM), whereas the exclusion of those with ≥15 headache days per month from the acute RCTs means CM is excluded. Other differences compared to the acute RCTs are the inclusion of a group that received every other day (EOD) rimegepant as

well “as needed”/*pro re nata* (PRN) treatment with rimegepant, and rimegepant being taken at the onset of mild to severe migraine, whereas in the acute RCTs rimegepant was taken only for moderate to severe migraines and as a single dose (no EOD dosing).

Table 20. A summary of the EAG's critique of the design, conduct and analysis of included acute RCTs

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique			
		BHV3000-303	BHV3000-301	BHV3000-302	BHV3000-310
Randomisation	Section 9.3.3 (studies -303, -301 and -302) or 9.4.3 (study -310) of the CSRs	**Appropriate** Randomised 1:1 to rimegepant and placebo groups using IWRS. Stratified by use of prophylactic migraine medication (yes or no).			**Appropriate** As for other studies but also stratified by country (China or Korea).
Concealment of treatment allocation	Section 9.3.3 of the CSRs	**Appropriate** Randomisation schedule kept by third-party (IWRS vendor).			
Eligibility criteria	Table 7 of the CS (studies -303, -301 and -302) and Table 79 of the CS appendices (study -310)	**Appropriate but not in line with decision problem** Inclusion criteria relevant but not specific to those failing triptans and less applicable to the chronic migraine population as only those with <15 headache days per month are included. See Section 2.3.1 for further details.			
Blinding	Table 13 of the CS appendices (studies -303, -301 and -302) and company response to clarification question A10 (study -310)	**Appropriate** All studies were described as being at least double-blind. Some provided further detail and described participants and investigators as being blinded. Study personnel and sponsors were also said to be blinded in one study each. All describe attempts within the study to ensure that treatments were matched to avoid obvious differences between groups leading to unmasking (for example, matched on taste and appearance).			
Baseline characteristics	Company response to clarification question A5	**Well-balanced between groups** Baseline characteristics for the mITT population are well-balanced between rimegepant and placebo groups, including migraine history characteristics. Medication overuse headache was not actively investigated during enrolment but there were thought to be [redacted] Applicability of the baseline characteristics in the trial to the decision problem and UK practice is discussed in Section 2.3.1.1.			**Well-balanced between groups** In general, as for other three studies. Although the proportion of [redacted] was less well-matched compared to the other RCTs, with a [redacted]

			proportion of males in the rimegepant arm ([redacted]% vs [redacted]%), this was not thought to be a factor that would affect results.
Dropouts	Section 10.3 (studies -303, -301 and -302) or 10.1 (study -310) of the CSRs and company response to clarification question A6	**Balanced between groups** Of those randomised, for all studies the proportion that were not subsequently treated (population used to assess safety outcomes) with rimegepant was similar between arms. Reasons patients were not treated were also similar between arms. Similarly, of those randomised, the proportion missing from the mITT population (population used for efficacy outcomes) was similar between arms in all studies. It is unclear whether reasons that treated patients were excluded from the mITT population were balanced across groups.	
Statistical analysis			
Sample size and power	Table 11 of the CS (studies -303, -301 and -302) and Section 9.7.2 of the CSR for study -310	**Appropriate** Sample size calculations across all studies were estimated to provide 95% power to detect a significant difference between the treatment groups for each of the two co-primary endpoints and 90% power to detect a significant difference jointly across both co-primary endpoints. Calculations were informed by prior studies involving rimegepant (BHV3000-301 and -302 studies and/or a phase 2 b study of rimegepant). Numbers analysed in the mITT population were higher than the required sample size in all studies. The outcome used in the economic model (pain relief at 2 h) was not one of the co-primary endpoints in the trials, meaning the power calculation for the trials was not based on this outcome and it is unclear if the trials were powered to detect a difference for this outcome.	
Analysis for estimate of effect	Table 11 of the CS (studies -303, -301 and -302), and Sections 9.7.1.3 and 10.1 of the CSR for study -310	**Some concerns for efficacy outcomes** All efficacy analyses were performed in the mITT population, described in the CS as those that were randomised, had a migraine attack of moderate to severe pain intensity, took a dose of study treatment and had at least one efficacy assessment after dose administration. The EAG notes that limiting the analysis in this way may introduce bias, particularly if the reason for those not meeting these criteria is in any way related to efficacy (for example, if the reason someone was lost to follow-up is because of lack of efficacy) and if this differs between arms. Reasons people did not reach this stage of the study are unclear meaning it is difficult to assess. Assessments of adverse events were conducted in the safety analysis set, defined as those receiving a dose of study treatment. This was considered by the EAG to be appropriate.	

Handling of missing data	Table 11 of the CS (studies -303, -301 and -302) and Section 11.4.2.2 of the CSR for study -310	**Some concerns** The proportion with missing data within the mITT population for any of the outcomes, and whether this was balanced between treatment arms, was unclear. For most outcomes, including pain relief at 2 h used in the economic model, patients with missing data and those using rescue medication within 2 h were categorised as having failed. For MBS outcomes, those reporting the MBS after taking investigational product or who did not provide an MBS were also considered failures. Although the EAG consider this to be a strong assumption for those where data is missing (but more likely for those using rescue medication) it is an assumption that is conservative in terms of the treatment effect in each treatment arm and may be the most plausible assumption. It is unclear how this assumption affects the relative treatment effect of rimegepant compared to placebo as the proportion in each treatment arm that had data imputed using this assumption is unclear.			
Outcome assessment	Section 9.4 (studies -303, -301 and -302) or 9.5 (study -310) of the CSRs	**Appropriate** Most migraine outcomes, including the co-primary outcomes of pain freedom and freedom from MBS at 2 h, were assessed using eDiaries completed by patients at the relevant time-points. Although these may be associated with issues in terms of participants remembering to complete them and at the correct time-point, the EAG notes that this method seems appropriate given patients would experience a qualifying migraine at different times and it would not be feasible to be done in clinic. There is no evidence to suggest that additional outcomes of relevance were measured but not reported.			
Additional points	Company response to clarification question A14	N/A	N/A	**Loss of data reported but no concerns about effect on results** The company describe loss of data in this study due to eDiary issues. A sensitivity analysis was performed to assess the impact of this. The EAG notes that although risk differences between rimegepant and placebo [redacted] prior to and after the date a patch to fix the issue was implemented, [redacted]. In addition, response rates in the rimegepant groups [redacted]. Results in [redacted] are [redacted] to those observed [redacted]	N/A

Abbreviations: CS, company submission; CSR, clinical study report; EAG, External Assessment Group; IWRS, interactive web-response system; MBS, most bothersome symptom; mITT, modified intention to treat; N/A, not applicable; RCT, randomised controlled trial.

3.1.3 Critique of the clinical effectiveness analysis

Although the company prefers to focus on data from the subgroup with at least two triptan failures (from BHV3000-301, -302 and -303 trials; Table 20 of the CS), the EAG considers the full trial population to be more appropriate, for reasons described in Section 2.3.1.1. In addition, the EAG prefers pooled mITT results when a fourth RCT (BHV3000-310) is included (provided in response to clarification questions A4, A11b and A12). Based on the results provided at the clarification stage (questions A11 and A12), the EAG considers it reasonable to use pooled results from studies using different rimegepant formulations (ODT and non-ODT); results are [redacted] but studies using ODT formulations show [redacted] results, which may be because [redacted]. However, the EAG notes that in Section 4.2.3.1.1 the difference in cost-effectiveness results is counterintuitive when comparing analyses using pooled results from ODT only RCTs to pooled results when both rimegepant formulations.

Results for the open-label long-term study (BHV3000-201) are discussed in Sections B.2.6.3.4.A. B.3.3.2.4.A, B.3.3.2.5.A and B.3.4.A of the CS.

A brief outline of the results of the RCTs and open-label long-term study are provided below, with focus mostly on the outcomes feeding into the model. Results for the company's and the EAG's preferred analyses are provided.

3.1.3.1 Pain relief and pain freedom at 2 h

Pain relief at 2 h was not one of the co-primary endpoints in the RCTs but was used to define responders in the economic model. Pooled results for the EAG's and company's preferred analyses are provided in Table 21 below. Results for pain freedom at 2 h (one of the co-primary endpoints in the trials) are also provided in this table.

The EAG notes that both analyses demonstrate [redacted] for both outcomes, with [redacted] results in the rimegepant group; however, for the outcome used to define response in the economic model (pain relief at 2 h), the EAG's preferred analysis has a [redacted] response rate in the rimegepant group and [redacted] in the placebo group compared to the company's preferred analysis. These differences lead to a risk difference between groups that is [redacted] in the company's preferred analysis. Given the limitations associated with the triptan failure

subgroup, as described in Section 2.3.1.1, the EAG considers the mITT population to be more robust. In terms of the inclusion of the BHV3000-310 study in the mITT analysis, the EAG notes that while it does lead to [redacted] rimegepant response compared to the results for the mITT population without this study (see Section 8.1), response rates for the pain relief at 2 h outcome are still [redacted] for rimegepant compared to the company's preferred analysis and risk differences are [redacted] for [redacted] analyses requested in the mITT population.

Table 21. Proportion with pain relief at 2 h and pain freedom at 2 h in rimegepant and placebo groups in the EAG's and company's preferred analyses

	EAG's preferred analysis (four included RCTs, mITT population)			Company's preferred analysis (three included RCTs, subgroup with ≥2 triptan failures)		
Outcome	Rimegepant n/N (%)	Placebo n/N (%)	Risk difference (95% CI; p-value)	Rimegepant n/N (%)	Placebo n/N (%)	Risk difference (95% CI; p-value)
Pain relief at 2 h	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain freedom at 2 h	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; CS, company submission; EAG, External Assessment Group; mITT, modified intention to treat; RCTs, randomised controlled trials.

Data for the EAG's preferred analysis are from the response to clarification questions A4, A5 and A12. Data for the company's preferred analysis are from Table 20 of the CS.

[a]The EAG notes that calculated percentages have been corrected where applicable. In the company's preferred analysis for pain freedom at 2 h, slight errors in percentages calculated ([redacted]) appears to have led to an incorrect risk difference ([redacted]).

3.1.3.2 Pain trajectories over 48 h

Pain trajectories from pooled trials over 48 h were used to inform the modelling of pain hours described in Section B.3.3.2.3 of the CS. At the clarification stage (response to clarification question A4), this data was also provided for the EAG's preferred analysis (four pooled RCTs in the mITT population). This is further discussed in Section 4.2.7.1.2.

3.1.3.3 Quality of life

Health-related quality of life (HRQoL)was not measured in the acute RCTs, which is not unexpected given the short duration of the trials as they only cover single attacks. To inform the baseline utility value for patients not experiencing a migraine attack in every 48-hour cycle in the economic model,

Migraine-Specific Questionnaire Version 2 (MSQv2) responses from the long-term study (BHV3000-201) were mapped to EQ-5D utilities. The company also employed EQ-5D utilities from the literature to inform the health state utility values according to pain severity as these were not captured in the long-term study . Please refer to Section 4.2.11.1 for further details on the HRQoL data applied in the economic model.

3.1.3.4 Discontinuation

Although discontinuation could not be assessed in the acute RCTs given that they were only single-attack studies with only one dose of rimegepant taken, assumptions about discontinuation in the economic model (see Section 4.2.8.1) were made based on data from the long-term study (BHV3000-201).

3.1.3.5 Long-term MMDs

The company asserts that the long-term study (BHV3000-201) provides evidence of migraine reduction with use of PRN rimegepant; the economic model therefore included a reduction in MMDs for the rimegepant group in addition to acute pain relief (see Section 4.2.7.1.4).

As discussed in Section 4.2.7.1.4, the EAG considers the long-term reductions in MMD with PRN rimegepant to be highly uncertain as this is based on a *post-hoc* analysis of the long-term safety study which may suffer from confounding (including but not limited to a possible placebo effect). Also, compared to the time horizon of the economic model (20 years), the long-term reductions in MMD with PRN rimegepant are based on a relatively short follow-up period (1 year), and small numbers of patients at risk during the last few weeks of follow-up. The EAG is aware that clinical expert feedback to the company was supportive of including reductions in MMD by PRN rimegepant in the economic model. However, in the absence of long-term comparative evidence, the EAG considers it more appropriate to remove reductions in MMD by PRN rimegepant from the base case analysis and include them in a scenario analysis.

3.1.3.6 Adverse events

Adverse events in the acute RCTs and long-term open-label study are described in the CS as being mostly mild or moderate in intensity, not related to the study treatment and resolved without treatment. The EAG notes that adverse events are not included in the economic model given the low incidence observed in clinical trials (Section B.3.5.4.A of the CS). The EAG's clinical experts are not aware of any specific adverse events of concern for rimegepant. A summary of the adverse events reported for the EAG's and company's preferred analyses (with and without inclusion of study BHV3000-310, respectively) is provided in Table 22 below. Results are for the safety population, which includes those randomised and having at least one dose of double-blind treatment (DBT; for the acute RCTs) or those taking any dose of rimegepant (for the long-term safety study).

At the clarification stage, the company provided further detail about "potential drug abuse" adverse events included in Table 22 for the long-term open-label study. This was defined as subjects taking study drug for non-therapeutic purposes, such as for psychoactive effects such as a high or euphoria. In the long-term study, [redacted]) possibly related to the study drug [redacted] reported (see company response to clarification questions A15 and A30).

The EAG agrees that, overall, the majority of observed events are mild to moderate, with only low rates of severe or serious adverse events occurring and [redacted] in the two PRN groups of study BHV3000-201 and [redacted] in the rimegepant groups of RCTs) serious events judged to be related to rimegepant treatment up to 52 weeks. No deaths occurred either in the acute RCTs or the long-term study. Of any adverse events reported in the RCTs, rates are similar between the rimegepant and placebo groups. Inclusion of the BHV3000-310 study does not change these observations for the acute RCTs (Table 22), nor does looking only at studies using the ODT formulation.

Table 22. Summary of adverse events in the safety population – acute migraine treatment

Incidence, n(%)	Pooled single-dose RCTs (four RCTs included, as per EAG's preference) – safety population		Pooled single-dose RCTs (three RCTs included, as per company's preference) – safety population		Long-term open-label study (BHV3000-201) – safety population, up to 52 weeks		
	Rimegepant (N=[redacted])	Placebo (N=[redacted])	Rimegepant (N=1771)	Placebo (N=1785)	PRN 2-8 (N=1033)	PRN 9-14 (N=481)	EOD + PRN (N=286)
Any AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs reported by ≥1% of patients in any group (pooled RCTs)							
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A
Treatment-related AE (any severity)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related AEs (any severity) reported in ≥1% of any group							
Nausea	[redacted]	[redacted]	[redacted]	[redacted]			
Severe AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related serious AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	24 (2.3%)	16 (3.3%)	8 (2.8%)
Potential drug abuse AEs	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]
MOH	NR	NR	NR	NR	[redacted]		
Cardiovascular AEs	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]
Suicidality AEs	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]
Deaths	[redacted]	[redacted]	[redacted]	[redacted]	0 (0.0%)	0 (0.0%)	0 (0.0%)
AEs reported by ≥2% of patients in any group of the long-term study							

Upper respiratory tract infection	N/A	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]
Nasopharyngitis					[redacted]	[redacted]	[redacted]
Sinusitis					[redacted]	[redacted]	[redacted]
UTI					[redacted]	[redacted]	[redacted]
Influenza					[redacted]	[redacted]	[redacted]
Back pain					[redacted]	[redacted]	[redacted]
Bronchitis					[redacted]	[redacted]	[redacted]
Nausea					[redacted]	[redacted]	[redacted]
Dizziness					[redacted]	[redacted]	[redacted]
Arthralgia					[redacted]	[redacted]	[redacted]

Abbreviations: AEs, adverse events; CS, company submission; CSR, clinical study report; DBT, double-blind treatment; EAG, External Assessment Group; EOD, every other day; MOH, medication overuse headache; N/A, not applicable; NR, not reported; PRN, *pro re nata*/"as-needed" dosing; RCTs, randomised controlled trials; UTI, urinary tract infection;

Results are from Tables 44 and 45 of the CS, response to clarification question A4 and individual study CSRs. Note that where values in this table do not match either the CS or response to clarification question A4, this is because values are taken from the CSR and summed across studies as there was a discrepancy between the two. This applied for the following events for the pooled RCTs: any AE, any AE reported by ≥1% in any group (nausea and UTI), treatment-related AE (any severity), treatment-related AE (any severity) reported by ≥1% in any group (nausea), serious AE, serious AE related to study drug, severe AE, AEs leading to discontinuation.

Severe AEs were not reported in the CSR for the BHV3000-310 study meaning numbers for the four pooled studies could not be confirmed.

Serious AEs were defined in most studies (definition not provided in study -310) as those meeting any of the following criteria: death; life-threatening; inpatient hospitalisation or prolongation of existing hospitalisation; persistent or significant disability/incapacity; congenital anomaly/birth defect in the offspring of someone that received rimegepant; or other, including important medical events that, based on medical judgement, may require medical or surgical intervention to prevent one of the earlier outcomes listed in this definition from occurring.

3.1.3.7 Subgroups

The company provides results for prespecified subgroups in the mITT population (for studies BHV3000-301, -302 and -303) in clarification question responses (A13 and Addendum 3). This is only provided for the co-primary endpoints of the RCTs and not for pain relief at 2 h used in the economic model.

The company's preferred analysis is the subgroup with at least two triptan failures, despite trials not being stratified for this at randomisation, with results provided in Section 3.1.3 alongside the EAG's preferred analysis. This subgroup is defined in the CS as treatment failure due to intolerability or efficacy (not required to fail on all routes of administration) on at least two triptans. This definition differs to that used in the individual trials (defined as treatment failure due to a lack of efficacy, patients had to fail on all routes of administration for a single treatment) to improve the clinical relevance of the analyses, something which was amended *post-hoc* for the purpose of this appraisal. See Table 17 in the CS for a comparison of the two definitions. For reasons described in Section 2.3.1.1, the EAG prefers the analysis in the mITT population.

Of other subgroup analyses, only use of a preventive medication at randomisation was stratified for at randomisation. Results for this subgrouping strategy for all four included RCTs were provided in response to clarification question A13. Although, based on their experience, the EAG's clinical experts do not expect preventive treatment use to influence the efficacy of acute migraine treatments, they note that it is a possibility. The results across most studies for both co-primary outcomes suggest a [redacted] for those using a preventive medication. Despite this, as the acute migraine population will include some patients taking a preventive medication in practice, the EAG considers the overall trial population, rather than any one of these two subgroups alone, to be appropriate for analysis. The EAG's clinical experts note that the proportion taking a preventive medication in the trials ([redacted]% to [redacted]% depending on the trial) was fairly reflective of the proportion with EM in practice that would also be taking a preventive medication; however, they note that this percentage would be higher for CM patients.

3.1.4 Conclusions of the clinical effectiveness section

Evidence submitted by the company in support of the clinical efficacy and safety of rimegepant for the acute treatment of migraine (EM or CM) is from three double-blind RCTs (BHV3000-301, -302

and -303) and a long-term open-label study (BHV3000-201). The EAG disagrees with the exclusion of another study (BHV3000-310) in an Asian population (Section 3.1.2), which is included in the EAG's preferred analysis.

The RCTs are generally considered to be of good quality; although some areas were flagged as having a potential for risk of bias, there was insufficient information to be certain and the methods used were consistent across all four studies (Section 3.1.2). Despite the long-term open-label study being limited by a lack of blinding and lack of a control group, the EAG considers it useful for assessing the safety of rimegepant. It also differs to the RCTs in terms of the population enrolled (CM patients were not excluded), making it more applicable to the decision problem population. While the long-term study also differs in terms of dosing (treatment of mild to severe migraines rather than moderate to severe and inclusion of a group that received EOD as well as PRN rimegepant) and the SmPC[1] does not specify migraine severity, at the clarification stage the company confirmed that they would expect rimegepant to be used to treat moderate to severe migraines and data from the two PRN groups (not PRN + EOD) are used to inform the economic model (Sections 2.3.1.1 and 3.1.2).

The EAG considers the narrower population (compared to the marketing authorisation and the NICE final scope) the company focus on in the decision problem (patients that have failed on [or are intolerant of or contraindicated to] at least two triptans and where other acute options, such as NSAIDs and paracetamol, have been exhausted) to be reasonable. This is a population with a particularly high unmet need and BSC is the only option in terms of acute treatments. In addition, as a new treatment, rimegepant is likely to be prescribed by a specialist at least initially. In line with this decision problem population, the company prefers an analysis specific to the subgroup with a history of at least two triptan discontinuations (from BHV3000-301, -302 and -303 trials). However, as discussed in Section 2.3.1.1, limitations of this subgroup analysis mean the EAG favours the analysis in the mITT population (and with study BHV3000-310 included).

Although the appraisal focuses on the ODT formulation of rimegepant, based on responses provided at the at the clarification stage, the EAG considers the pooling of ODT and non-ODT RCTs to be reasonable. The inclusion of RCTs using non-ODT formulations is likely to be [redacted] as the ODT formulation may be [redacted] (Section 2.3.1.2). However, the EAG notes that in Section 4.2.3.1.1 the difference in cost-effectiveness results is counterintuitive when comparing

analyses using pooled results from ODT only RCTs to pooled results when both rimegepant formulations are included.

The applicability of the RCTs to the decision problem and potential use of rimegepant in practice is limited as CM patients are not included and they are only single-attack trials. In clinical practice the same acute treatment would be tried for multiple migraine attacks before decisions about whether a patient is a non-responder are made. While the long-term study did include CM patients and rimegepant use up to 52 weeks for acute treatment was assessed, only non-comparative data is available. Although clinical expert feedback and [redacted] MOH [redacted] across longer term clinical evidence covering CM and EM patients (BHV3000-201 and also the OLE phase of study BHV3000-305 included in the company's submission for EM prevention) suggest it may be reasonable to extrapolate data from the acute trials in EM to the CM population, the EAG considers that there is uncertainty about this and it would be preferable to also have data for acute efficacy in CM patients or evidence to support the idea that efficacy of acute migraine treatments does not differ between EM and CM patients (Section 2.3.1.1). This is highlighted as a key issue in Section 1.3.1 (Table 2)

Results for the company's and EAG's preferred analyses lead to the same overall clinical conclusions; there is [redacted] between rimegepant and placebo groups ([redacted] outcome in the rimegepant group) for pain freedom at 2 h and pain relief at 2 h. However, the [redacted] relative to placebo is [redacted] in the company's preferred analysis for both outcomes, particularly for the outcome used in the economic model (pain relief at 2 h) where the risk difference is [redacted] compared to the EAG's preferred analysis (Section 3.1.3.1).

For both the EAG's and company's preferred analyses, the adverse events observed across the acute RCTs and long-term open-label study were mostly mild to moderate with only low rates of severe or serious adverse events occurring, [redacted] in the two PRN groups of the long-term study and [redacted] in the rimegepant arms of acute RCTs) serious events judged to be related to rimegepant treatment up to 52 weeks. The EAG's clinical experts were not aware of any specific adverse events to be aware of for rimegepant (Section 3.1.3.6).

3.2 Migraine prevention

3.2.1 Critique of the methods review

The company conducted a SLR to identify RCTs of rimegepant and relevant comparators. The SLR was conducted according to best practice guidance provided by Cochrane and reported according to the guidance provided by NICE and PRISMA guidelines.[60] The company present the methods and results of the SLR in Appendix D of the CS, and the EAG's critique is presented in Table 23 below.

A SLR was conducted to identify RCTs of rimegepant, and its relevant comparators, including but not limited to erenumab, fremanezumab and galcanezumab, in the prevention of migraine. In total, 22 RCTs (442 publications) evaluating interventions for the prevention of migraine were included in the SLR, with one of these trials (BHV3000-305, five publications) providing direct clinical evidence for the efficacy and safety of rimegepant.[68] As well as a 12-week RCT phase, this study also involved a 52-week open-label extension (OLE) phase where all participants received rimegepant. See Section 3.2.2 below for further details and a critique of the rimegepant trial.

The scope of the prevention SLR was broader than that of the NMA. Therefore, inclusion criteria specific to the NMA (Table 28 of the CS appendices) were applied to the 22 primary publications included in the prevention SLR. Ten of the 22 studies informed the evidence base for the original NMA. Of the 12 studies excluded from the NMA, three studies evaluated erenumab at the 70 mg dose, which is not recommended by NICE for use in the UK, five studies were phase II RCTs, and four studies only reported safety outcomes. The EAG does not agree with the exclusion of phase II trials and therefore asked the company to explore the impact of including these studies in the NMA. One of the five phase II trials (ART-01 - Dodick 2014[69]) examined a dose of galcanezumab not authorised for use in the UK and was therefore also excluded from the sensitivity analysis (see response to clarification question A18). As baseline characteristics of these additional trials were similar and the company conclude that there are no additional concerns about heterogeneity with these included, the EAG prefer the NMA with phase II studies included (see company response to clarification question A18). The results of this sensitivity analysis, which included 14 RCTs, are reported in response to clarification question A18 and form part of the EAG's preferred analyses in Section 3.2.4.4 of this report.

Table 23. Summary of EAG's critique of the methods implemented by the company to identify evidence relevant to the decision problem – migraine prevention

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods
Data sources	Appendix D.6	**The EAG considers the sources and dates searched to be comprehensive.** Databases searched: • Embase; MEDLINE; CENTRAL, CDSR and DARE. Registries: • ClinicalTrials.gov Conference proceedings: • EAN; EHF; IHS; MTIS; WCN Congress Other Grey Literature: • Reference list searches of relevant SLRs and NMAs, The original database search was conducted in November 2021, which were updated in February 2022. Conferences were searched between 2019 and 2021.
Search strategies	Appendix D.6.1	**The EAG is satisfied that the company's searches have identified all evidence relevant to the decision problem.** The search strategies for the literature review used appropriate free-text keywords, medical subject headings (MeSH) and EMTREE terms for the population and interventions of interest, and the validated RCT filter by SIGN.[70]
Inclusion criteria	Appendix D.6.2.3 (Table 21)	**The EAG considers it likely that no relevant evidence was excluded based on the eligibility criteria used.** The eligibility criteria matched the target population, intervention, comparators, outcomes defined by NICE in the final scope. Records were limited to English language studies. A reference list of records excluded at full text review with reason for exclusion was provided in Appendix D, Table 23.
Screening	Appendix D.6.2	**The EAG considers the reporting of methods for screening to be adequate.** Records were dual screened at both the abstract and full text review stage.
Data extraction	Appendix D.6.2.3	Data extraction was conducted on the four studies included in the SLR. Data were extracted by a single reviewer, with a second reviewer independently verifying the extracted information and checking that no relevant information had been missed. Data were extracted into pre-specified data extraction tables in Microsoft Word.
Tool for quality assessment of included study or studies	Appendix D.6.2.3 and D.10 (Table 33 and Table 34)	**The EAG agrees with the company's choice of quality assessment tool.** The company used an appropriate method to assess the quality of the included RCTs and provided justification for each of the quality assessment answers. At the clarification stage the company provided a quality assessment of the open label extension phase of BHV3000-305 using the NICE assessment tool. The EAG considers an alternative assessment tool such as the Cochrane ROBINS-I tool would have been more appropriate.

		The EAG's assessments of the included studies are presented in Section 3.2.2.

Abbreviations: CDSR, Cochrane Database of Systematic Reviews; EAG: External Assessment Group; EAN, European Academy of Neurology; EHF, European Headache Federation; IHS, International Headache Society; MTIS, Migraine Trust International Symposium; NICE, National Institute for Health and Care Excellence; PICOS, population intervention comparator outcome study design; NMA, network meta-analysis; RCT, randomised controlled trial; SIGN, Scottish Intercollegiate Guidelines Network; SLR, systematic literature review; WCN, World Congress of Neurology; WHO ICTRP: World Health Organisation International Clinical Trials Registry Platform

3.2.2 Critique of trials of the technology of interest

One RCT (BHV3000-305) was included in the CS for rimegepant in EM prevention, which was used to inform the economic model and in the NMA. Details of the methods employed in this RCT are provided in Sections B.2.3.P and B.2.4.P of the CS.

A long-term OLE phase of this RCT, where everyone received rimegepant (75 mg EOD), was used to inform discontinuation in the economic model. This OLE phase extended the duration and exposure of rimegepant treatment, with a median duration of [redacted] weeks and exposure of [redacted] tablets per month. Of those treated in the RCT phase, [redacted]% in the rimegepant group and [redacted]% in the placebo group were included in the OLE phase. Of these, [redacted]% did not complete the OLE phase (see response to clarification question A19). One difference compared to the RCT phase is that if a patient had a migraine on a day that they were not scheduled to dose with rimegepant, they could take one 75 mg rimegepant tablet on that calendar day to treat the migraine. The maximum dose of rimegepant during the OLE phase was therefore 75 mg tablet per calendar day; in the RCT phase, migraines that occurred were treated with other acute medications, not rimegepant. The EAG notes that the lack of a control group for the OLE phase and the open-label treatment are limitations of the OLE phase but that it provides information to inform longer term parameters for rimegepant in the absence of any comparative long-term data.

The EAG provides a critique of the internal validity of the BHV3000-305 RCT in Table 24 below, including the design, conduct and analysis. The EAG agrees mostly with the company's risk of bias assessment provided in Table 24 of the CS and Table 33 of the CS appendices but notes that baseline characteristics for the evaluable mITT population analysed have not been provided (see Section 3.2.2.1). In addition, the EAG has some concerns about whether use of the evaluable mITT population within the RCT phase may introduce bias and whether the method used to account for missing data (taking an average of the earlier assessments from the participant with missing data) in

those not completing the DBT period but meeting criteria to be analysed within the evaluable mITT population is appropriate. The EAG, therefore, notes there is a potential risk of bias associated with the RCT phase of the study, but this is unclear due to insufficient information.

Table 24. A summary of the EAG's critique of the design, conduct and analysis of BHV3000-305 (RCT phase)

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Randomisation	Section 9.3.3 of the CSR	**Appropriate** Participants were randomised 1:1 to rimegepant 75 mg EOD and placebo using an IWRS. Randomisation was stratified by use of other preventive migraine medications at randomisation (yes or no).
Concealment of treatment allocation	Section 9.3.3 of the CSR	**Appropriate** Allocation concealment is not well described but the description of the IWRS process in the CSR suggests concealment should have been maintained. Although matching tablets and participants, investigators and study personnel being unaware of treatment assignments under allocation concealment are mentioned in the company's critique (Table 34 of the CS appendices), these are features used to assess whether blinding is maintained, not whether treatment allocation is concealed.
Eligibility criteria	Table 22 of the CS	**Appropriate but not in line with decision problem** While the inclusion criteria were appropriate for the aims of the trial (to investigate rimegepant in the prevention of migraine, regardless of whether it is episodic or chronic), the population is less applicable to the population specified in the decision problem, as discussed in Section 2.3.2.1. The trial may also miss a group of episodic patients covered in the decision problem, as those with one to three moderate to severe migraine attacks per month are not included. However, the EAG notes that the SmPC[1] for rimegepant specifies use only in those with at least four migraine attacks per month (any severity) in the preventive setting for episodic migraine patients. In addition, the EAG's clinical experts note that in practice the number of moderate to severe attacks per month on average for episodic patients would be four to five.
Blinding	Table 34 of the CS appendices	**Appropriate** BHV3000-305 is described as a double-blind study (for the RCT phase), with participants, investigators and study personnel being unaware of treatment assignments. Placebo tablets were matched to rimegepant in appearance.
Baseline characteristics	Tables 25 and 32 of the CS, and Section 10.5.1 of the CSR	**Characteristics in the CS are provided for those treated, which differs to the group used for analysis, but the CSR suggests characteristics for this group were similar** The EAG agrees that for the treated population (n=370 vs n=371 in rimegepant and placebo groups, respectively) most of the reported baseline characteristics were well-balanced between the rimegepant and placebo arms of the trial, including those related to migraine history such as number of moderate to severe attacks per month and proportion using an additional preventive treatment at randomisation. A discussion of an imbalance for

		history of chronic migraine and between arms and limited reporting of baseline characteristics for the evaluable mITT group are discussed in Section 3.2.2.1 below. Applicability of the baseline characteristics in the trial to the decision problem and UK practice is discussed in Section 2.3.2.1.
Dropouts	Section 10.2 of the CSR	**Balanced between groups** Of n=747 patients randomised (n=373 for rimegepant and n=374 for placebo), [redacted] in [redacted] group were not treated, with reasons being the same for each group. Of those that were treated, [redacted] were reported not to have completed the DBT, with similar proportions in rimegepant and placebo groups not completing this phase ([redacted], respectively). There was a [redacted] proportion in the placebo group not completing the DBT phase due to the patient withdrawing ([redacted] for placebo vs [redacted] for rimegepant), but the EAG notes that this may [redacted] given the [redacted] between rimegepant and placebo.
Statistical analysis		
Sample size and power	Table 23 of the CS	**Appropriate** Based on an expected sample size of ~370 participants per treatment group in the evaluable mITT population, and assuming rimegepant would provide roughly a one-day advantage over placebo for the primary endpoint (change in mean number of MMDs in last month of DBT phase, weeks 9 to 12) with a common SD of 3.75 days, the study would have ~95% power for the primary endpoint. The estimates used for change in migraine days per month and the SD were based on publicly available information from another investigational CGRP antagonist for the same indication.[71] Although the numbers included in each arm in the evaluable mITT population did not reach at least 370 participants as estimated by the company in the power calculations (n=348 vs n=347), a significant difference between rimegepant and placebo was still detected. The difference observed between rimegepant and placebo groups was slightly smaller than the one-day estimate included in the power calculation (see Table 27 of the CS). The outcome informing the economic model (50% reduction in MMDs compared to baseline) was not the primary outcome in the trial meaning the power calculation for the trial was not based on this outcome and it is unclear if the trial was powered to detect a difference for this outcome.
Analysis for estimate of effect	Table 23 of the CS and Section 12 of the CSR	**Some concerns for efficacy outcomes** The company performed all efficacy analyses on the evaluable mITT population (n=348 vs n=347, compared to n=373 vs n=374 randomised, in rimegepant and placebo groups, respectively), described in the CS as those that were randomised and received at least one dose of double-blind study medication (rimegepant or placebo) and ≥14 days eDiary efficacy data in the OP and at least one month (4-week interval) in DBT phase. The EAG notes that limiting the analysis to those that were treated and have a certain level of outcome data may introduce bias, particularly if the reason for those not having this level of data is because of a lack of efficacy and if this differs between arms. However, there is insufficient reporting of the reasons people did not have this level of outcome data meaning it is difficult to assess.

		Assessments of adverse events were conducted in the safety analysis set (n=370 vs n=371 in rimegepant and placebo groups, respectively), which was defined as those receiving at least one dose of double-blind study medication (rimegepant or placebo). This was considered by the EAG to be appropriate.
Handling of missing data	Table 23 of the CS	**Some concerns** The evaluable mITT population included those that were randomised and received at least one dose of double-blind study medication (rimegepant or placebo) and ≥14 days eDiary efficacy data in the OP and at least one month (4-week interval) in DBT phase. Therefore, some patients included in this analysis only had one or two 4-week interval measurements during the DBT phase. The proportion not completing the DBT phase but included in the analysis was [redacted] The breakdown of reasons for not completing the DBT phase among this group were also provided by the company at clarification, which indicated a slightly [redacted] proportion not completing treatment in the placebo group ([redacted] vs [redacted] of those analysed). However, the EAG notes that only the most common reasons were reported per arm, meaning [redacted] patients were not reported and so it was unclear whether these additional patients were evenly spread between rimegepant and placebo arms (see company response to clarification question A19). Missing data for the primary outcome was said to have been prorated, where, for participants dropping out of the DBT phase, an average of the available measurements taken before they left the DBT phase is taken. This could introduce bias given migraine burden can differ across months and the strong assumption that leaving the trial is not due to any change in efficacy compared to before they left is made; however, it is unclear in which direction this would bias results. It is unclear how missing data for other outcomes was addressed.
Hierarchical analysis	Table 23 of the CS and Section 9.6.4.5 of the CSR	Statistical significance of the primary endpoint (change from baseline in MMDs at 9-12 weeks) was evaluated at the 0.05 level. If the primary endpoint was significant, secondary endpoints were tested hierarchically in the order listed in Table 28 of the CS, each at the 0.05 level. A secondary endpoint was tested only if the preceding secondary endpoint was determined to be significant. Descriptive p-values were provided for any non-significant secondary endpoints and comparative exploratory endpoints.
Outcome assessment	Section B.2.6.3.P of the CS, and Sections 9.4.2 and 11 of the CSR	**Appropriate** Most migraine outcomes, including the primary outcome of MMDs, were assessed using eDiaries completed by patients over the course of the study. Although these may be associated with issues in terms of participants remembering to complete them, the EAG notes that this method seems appropriate for assessing changes in migraine over a period of months. There is no evidence to suggest that additional outcomes of relevance were measured but not reported.

Abbreviations: CGRP, calcitonin gene-related peptide; CS, company submission; CSR, clinical study report; DBT, double-blind treatment; EAG, External Assessment Group; EOD, every other day; IWRS, interactive web-response system; mITT, modified intention to treat; MMDs, monthly migraine days; NICE, The National Institute for Health and Care Excellence; NMA, network meta-analysis; OP, observation period; RCT, randomised controlled trial; SD, standard deviation.

3.2.2.1 Baseline characteristics

As summarised in Table 24 above, baseline characteristics provided in the CS (Tables 25 and 32 of the CS) for the treated population in the BHV3000-305 trial are mostly well-balanced, apart from history of CM where there is a larger difference between arms (26.0% vs 21.0% in placebo and rimegepant arms, respectively). The EAG's clinical experts note that CM can be more difficult to treat and having a higher proportion in the placebo arm might therefore be an important imbalance in terms of efficacy (making the placebo group more difficult to treat). At clarification, the EAG requested that a within-trial analysis be performed to assess whether results differed between those with EM and CM. As discussed in Section 2.3.2.1, the results of this analysis indicate [redacted] in the outcome used in the economic model, but [redacted] in the CM group meaning that the imbalance may have favoured the [redacted].

Although the baseline characteristics provided in Tables 25 and 32 of the CS for study BHV3000-305 are for the treated population (n=370 for rimegepant vs 371 for placebo) rather than the evaluable mITT population that was focused on and included in the NMA (n=348 for rimegepant and n=347 for placebo), information provided in the clinical study report (CSR; Sections 10.5.1 and 10.5.2) suggests [redacted]:

- characteristics provided in Table 10-1 of the CSR for the evaluable mITT population, such as [redacted] compared to those reported in the CS for the treated population;
- in terms of migraine history characteristics, Section 10.5.2.1 of the CSR describes treatment groups in the evaluable mITT population as [redacted];
- and Section 10.5.2.1 of the CSR also highlights [redacted] between treatment groups for [redacted] for placebo vs [redacted] for rimegepant), which is consistent [redacted] within the treated population in the CS.

3.2.3 Critique of the clinical effectiveness analysis

A brief outline of the results of the DBT RCT phase and long-term OLE phase of the BHV3000-305 study are provided below, with focus mostly on the outcomes feeding into the model. Although the DBT phase of this study compares rimegepant EOD to placebo (representing best supportive care; BSC), BSC is not a comparator included by the company in the appraisal for rimegepant in EM prevention. The data from the study is used in the NMA and the results of the NMA are used to populate the economic model. The NMA is discussed further in Section 3.2.4 below. Outcomes reported for the DBT phase can be found in Tables 27 to 29 of the CS and results for the long-term OLE phase are discussed in Sections B.2.6.4.P of the CS.

3.2.3.1 Proportion with ≥50% reduction in MMDs from baseline

To determine response at 12 weeks in the economic model, the outcome of ≥50% reduction in MMDs compared to baseline was used (Section 4.2.7.2).

The outcome definition used in the NMA differs to for the original definition in this trial, which was the proportion with a ≥50% reduction in mean number of moderate or severe MMDs compared to baseline during weeks 9 to 12. To ensure outcomes across studies included in the NMA were comparable, data for this outcome was brought in line with the definitions used in the monoclonal antibody (mAb) trials, meaning the proportion with ≥50% reduction in the mean number of any severity of MMDs as an average across the whole 12-week DBT period was also reported for the BHV3000-305 trial. Results for both of these definitions are presented in

Table 25 below (adapted from Table 35 in the CS, with data for row 2 corrected based on information provided in response to clarification question A18 and Addendum 3 of the clarification questions).

The EAG notes that in the economic model, the company has used the definition in row 1 of

Table 25 for rimegepant response probability but used odds ratios (ORs) for the comparators obtained from the NMA, which were based on the definition described in row 2 of the table. The EAG disagrees with this approach as the definition used for rimegepant differs from that used to calculate the mAb ORs in two ways: at 9-12 weeks vs average over 12 weeks; and 50% reduction in

moderate to severe MMDs vs 50% reduction in MMDs of any severity. As discussed in Section 4.2.7.2, the EAG considers using data in row 2 of

Table 25 below resolves both of these issues.

Table 25. Proportions reaching 50% responder status according to definitions as reported in the trial and as used in the NMA and economic model (adapted from Table 35 of the CS)

End-point definition	n (%)		Source
	Rimegepant (n=348)	Placebo (n=347)	
≥50% reduction in mean number of moderate or severe migraine days per month during weeks 9 to 12 (original definition in rimegepant -305 study and used for response probability for rimegepant in the company's economic model base case)	171 (49.1%)	144 (41.5%)	Croop *et al.* 2021[72]
≥50% reduction in mean number of migraine days (any severity) per month overall during the DBT period (definition used in the economic model and NMA for mAbs in the company's base case, also used for rimegepant in the EAG's base case)	[redacted]	[redacted]	CSR for BHV3000-305[68]

Abbreviations: CS, company submission; CSR, clinical study report; DBT, double-blind treatment; EAG, External Assessment Group; mAb, monoclonal antibody; NMA, network meta-analysis.

Row 1 refers to the definition used originally in the BHV3000-305 trial (and used in the company's base case of the economic model for rimegepant response probability) and row 2 refers to the definition included in the NMA and economic model (mAbs only for company's base case; rimegepant and mAbs in EAG's base case), which is in line with definitions used in the comparator mAb trials. Note that the time-points also differ between the two definitions as in the NMA, attempts to align this across studies were made and it was possible to obtain data from all trials as an average over 12 weeks.

Data for row 2 were corrected based on information provided in response to clarification question A18 and Addendum 3 of the clarification questions.

The results for the original definition in the BHV3000-305 study are reported in Table 28 of the CS, with a statistically significantly higher proportion reported in the rimegepant group compared to placebo (difference 7.6%, 95% CI: 0.2 to 14.9, p-value 0.0438). Although no statistical test is provided for the definition used in the NMA (second row in

Table 25 above), the EAG notes that the difference in proportions between rimegepant and placebo for this definition [redacted] and so [redacted], with a [redacted] in the rimegepant group.

3.2.3.2 Change from baseline in mean number of total MMD

Although not used in the economic model, the primary endpoint of the DBT phase of the BHV3000-305 trial was change in the mean number of MMDs (regardless of severity) within the last month of treatment (weeks 9 to 12) compared to baseline. A statistically significant difference, with a better outcome in the rimegepant group, was reported for the evaluable mITT group (

Table 26 below, adapted from Table 27 of the CS), but the EAG notes that the difference is small (less than one day).

Table 26. Change in mean number of total MMDs in weeks 9 to 12 of the DBT phase compared to baseline (adapted from Table 27 of the CS)

Measure	Rimegepant (n=348)	Placebo (n=347)
LSM (95% CI), days	-4.3 (-4.83 to -3.87)	-3.5 (-4.00 to -3.04)
Difference from placebo (95% CI), days	-0.8 (-1.46 to -0.20)	N/A
p-value	0.0099*	N/A

Abbreviations: CI, confidence interval; CS, company submission; DBT, double-blind treatment; GLMEM, generalised linear mixed-effect model; LSM, least squares mean; MMDs, monthly migraine days; N/A, not applicable.

*indicates significant p-value in hierarchical testing.

Calculated using a GLMEM: change from baseline in number of total MMDs is dependent variable, patient is random effect, number of total MMDs in the baseline period is covariate, and treatment group, prophylactic migraine medication use at randomisation, month, and month-by-treatment group interaction are fixed effects.

3.2.3.3 Quality of life

Quality of life was assessed in the BHV3000-305 trial using Version 2.1 of the Migraine-Specific Quality of Life Questionnaire (MSQv2.1), which is scored on a 0 to 100 scale with higher scores indicating better quality of life. Scores at week 12 of the DBT phase were used to inform the economic model by mapping individual patient-level MSQv2.1 data (role function restrictive, role function preventive and emotional function domains) to EQ-5D-3L scores (Section 4.2.11.2).

Results provided in the CS for this outcome are limited to the restrictive role function domain and reported as a change from baseline measure. As demonstrated in Table 27 (adapted from Table 28 of the CS), the rimegepant and placebo groups experienced an improvement in quality of life at 12 weeks, with this being higher in the rimegepant group. Although the p-value was <0.05 and consistent with a statistically significant difference between groups, the company notes that statistical significance was not formally assessed for this secondary outcome as a secondary outcome earlier in the hierarchical statistical analysis plan had failed to achieve significance.

Table 27. MSQv2.1 restrictive role function domain score at week 12 compared to baseline (adapted from Table 28 of the CS)

Measure	Rimegepant (n=269)	Placebo (n=266)
LSM (95% CI)	18.00 (15.54 to 20.56)	14.6 (12.07 to 17.10)
Difference from placebo (95% CI)	3.5 (0.23 to 6.70)	N/A
p-value	0.0358*	N/A

Abbreviations: CI, confidence interval; CS, company submission; GLMEM, generalised linear mixed-effect model; LSM, least squares mean; MSQv2.1, Version 2.1 of the Migraine-Specific Quality of Life Questionnaire; N/A, not applicable.

*Nominal P-value in hierarchical testing; although P<0.05, this outcome was not formally included in the hierarchical statistical analysis as a secondary outcome earlier in the hierarchical analysis plan had failed to reach significance.

Calculated using a GLMEM: Week 12 change from baseline score is dependent variable, baseline domain score is covariate, and treatment group and prophylactic migraine medication use at randomisation are fixed effects.

3.2.3.4 Discontinuation

To inform discontinuation in the economic model after 12 weeks for those that are classed as responders at 12 weeks (≥50% reduction in MMDs compared to baseline), the long-term OLE phase of the BHV3000-305 was used, which is described in Section B.3.3.2.3.P of the CS. This is further discussed in Section 4.2.8.2.

3.2.3.5 Adverse events

Adverse events in the DBT phase and long-term OLE phase of the BHV3000-305 study are described in the CS as being mostly mild or moderate in intensity, not related to the study treatment and/or resolved without treatment. The EAG notes that adverse events are not included in the economic model as they were not thought to be important in terms of resource use, costs or health-related

quality of life (Section B.3.3.2.4.P of the CS). The EAG's clinical experts are not aware of any specific adverse events of concern for rimegepant. A summary of the adverse events reported in the CS is provided in Table 28 below (adapted from Table 46 of the CS). Results are for the safety population, which includes those randomised and having at least one dose of DBT (for the double-blind phase) or those receiving at least one dose of DBT or open-label rimegepant (for the time-point up to 64 weeks).

At the clarification stage, the company provided further detail about "potential drug abuse" adverse events included in Table 28. This was defined as subjects taking study drug for non-therapeutic purposes, such as for psychoactive effects such as a high or euphoria. In this trial, there was not considered to be any indication of abuse potential related to rimegepant and no cases of MOH were reported (see company response to clarification questions A15 and A30).

The EAG agrees that, overall, the majority of observed events are mild to moderate, with only low rates of severe or serious adverse events occurring [redacted] serious events judged to be related to rimegepant treatment up to 64 weeks. [redacted] occurred during the OLE period [redacted] of these were considered to be related to study treatment. Of any adverse events occurring up to 12 weeks in the DBT phase, rates across different severities are similar between the rimegepant and placebo groups, which is also the case for most of the specific adverse events that were observed in ≥2% of any group. Of those where the rate is higher in the rimegepant group compared to placebo (nasopharyngitis and nausea), there is only a 2% difference (based on a difference of four to seven patients between the groups), they are likely to be non-severe events and not likely to require a large resource to treat.

Table 28. Summary of adverse events in the safety population – migraine prevention (adapted from Table 46 of the CS)

Incidence, n(%)	DBT - rimegepant (n=370), up to 12 weeks	DBT - placebo (n=371), up to 12 weeks	DBT or open-label rimegepant (n=***), up to 64 weeks
Any AE	133 (35.9%)	133 (35.8%)	[redacted]
Treatment-related AE (any severity)	40 (10.8%)	32 (8.6%)	[redacted]
Mild AE	92 (24.9%)	91 (24.5%)	[redacted]
Moderate AE	64 (17.3%)	62 (16.7%)	[redacted]
Severe AE	[redacted]	[redacted]	[redacted]
Serious AE	3 (0.8%)	4 (1.1%)	[redacted]

Treatment-related serious AE	0 (0.0%)	1 (0.3%)	[redacted]
AEs leading to discontinuation	7 (1.9%)	4 (1.1%)	[redacted]
Potential drug abuse AEs	[redacted]	[redacted]	[redacted]
MOH	NR	NR	[redacted]
Cardiovascular AEs	[redacted]	[redacted]	[redacted]
Suicidality AEs	[redacted]	[redacted]	[redacted]
Deaths	[redacted]	[redacted]	[redacted]
AEs reported by ≥2% of patients in any group			
Nasopharyngitis	13 (3.5%)	9 (2.4%)	[redacted]
Nausea	10 (2.7%)	3 (0.8%)	[redacted]
Urinary tract infection	9 (2.4%)	8 (2.2%)	[redacted]
Upper respiratory tract infection	8 (2.2%)	10 (2.7%)	[redacted]
Influenza	[redacted]	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]

Abbreviations: AEs, adverse events; CS, company submission; CSR, clinical study report; DBT, double-blind treatment.

Adapted from Table 46 of the CS, with some additional data taken from the CSR and results for the open-label phase also presented. Note that given some discrepancy between values provided for the most common AEs in the CS and the CSR for the combined DBT and open-label rimegepant group, values from the CSR were used.

Serious AEs were defined as those meeting any of the following criteria: death; life-threatening; inpatient hospitalisation or prolongation of existing hospitalisation; persistent or significant disability/incapacity; congenital anomaly/birth defect in the offspring of someone that received rimegepant; or other, including important medical events that, based on medical judgement, may require medical or surgical intervention to prevent one of the earlier outcomes listed in this definition from occurring.

3.2.3.6 Subgroups

The company provides results for prespecified and *post-hoc* subgroup analyses in Table 38 of the CS appendices for the efficacy outcome used in the NMA and economic model to determine a responder (≥50% reduction in MMDs over 12 weeks compared to baseline).

Although the point estimate for the risk difference between rimegepant and placebo arms suggests a [redacted] between groups for some subgroups (including [redacted]

[redacted]), these were all subgroups that were not stratified for at randomisation, meaning randomisation is broken, and [redacted] for all subgroups [redacted]. As such, the EAG would caution at overinterpreting the differences in point estimates being an indicator of an actual difference between subgroups.

Given concerns about the applicability of the BHV3000-305 trial, as it includes a proportion with CM rather than limiting to EM, the EAG were interested in how results may differ between these two groups. At the clarification stage, the company performed a within-trial analysis of EM vs CM to determine whether the results for the outcome used in the NMA may differ between these two groups. As discussed in Section 2.3.2.1, the EAG concludes that using the overall population rather than the EM subgroup is reasonable.

The EAG notes that the only subgroup analysis that was stratified for at randomisation was the use of any concurrent preventive migraine medication at randomisation, which was permitted if it had been stable for at least three months and continued to be stable throughout the trial. Although there is [redacted] in risk difference with rimegepant relative to placebo between the two subgroups, with the risk difference [redacted] in those using another prophylactic medication (risk difference vs placebo: [redacted] vs [redacted]), the [redacted] of the two subgroups [redacted], possibly due to [redacted] within the group [redacted]. In addition, [redacted] appears to be primarily driven by [redacted] in the response rate of the [redacted] group, which is [redacted] in the group using an additional prophylactic medication compared to those not using one [redacted], as the response rate in the [redacted] arm is actually [redacted] in the group [redacted]. Given that the proportions achieving [redacted] in the [redacted] arm of the two subgroups [redacted], the EAG considers that the use of the full population is most appropriate option.

3.2.4 Critique of the indirect comparison and/or multiple treatment comparison

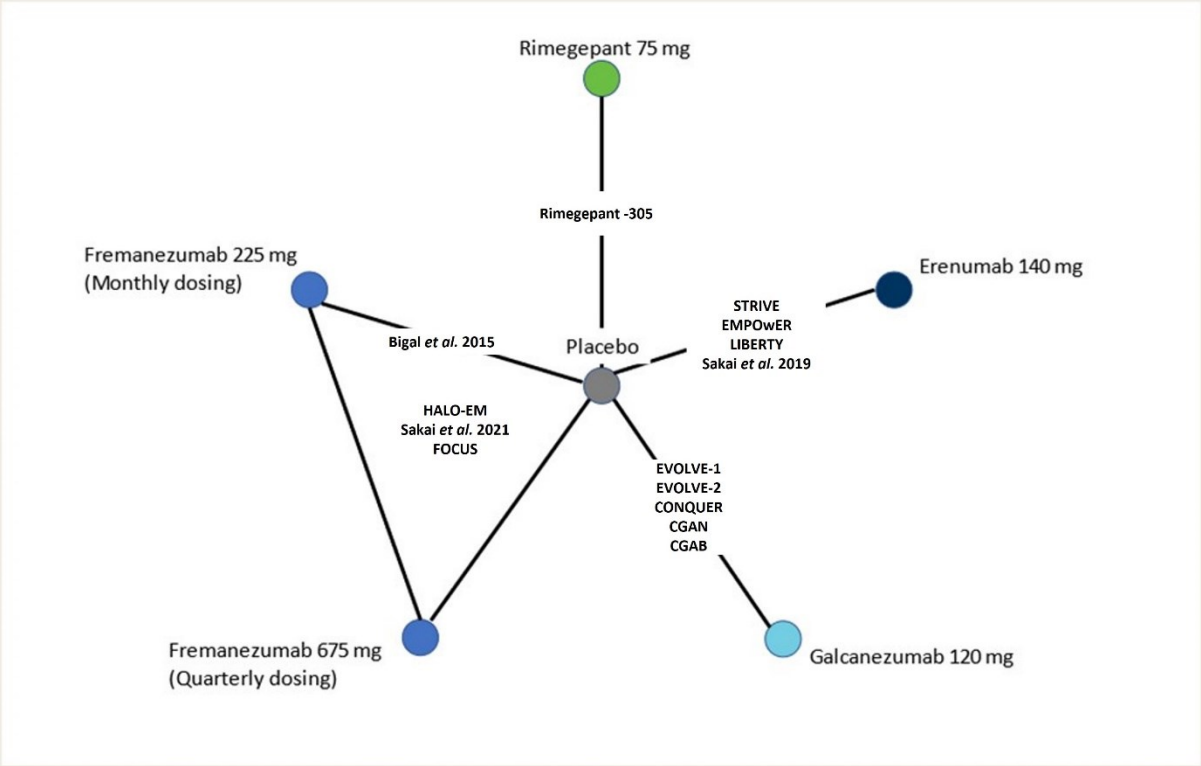
3.2.4.1 Overview and included studies

Given the lack of head-to-head RCTs comparing rimegepant to mAbs (specifically erenumab, fremanezumab and galcanezumab as recommended by NICE)[25-27] in the prevention of EM, the company performed a NMA to obtain indirect comparative evidence (Section B.2.9.P of the CS, company response to clarification question A18 and Addendum 3 of the clarification questions).

NMAs were performed for two outcomes (≥50% reduction from baseline in MMD and mean change from baseline in MMD); however, only the ≥50% reduction from baseline in MMD analysis was used in the economic model. The EAG requested at clarification that an NMA also be performed to inform treatment-specific discontinuation rates in the economic model (Section 4.2.8.2), but the company explained that this was not performed given a lack of data for the mAbs trials, in particular, a concern about how well 12-week discontinuation rates reflect annual discontinuation rates and the need for data to be specific to responders at 12 weeks (see company response to clarification question A25).

The clinical SLR performed for migraine prevention, as critiqued by the EAG in Section 3.2.1, was used to identify studies relevant for inclusion in the NMA. The company originally included 10 RCTs (Figure 9 of the CS) and maintained this preference after clarification, but 14 RCTs were included in the EAG's preferred NMA, as summarised in the network diagram below in Figure 3 (adapted from Figure 9 of the CS to include additional phase II studies).

Figure 3. Network diagram for the NMA in episodic migraine prevention – EAG's preferred NMA (adapted from Figure 9 of the CS)



All included studies were compared to placebo, which, for the EAG's preferred analysis, included one study (BHV3000-305[68, 72]) for 75 mg rimegepant, four studies (STRIVE[73], EMPOWER[74], LIBERTY[57] and Sakai *et al.* 2019[75]) for 140 mg erenumab, five studies for 120 mg galcanezumab (EVOLVE-1[76, 77], EVOLVE-2[77, 78], CONQUER[59], CGAN[79] and CGAB[80]), four studies for 225 mg (monthly dosing) fremanezumab (HALO-EM[81], Sakai *et al.* 2021[82], FOCUS[58] and Bigal *et al.* 2015[83]) and three studies for 675 mg (quarterly dosing) fremanezumab (HALO-EM[81], Sakai *et al.* 2021[82] and FOCUS[58]). Note that all 14 studies were included for the change from baseline in MMD outcome but only 12 were included for the ≥50% reduction in MMD outcome (CGAN and CGAB studies not included as data could not be obtained for the outcome matching the format used in the NMA for other studies).

A comparison of baseline characteristics across included studies is provided in

Table 90 of Section 8.2 (adapted from Table 32 of the company's response to clarification question A18). The EAG notes that mean age (37.1 years to 46.8 years depending on the study and treatment arm) and the proportion female (79.6% to 91.0% across studies and treatment arms) are similar across included studies. Other characteristics such as migraine with aura are not well-reported across studies, making a comparison difficult. Characteristics differing across studies that are a concern are discussed below in Section 3.2.4.2.

Based on the company's risk of bias assessment, presented in Table 33 of the CS appendices (and trial publications where further detail was required), key features of the studies were similar (Table 29).

Table 29. Summary of design, conduct and analysis features of studies included in the NMA (EAG's preferred analysis)

Feature	Summary
Randomisation and concealment	All were randomised using electronic IRT, which also served a role in allocation concealment in some cases (LIBERTY[57] for erenumab and Sakai *et al.* 2021[82] for fremanezumab) as the technology was provided by a third party and there was a clear statement that randomisation schedules were maintained independently or that randomisation was performed by the third party. For other studies, this level of detail was not provided, and allocation concealment was unclear (although the company suggest that allocation concealment is described for most studies, the EAG notes that reasons mentioned by the company, such as matching treatments, are factors that ensure blinding rather than allocation concealment).
Baseline characteristics and potential prognostic factors	The company concludes that for all included trials, treatment arms were similar in terms of baseline characteristics and potential prognostic factors.
Blinding	All were said to be at least double-blind (participants, investigators and study staff most often being mentioned as blinded to treatment assignment and some also mention study sponsors) and most describe attempts within the study to ensure that treatment administration and schedules were matched to avoid obvious differences between groups leading to unmasking.
Imbalances in dropouts	No imbalances in dropouts between groups for any of the included studies were reported.
Outcome measurement	In most cases there was no suggestion of more outcomes being measured than were reported; where this was not the case, it was some secondary end-points that may not have been reported (CGAN[79] for galcanezumab), reporting of certain outcomes only for a specific dose (CGAB[80] for galcanezumab) or only reporting results for a specific time-point (CONQUER[59] for galcanezumab).
Analysis population and imputation of missing data	A discussion of the analysis populations and methods for imputation across included studies is provided in Section 3.2.4.3.4.

Abbreviations: EAG, External Assessment Group; IRT, interactive response technology.

3.2.4.2 Methods

Studies in an EM population and a mixed EM/CM population were included. For studies with mixed populations that had been stratified for EM vs CM at randomisation, subgroup results for those with EM were used. If not stratified, the overall population was used as the company considered that breaking randomisation and using the EM subgroup would introduce more bias than including CM

patients would lead to. In addition, aligning outcome definitions across studies in the network was prioritised over using data specifically for the EM subgroup in one study.[58]

To align outcome definitions across studies in the network in terms of time-point (12 weeks vs 24 weeks) and method of calculation (measured at 9-12 weeks or as an average across the 12-week period), data from all studies were reviewed and final outcome definitions used in the NMA were based on the most commonly used definitions across studies and the availability of data to manually calculate an average from monthly 50% responder rates (see Table 33 of the CS and company response to clarification question A18). For the outcome informing the economic model, the final end-point definition used in the NMA was ≥50% reduction in mean number of MMDs (any severity) over the 12-week DBT period, as included in row 2 of

Table 25. For the change from baseline in MMD NMA, the final definition used was change from baseline in MMD to 12 weeks (measured at 9 to 12 weeks).

A Bayesian framework was used to fit NMA models in line with NICE Decision Support Unit (DSU) guidance (Technical Support Documents 2[84] and 3[85]), which included fixed effects and random effects (with and without adjustment for baseline risk). Adjustment for baseline risk was performed to account for differences in placebo effect observed across the included trials.

The most appropriate model for each outcome was selected by the company based on the deviance information criterion (DIC), a measure of goodness of fit; when the difference between the DICs of two models was less than three units, the least complex model was selected. The EAG was concerned about basing the decision solely on the least complex model if there was a difference of less than three units between models. Models favoured by the company and the EAG's preferred models are described below in Section 3.2.4.4.

Other than issues that are discussed in the following section (Section 3.2.4.2), the EAG consider that, overall, the methods used are appropriate. Full details of methods used are provided in Section B.2.9.P of the CS, Section D.8.P of the CS appendices and clarification question responses (A18 and Addendum 3).

3.2.4.3 EAG critique of the NMA methods and study selection

3.2.4.3.1 Inclusion of CM patients

One limitation of the NMA described by the company is the inclusion of some patients with CM, as the marketing authorisation for rimegepant in migraine prevention and this technology appraisal are specific to EM.[1] Data used for two of the 14 trials included in the EAG's preferred analysis (BHV3000-305[68, 72] for rimegepant and FOCUS[58] for fremanezumab) were based on a mixed EM/CM population, either because the trial was not stratified for EM/CM at randomisation (and breaking randomisation to include only EM patients was thought to represent a bigger risk of bias than including some CM patients) or because aligning outcome definitions was favoured over including EM-specific data. These two trials were also included in the company's preferred analysis and so the same issue applies. These trials have a higher mean baseline MMD compared to most of the other trials (10.1 to 10.3 for rimegepant study and 14.1 to 14.3 for the fremanezumab trial, compared to 8.2 to 9.5 for most other trials), apart from the Bigal *et al.* 2015[83] study (11.5 in both treatment arms), which may be explained as this trial only included those with high-frequency EM. A minority had CM in the rimegepant trial (33%), while this was much higher in the FOCUS trial for fremanezumab (60% CM).

By including these mixed trials in the NMA, the company assumes that, as long as there is a balance between treatment arms, baseline MMD does not modify the relative treatment effect of each treatment compared to placebo. The EAG's clinical experts note that CM can be more difficult to treat, meaning a study with a higher proportion of CM patients could have a different treatment effect relative to placebo. In addition, with higher baseline MMDs in CM patients, this makes reaching the ≥50% reduction threshold in MMDs outcome more difficult; however, the EAG notes that it is unclear whether this would affect the treatment arm more or whether placebo and treatment arms would be equally affected. Based on clinical expert feedback, at clarification, the EAG asked that the company explore the effect of migraine frequency (EM vs CM) on the results of the rimegepant trial. As discussed in Section 2.3.2.1, the results [redacted] between EM and CM groups, though there appeared to be a [redacted] in the CM group, which was [redacted] predicted if CM is more difficult to treat. The EAG concludes that using the overall population rather than the EM subgroup, which was not stratified for at randomisation, is reasonable, particularly as the results [redacted] are [redacted] results when [redacted].

The inclusion of CM patients was thought to be more of an issue for the FOCUS trial for fremanezumab as a larger proportion were included (60%). Although the EAG notes that the proportion with ≥50% reduction in MMDs was lower in the fremanezumab treatment arms of this study[58] compared to the other three fremanezumab studies[81-83] (response to clarification question A18), this was also the case for the placebo arm and the population of FOCUS also differs to the other studies based on prior treatment failures (see Section 3.2.4.3.2 below). Although the EAG considered whether exclusion of the FOCUS trial from the NMA may be appropriate given it is the only trial with a majority of CM patients rather than EM patients included, this was not thought to be preferable as it is also the only fremanezumab study limiting to patients that have failed two or more prior treatments and it is unclear whether the inclusion of CM patients in this study introduces additional heterogeneity that is not already accounted for in the NMA models adjusted for baseline risk. Concerns about the inclusion of CM patients was taken into account by the EAG when selecting their preferred NMA base case for each outcome, as discussed in Section 3.2.4.4 below.

3.2.4.3.2 Treatment failure history

The studies included in the NMA (EAG's preferred analysis and company's preferred analysis) also differ with regards to the number of prior treatment failures. While 11 of the 14 studies in the EAG's preferred analysis (including the rimegepant study) excluded patients based on prior treatment history, meaning they may be less applicable to the population with at least three prior treatment failures set out in the decision problem, there were three studies focusing on refractory populations (LIBERTY,[57] FOCUS[58] and CONQUER[59] for erenumab, fremanezumab and galcanezumab, respectively) where all patients had failed between two and four classes of preventive migraine treatments.

The company explain in the CS that a sensitivity analysis to investigate the impact of this on results was not feasible as detailed information regarding prior treatment history was not recorded in the BHV3000-305 rimegepant trial, meaning results between patients that had not failed a preventive treatment or had failed one or two types of preventive treatments could not be compared. They, therefore, highlight treatment history heterogeneity as a limitation of the NMA and the analysis assumes that relative treatment effect does not differ based on line of therapy. While the EAG's clinical experts note that failure on one treatment class does not necessarily mean someone has a higher chance of failing on another if the mechanism of action is different, they do highlight that when migraine shows no or limited response to multiple treatment classes this could mean the migraine is generally more difficult to treat and they may have a higher risk of failing on a new

treatment. The company suggests in Section B.2.9.8 of the CS that,

[redacted] the results from the BHV3000-305 trial for rimegepant may provide a conservative estimate of treatment effect for a refractory population; however, the EAG do not agree with this conclusion (see Sections 1.3.2 and 2.3.2.1). Therefore, the EAG consider treatment history heterogeneity to be a limitation of the NMA. This was taken into account by the EAG when selecting their preferred NMA base case for each outcome, as discussed in Section 3.2.4.4 below.

3.2.4.3.3 Concomitant use of other preventive medications

The concomitant use of another migraine preventive therapy was permitted in most studies if the dose had been stable in the months leading up to study enrolment but was an exclusion criterion for the refractory population trials (patients on concurrent preventive medications were excluded). The proportion using an additional preventive treatment ranged from 0.0% to 34.4% (Table 32 of the company response to clarification question A18) across studies where this was not an exclusion criterion. In response to clarification question A23, the company note that they are not aware of published evidence to suggest that concurrent preventive migraine treatment is an independent treatment effect modifier and highlight that in the rimegepant BHV3000-305 study, event rates in rimegepant and placebo arms [redacted]. In addition, the EAG notes that the proportion using concomitant preventive medication was balanced between arms for all studies where this information was reported, meaning it is less likely to lead to any differences in relative treatment effects.

3.2.4.3.4 Analysis population and methods for imputation of missing data

The company reports that all trials included an intention-to-treat (ITT) analysis and that any methods used to account for missing data were appropriate. The EAG notes that while the analyses used across studies may have been described as modified intention-to-treat analyses or similar, the definition of those analysed and methods used to account for missing data differed. While the EAG

notes that differences in the population analysed and methods of accounting for missing data across studies is not ideal, opportunities to align these are limited by what is reported in publications for comparator interventions. Specifically, in terms of:

- the population analysed, this was either all of those randomised that had at least one dose of study treatment (four studies[59, 76, 79, 80]) or all of those randomised with at least one dose of study treatment and a certain level of post-baseline data (e.g. at least one efficacy assessment post-treatment initiation; ten studies[57, 58, 72-75, 78, 81-83]);
- accounting for missing data, methods varied and in some cases were not described, but the most common reported method for the outcome included in the economic model (≥50% reduction in MMDs) was assuming those with missing data were non-responders.

For studies comparing galcanezumab to placebo, there did not appear to be any pattern between analysis population used and results for either of the two outcomes an NMA was performed for; the EVOLVE-2 study[78] was the only study to use a different analysis population (those treated and with a certain level of post-baseline outcome data) and results were similar to the other four studies (EVOLVE-1,[76] CONQUER,[59] CGAN,[79] and CGAB[80]), which analysed those taking at least one dose of study treatment). It was not possible to determine whether the imputation method used may have had an effect on results for galcanezumab as this was unclear for most galcanezumab studies.

For erenumab and fremanezumab trials, all used the same analysis population (treated with a certain level of post-baseline data) and imputation method for the 50% reduction in MMDs outcome (those with missing data considered non-responders). For the MMD change from baseline outcome, erenumab studies either had no imputation or it was unclear. For fremanezumab studies, three[81-83] used a form of proration (though this differed slightly between studies) and in the remaining study[58] this was unclear. Although the HALO EM study[81] reports a slightly lower relative effect of fremanezumab vs placebo compared to the other three studies, this study used a similar imputation method to another study (Sakai *et al.* 2021[82]) and it is unlikely that differences in imputation method explain this.

Therefore, the EAG highlights that differences in analysis population and imputation method may be an issue but based on available data do not consider it to be something that should affect the results substantially, particularly for the outcome used in the economic model as the majority have used the

same population (treated with some degree of post-baseline data) and imputation method for missing data (assumed to be non-responders).

3.2.4.3.5 Placebo response rate

The company also raise differences in placebo responses across the trials, which ranged from [redacted] to [redacted]% for the ≥50% reduction in MMDs outcome and from [redacted] for the MMD change from baseline outcome for the 14 studies included in the EAG's preferred analysis, as an important issue in the NMA. The EAG's clinical experts note that differing and often high placebo effects are an issue in migraine studies and that comparing results between trials with different placebo responses is difficult, meaning direct evidence from head-to-head trials is important. The company identify various factors that may affect placebo response in trials included in the NMA:

- higher frequency of drug administration may lead to a higher placebo effect (highest for the rimegepant study in this case as dosing is EOD rather than monthly or quarterly as for mAbs), which may be consistent with what was observed across the included studies as rimegepant had the highest or was among the highest placebo responses for both clinical outcomes;
- increased invasiveness of treatment, in this case associated with mAbs due to the need for injection, may confer a larger placebo effect compared to oral treatments such as rimegepant. There was no evidence of this within the included trials as the oral rimegepant treatment had one of the highest placebo responses for both clinical outcomes;
- increased number of prior treatment failures may be associated with a lower placebo effect, which was supported by the included studies as the three refractory trials (LIBERTY,[57] FOCUS[58] and CONQUER[59]) were among lowest placebo responses for both clinical outcomes. The EAG's clinical experts agree that placebo effect can be lower in those that have had more treatment failures, possibly due to lower expectations for future treatments.

The EAG agree with the company's efforts to control for this difference in placebo response by performing versions of the fixed and random effects NMAs that also incorporate adjustment for baseline risk. The difficulty of comparing between studies that differ in terms of placebo effect was taken into account by the EAG when selecting their preferred NMA base case for each outcome, as discussed in Section 3.2.4.4 below.

3.2.4.4 Results

3.2.4.4.1 ≥50% reduction in MMDs over 12 weeks

The company selected the fixed effects model with adjustment for baseline risk and with phase II RCTs excluded as the base case for this outcome based on DIC values and model complexity (see Addendum 3 of clarification responses). However, as the company accepts there could be some unresolved heterogeneity not accounted for by the baseline adjustment (as discussed in Section 3.2.4.2 above), the EAG considers the random effects model with adjustment for baseline risk to be more appropriate, which has a similar DIC value. In addition, the EAG prefers the NMA with inclusion of phase II RCTs as it is based on more data and the company concludes that their inclusion does not introduce further heterogeneity (see company response to clarification question A18).

Results for analyses are provided in Table 30 (data taken from results tables provided in response to clarification question A18 and Addendum 3 of the clarification questions). Values used to inform the health economic model are the median ORs for each mAb vs rimegepant (though only the 225 mg value for fremanezumab was incorporated in the economic model) but values for each intervention compared to placebo are also provided.

The EAG notes that the results for both analyses are similar and indicate [redacted] with mAbs compared to rimegepant based on point estimates, though [redacted] of these are [redacted] in both analyses. The random effects adjusted model (with phase II studies included) estimates [redacted] median ORs compared to the fixed effects adjusted model (with phase II studies excluded) for erenumab 140 mg and fremanezumab 225 mg vs rimegepant and slightly [redacted] median ORs for galcanezumab 120 mg and fremanezumab 675 mg vs rimegepant. In the EAG's preferred model, the relative effects of 140 mg erenumab and 675 mg fremanezumab vs rimegepant are [redacted]; the relative effects of the other two mAbs vs rimegepant (120 mg galcanezumab and 225 fremanezumab) are [redacted] in both of the models. For comparisons to placebo, results from both analyses are similar, with [redacted] efficacy for all mAbs and rimegepant vs placebo.

Results from other versions of the NMA model that may be of interest (random effects adjusted for baseline risk with phase II studies excluded and fixed effects adjusted for baseline risk with phase II studies included) are provided in Section 8.3.1.

Table 30. ≥50% reduction in MMDs from baseline over 12 weeks – median ORs for rimegepant and mAbs vs placebo and mAbs vs rimegepant (EAG's and company's preferred NMAs)

Intervention	Random effects adjusted for baseline risk (phase II studies included) – EAG's preferred NMA Median OR (95% CrI)	Fixed effects adjusted for baseline risk (phase II studies excluded) – company's preferred NMA Median OR (95% CrI)
Compared to placebo		
Erenumab 140 mg	[redacted]	[redacted]
Galcanezumab 120 mg	[redacted]	[redacted]
Fremanezumab 225 mg	[redacted]	[redacted]
Fremanezumab 675 mg	[redacted]	[redacted]
Rimegepant 75 mg	[redacted]	[redacted]
Compared to rimegepant		
Erenumab 140 mg	[redacted]	[redacted]
Galcanezumab 120 mg	[redacted]	[redacted]
Fremanezumab 225 mg	[redacted]	[redacted]
Fremanezumab 675 mg	[redacted]	[redacted]

Abbreviations: CrI, credible interval; EAG, External Assessment Group; mAbs, monoclonal antibodies; MMDs, monthly migraine days; NMA, network meta-analysis; OR, odds ratio.

Bold text indicates values that are significant at a 5% level.

Figures for the EAG's preferred NMA are from the company's response to clarification question A18 and figures for the company's preferred NMA are from Addendum 3 of the clarification questions.

3.2.4.4.2 Change in MMDs from baseline at 12 weeks

The company selected the random effects model (unadjusted for baseline risk, with phase II studies excluded) as the base case for this outcome based on DIC values and model complexity (see Section B.2.9.3 of the CS). However, given that the company and the EAG's clinical experts highlight differing placebo effects as a concern when comparing between studies (as discussed in Section 3.2.4.3.4) and that the between-study heterogeneity (median SD) is lower for the adjusted random effects model compared to the unadjusted random effects model ([redacted]; Section B.2.9.4.P of the CS), the EAG consider the random effects model with adjustment for baseline risk to be more appropriate. In addition, the EAG prefers the NMA with inclusion of phase II RCTs as it is based on more data and their inclusion does not introduce further heterogeneity as the median between-study SD of random effects analyses (adjusted and unadjusted) are similar and slightly lower than when these studies are excluded ([redacted] for unadjusted and [redacted] for adjusted; see company response to clarification question A18).

Results for analyses favoured by the EAG and the company are provided in Table 31 below (data taken from results tables provided in Table 38 of the CS and the company's response to clarification question A18). Results for this outcome were not used to inform the economic model, but the results in general for the EAG's preferred model demonstrate [redacted] efficacy) of mAbs and rimegepant vs placebo, though this effect for rimegepant is [redacted] compared to mAbs. There are [redacted] for [redacted] of the mAbs compared to rimegepant for the adjusted random effects model. The conclusions for the company's preferred model are the same other than that there is [redacted] for rimegepant vs placebo.

Results from other versions of the NMA model that may be of interest (random effects adjusted for baseline risk with phase 2 studies excluded and random effects with no adjustment for baseline risk with phase 2 studies included) are provided in Section 8.3.2.

Table 31. Change from baseline in MMDs at 12 weeks (weeks 9-12) – median mean differences for rimegepant and mAbs vs placebo and mAbs vs. rimegepant (EAG's and company's preferred NMAs)

Intervention	Random effects adjusted for baseline risk (phase II studies included) – EAG's preferred NMA Median mean difference (95% CrI)	Random effects with no adjustment (phase II studies excluded) – company's preferred NMA Median mean difference (95% CrI)
Compared to placebo		
Erenumab 140 mg	[redacted]	[redacted]
Galcanezumab 120 mg	[redacted]	[redacted]
Fremanezumab 225 mg	[redacted]	[redacted]
Fremanezumab 675 mg	[redacted]	[redacted]
Rimegepant 75 mg	[redacted]	[redacted]
Compared to rimegepant		
Erenumab 140 mg	[redacted]	[redacted]
Galcanezumab 120 mg	[redacted]	[redacted]
Fremanezumab 225 mg	[redacted]	[redacted]
Fremanezumab 675 mg	[redacted]	[redacted]

Abbreviations: CrI, credible interval; CS, company submission; EAG, External Assessment Group; mAbs, monoclonal antibodies; MMDs, monthly migraine days; NMA, network meta-analysis.

Bold text indicates values that are significant at a 5% level.

Figures for the EAG's preferred NMA are from the company's response to clarification question A18 and figures for the company's preferred NMA are from Table 38 of the CS.

3.2.5 Conclusions of the clinical effectiveness section

Evidence submitted to support the clinical efficacy and safety of rimegepant for EM prevention is from one double-blind RCT compared to placebo (with a long-term OLE phase; BHV3000-305). While this study is included as it contributes to the NMA and provides information on adverse events, it is not the focus of the submission as BSC is not included as a comparator in the appraisal for migraine prevention. The EAG considers the RCT to be of good quality; although some areas were flagged as having a potential for risk of bias, there was insufficient information to be certain and the methods used were similar to those of comparator studies in the NMA (Sections 3.2.2 and 3.2.4). Despite the long-term OLE phase being limited by the lack of blinding and lack of a control group, the EAG considers it useful for informing longer term parameters for rimegepant and assessing long-term adverse events in the absence of comparative long-term data. An important difference between the OLE and DBT phase is that patients could take rimegepant as an acute treatment for any migraine events that did occur during this phase (if not already taking a scheduled dose that day), while during the DBT phase other acute treatments were used.

The EAG considers the narrower population (compared to the marketing authorisation and NICE final scope) in the decision problem (patients with EM, at least four MMDs and who have failed three prior preventive drug treatments) to be reasonable given it is a group where existing oral treatments have been exhausted and other treatments recommended for this group are all injectables. However, as migraine attacks can last ≥24 h, the EAG notes that there is a discrepancy between the marketing authorisation population in terms of migraine events (EM with at least four migraine attacks per month) and the decision problem described by the company (EM with at least four MMDs), which is highlighted as a key issue in Section 1.3.2 (Table 7).

Botulinum toxin mentioned in the NICE final scope is not an appropriate comparator as the marketing authorisation and decision problem limit use in the preventive setting to EM. Focus on the group with failures on at least three prior preventive drug treatments also means earlier lines of oral preventives (such as topiramate) are not relevant comparators. The EAG agrees with the company's conclusion that BSC is not an appropriate comparator as the group described in the decision problem would be eligible for the mAbs recommended by NICE (erenumab,[25] fremanezumab[26] and galcanezumab[27]), but the EAG's clinical experts note that in practice only a small proportion of those with EM currently eligible for mAbs may be receiving them due to difficulties accessing specialists and long waiting lists. The EAG's clinical experts are not aware of a large group of patients that

would be contraindicated to mAbs but where rimegepant would be an option if recommended, other than patients that may prefer an oral treatment to injections (Section 2.3.2.3).

The applicability of the RCT to the decision problem is limited as the trial includes a proportion (23%) with CM (which may be more difficult to treat) and also excludes the specific population focused on in the appraisal (those with non-response to more than two preventive treatment classes are excluded). Based on results provided at the clarification stage indicating that results [redacted] compared to the [redacted], and as the trial was not stratified for EM vs CM at randomisation, the EAG agrees that focusing on the overall population of this trial is appropriate (Section 2.3.2.1). The EAG does not agree with the company's assertion that excluding those with failures on more than two preventive treatment classes from the trial is likely to be conservative, particularly as advice from the EAG's clinical experts was that this would be a more difficult to treat group (Section 2.3.2.1). This is a limitation of the clinical evidence highlighted as a key issue (Section 1.3.2, Table 8). However, it is likely to be unresolvable based on the rimegepant data alone as the company state that data was not collected to allow any assessment of how prior treatment failures may affect efficacy in the BHV3000-305 study (i.e., comparing groups with one, two or no prior treatment class failures).

While the appraisal focuses on the ODT formulation of rimegepant, a non-ODT formulation was used in the BHV3000-305 trial. The company describes the two formulations as being bioequivalent[56] and although the EAG's clinical experts raised this as a possible issue in terms of assessing efficacy for the acute treatment setting, there was less concern about the effect on outcomes in the preventive setting given outcomes are measured over a longer time-period to determine efficacy.

There is no direct evidence for comparisons between rimegepant and mAbs, and an NMA was performed to address this. The EAG's preferred analyses include phase II studies, which are excluded from the company's preferred analyses. In addition, while the company selects their preferred models based on a balance between DIC and least complex model, the EAG's preferred analysis for both outcomes is the random effects model adjusted for baseline risk due to uncertainties that exist within the network of evidence (Section 3.2.4.4). However, the conclusions of the EAG's and company's preferred analyses are similar for both outcomes; mAbs and rimegepant have [redacted] vs placebo, which were generally [redacted],

and mAbs [redacted] when compared to rimegepant, with [redacted] varying depending on the outcome and analysis (Section 3.2.4.4).

While the EAG considers the approaches taken by the company to limit uncertainty in the NMA to be appropriate, such as adjustment for baseline risk and alignment of outcome definitions across studies, limitations such as differing treatment histories, inclusion of CM patients in some studies and differences in analysis populations and missing data handling remain (Section 3.2.4.3). This is highlighted as a key issue in Section 1.3.2 (Table 9). These limitations contributed to the EAG's decision to focus on the random effects analysis adjusted for baseline risk. The EAG notes that these issues are unresolvable, particularly given that the only rimegepant trial is limited in terms of how well the population reflects the decision problem and that availability of data for comparator trials is likely to be too limited to better address any remaining concerns. In the absence of an RCT providing direct evidence for rimegepant compared to mAbs, the EAG considers the random effects NMAs with adjustment for baseline risk to provide a reasonable estimate of the efficacy for rimegepant vs mAbs.

The adverse event profile of rimegepant vs placebo in the BHV3000-305 study consists of mostly mild to moderate events in the DBT and OLE phases, with only low rates of severe or serious adverse events occurring [redacted] serious events judged to be related to rimegepant treatment up to 64 weeks. Of specific adverse events in the DBT phase where the rate is higher in the rimegepant group vs placebo, the difference is small, they are likely to be non-severe events and not likely to require a large resource to treat (Section 3.2.3.5).

4 Cost effectiveness

The company's deterministic base case results for acute treatment are given in Table 32. In the company's base case, rimegepant is associated with higher costs and higher quality-adjusted life years (QALYs) compared to best supportive care (BSC), resulting in an incremental cost-effectiveness ratio (ICER) of £17,160 per QALY gained.

Table 32. Company's revised deterministic base case results (acute treatment) (adapted from Table 65 of the company's clarification response)

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)
BSC	£2,396	7.72	-	-	-
Rimegepant	£9,704	8.14	£7,307	0.43	£17,160

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

The company's deterministic base case results for migraine prevention are given in Table 33. In the company's base case, the monoclonal antibodies (mAbs) are associated with higher costs and higher QALYs than rimegepant. Based on willingness-to-pay (WTP) thresholds of £20,000 or £30,000 per QALY, rimegepant could be considered cost-effective compared to each mAb as the ICERs are above these WTP thresholds and the incremental net monetary benefits (NMBs) are negative.

Table 33. Company's revised pairwise deterministic base case results (migraine prevention) (adapted from Table 84 of the company's clarification response)

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)	Inc. NMB (£20,000/ QALY WTP threshold)	Inc. NMB (£30,000/ QALY WTP threshold)
Rimegepant	£19,925	9.033	-	-	-	-	-
Erenumab	£23,134	9.068	£3,209	0.044	£92,671	-£2,516	-£2,170
Rimegepant	£19,925	9.033	-	-	-	-	-
Fremanezumab	£25,201	9.077	£5,276	0.035	£118,883	-£4,388	-£3,945
Rimegepant	£19,925	9.033	-	-	-	-	-
Galcanezumab	£25,987	9.086	£6,062	0.053	£115,211	-£5,010	-£4,484

Abbreviations: ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

4.1 EAG comment on the company's review of cost effectiveness evidence

4.1.1 Acute migraine treatment

The company carried out a systematic literature review (SLR), using a single search strategy, to identify existing:

- Economic evaluations for the treatment of acute migraines;
- Health-related quality of life (HRQoL) evidence (health-state utility values [HSUVs]) in the acute treatment of migraines; and,
- Cost and resource use evidence for the treatment of acute migraines conducted in the UK.

Searches were initially run in November 2021 and were last updated in March 2022. A summary of the EAG's critique of the methods implemented by the company to identify relevant evidence is

presented in Table 34. Due to time constraints, the EAG was unable to replicate the company's searches and appraisal of identified abstracts.

Table 34. EAG's critique of company's systematic literature review (acute treatment)

SLR step	Section of CS in which methods are reported			EAG assessment of robustness of methods
	Cost effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Data sources	Section 1.1 A of Appendix G	Section 1.1 A of Appendix G	Section 1.1 A of Appendix G	**Appropriate.** Electronic databases included: MEDLINE, MEDLINE In-Process, MEDLINE Epub Ahead of Print and Embase (searched separately via the Ovid SP platform), and HTAD and NHS EED (searched simultaneously through the CRD platform). The company manually searched major health economic conferences from the last two years and the EAG considers the date limit to be reasonable as any high-quality studies reported in abstract form before 2019 are likely to have been published in a peer-reviewed journal. The company also searched HTA websites (AWMSG, NCPE, NICE and SMC) and economic databases (CEA registry, EQ-5D publications database and ScHARRHUD) for HSUVs and cost-effectiveness analyses, to ensure that no relevant publications were missed.
Search terms	Table 39-44 Section 1.1 A of Appendix G	Table 39-44 Section 1.1 A of Appendix G	Table 39- 44 Section 1.1 A of Appendix G	**Appropriate.** For all applicable searches the search terms to capture economic studies are based on the validated SIGN filter set, with the addition of extra terms from other sources including the CADTH and NHS EED. The search terms for the Embase database (Table 40) are presented alongside bullets instead of numbers which makes the combined and final hits difficult to validate.
Inclusion criteria	Table 45 in Section 1.2.3 A of Appendix G	Table 62 in Section 1.1 A of Appendix H	Table 68 in Section 1.1 A of Appendix I	**Appropriate.** The EAG considers that the company could have broadened the inclusion criteria to identify HRQoL data by including migraine specific QoL measures (i.e., MSQ). This data could

				have then been used to validate the MSQ data used to inform the economic analysis.
Screening	Section 1.2 and 2.1 A of Appendix G	Section 1.2 of Appendix G and 2.1 A of Appendix H	Section 1.2 of Appendix G and 2.1 A of Appendix I	**Appropriate.**
Data extraction	Table 48 in Section 2.2 A of Appendix G	Table 64 in Section 2.2 A of Appendix H	Table 70 in Section 2.2 A of Appendix I.	**Appropriate.** For the economic evaluations review, five of the six unique included studies were extracted. One study was not extracted as the results were only presented graphically. For the HRQoL review, six of the nine unique studies were extracted. Utility values were not elicited directly from patients in one study and utility scores were determined using the QWS in two studies. These were deprioritised for extraction as values are not as applicable to the appraisal than those elicited directly from patients via EQ-5D questionnaire.
QA of included studies	Table 49 in Section 2.2 A of Appendix G using the Drummond checklist	No QA checklist completed, but uncertainty (limitations) around the utility values is provided.	No QA checklist completed, but uncertainty (limitations) around the analysis and the applicability to clinical practice in England is provided.	**Appropriate.**

Abbreviations: AWMSG, All Wales Medicines Strategy Group; CADTH, Canadian Agency for Drugs and Technologies in Health; CEA, cost-effectiveness analysis; CRD, University of York's Centre for Reviews and Dissemination; CS, company submission; EAG, External Assessment Group; HRQoL, health-related quality of life; HSUVs, health state utility values; HTA, Health Technology Assessment; HTAD, Health Technology Assessment Database; MSQ, Migraine Specific Questionnaire; NCPE, National Centre for Pharmacoeconomics; NHS EED, National Health Service Economic Evaluation Database; NICE, National Institute for Health and Care Excellence; QA, quality assessment; QWS, Quality of Wellbeing Scale; ScHARRHUD, University of Sheffield School of Health and Related Research Health Utilities Database; SIGN, Scottish Intercollegiate Guidelines Network; SLR, systematic literature review; SMC, Scottish Medicines Consortium.

The SLR identified a total of 2,545 records with 1,628 retrieved from electronic databases and 917 identified through supplementary searches. A total of 23 publications from 18 unique studies were included in the SLR as being relevant to one or more of the three types of evidence the SLR aimed to identify. This included: 7 cost-effectiveness papers (6 unique studies), 10 HRQoL papers (9 unique studies) and 7 cost papers (4 unique studies). Only primary publications were extracted.

The EAG notes that three of the six unique cost-effectiveness studies (Atlas *et al.* 2020 [ICER evidence report][52], Johnston *et al.* 2021[54] and Touchette *et al.* 2020[53]) assessed rimegepant for the acute treatment of migraine in the USA, thus, none considered the NHS perspective. All three studies considered cycle lengths of 48 hours and a time horizon of two years, and none appear to incorporate reductions in monthly migraine day (MMD) frequency. The key differences between these modelling assumptions and the company's modelling assumptions are discussed further in Sections 4.2.4.1 and 4.2.5.1.

Of the six extracted and unique HRQoL studies, five reported EQ-5D values directly and one reported Migraine Specific Questionnaire (MSQ) values mapped to EQ-5D. One of these studies was used to inform the base case (Stafford *et al.* 2012[86]) and one (Xu *et al.* 2011[87]) was explored in scenario analysis. The EAG also notes that Xu *et al.* 2011 was used to inform utility data in the ICER evidence report. Please refer to Section 4.2.11.1 for further details on the HRQoL data applied in the model.

The company considered none of the four cost papers to be useful to inform the economic analysis: Harris *et al.* 2021[88] did not report baseline characteristics; Irimia *et al*. 2020[89] did not report the cost year and presented costs in Euros; Southwell and Afridi 2021[90] included 16- and 17-year-olds; and Stafford *et al.* 2012[86] was inadequately detailed. However, the EAG does not consider this to be a major issue as the company reviewed previous migraine appraisals to identify UK-specific healthcare resource use (HCRU) data. Please refer to Section 4.2.12.1 for further details on the cost and resource use data applied in the model.

4.1.2 Migraine prevention

The company carried out a SLR, using a single search strategy, to identify existing:

- Economic evaluations for the prevention of migraines;
- HRQoL evidence (HSUVs) in the prevention of migraines; and
- Cost and resource use evidence in the prevention of migraines conducted in the UK.

Searches were initially run in November 2021 and were last updated in February 2022. A summary of the EAG's critique of the methods implemented by the company to identify relevant evidence is presented in Table 35. Due to time constraints, the EAG was unable to replicate the company's searches and appraisal of identified abstracts.

Table 35. EAG's critique of company's systematic literature review (migraine prevention)

SLR step	Section of CS in which methods are reported			EAG assessment of robustness of methods
	Cost effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Data sources	Section 3.1 P of Appendix G	Section 3.1 P of Appendix G	Section 3.1 P of Appendix G	Electronic databases included: MEDLINE, MEDLINE In-Process, MEDLINE Epub Ahead of Print and Embase (searched separately via the Ovid SP platform), and HTAD and NHS EED (searched simultaneously through the CRD platform). The company manually searched major health economic conferences from the last two years and the EAG considers the date limit to be reasonable as any high-quality studies reported in abstract form before 2019 are likely to have been published in a peer-reviewed journal. The company also searched HTA websites (AWMSG, NCPE, NICE and SMC) and economic databases (CEA registry, EQ-5D publications database and ScHARRHUD) for HSUVs and cost-effectiveness analyses, to ensure that no relevant publications were missed.
Search terms	Table 50-55 Section 3.1.1 P of Appendix G	Table 50-55 Section 3.1.1 P of Appendix G	Table 50-55 Section 3.1.1 P of Appendix G	**Appropriate.** For all applicable searches the search terms to capture economic studies are based on the validated SIGN filter set, with the addition of extra terms from other sources including the CADTH and NHS EED.
Inclusion criteria	Table 56 in Section 3.2.3 P of Appendix G	Table 65 in Section 3.1 P of Appendix H	Table 71 in Section 3.1 P of Appendix I	**Appropriate.** It is unclear if the company is only considering adults with migraine who require preventative treatment as the population considers (all) adults with migraine in the inclusion criteria. For the economic evaluations review, the company could have considered topiramate, propranolol and valproate (as per the TA682 SLR and NICE final scope), and candesartan, as additional interventions. However, the EAG does not consider this to be a major issue as the company has included interventions and

				comparators in line with the interventions and comparators included in their economic analysis. The EAG also notes that the company could have broadened the inclusion criteria in the HRQoL review to identify HRQoL data by including migraine specific QoL measures (e.g., MSQ). This data could have been used to validate the MSQ data used to inform the economic analysis.
Screening	Section 3.2 P and 4.1 P of Appendix G	Section 3.2 P of Appendix G and 4.1 P of Appendix H	Section 3.2 of Appendix G and 4.1 P of Appendix I	**Appropriate.**
Data extraction	Table 59 in Section 4.2 A of Appendix G	Table 67 in Section 4.2 P of Appendix H	Table 73 in Section 4.2 P of Appendix I.	**Appropriate.** For the economic evaluations review, 17 unique studies from 27 publications were extracted, but it is unclear if all relevant publications were considered for each extraction, or if only the results from one publication were chosen. For the HRQoL review, 10 of the 11 unique studies were extracted. Utility values were not elicited directly from patients from one study. This study was deprioritised for extraction as values are not as applicable to the appraisal than those elicited directly from patients via EQ-5D questionnaire. The EAG also notes that the extraction from Batty *et al.* 2013 is missing.
QA of included studies	Table 60 and 61 in Section 4.2 A of Appendix G using the Drummond checklist	No QA checklist completed, but uncertainty (limitations) around the utility values is provided.	No QA checklist completed, but uncertainty (limitations) around the analysis and the applicability to clinical practice in England is provided.	**Appropriate.**

Abbreviations: AWMSG, All Wales Medicines Strategy Group; CADTH, Canadian Agency for Drugs and Technologies in Health; CEA, cost-effectiveness analysis; CRD, University of York's Centre for Reviews and Dissemination; CS, company submission; EAG, External Assessment Group; HRQoL, health-related quality of life; HSUVs, health state utility values; HTA, Health Technology Assessment; HTAD, Health Technology Assessment Database; MSQ, Migraine Specific Questionnaire; NCPE, National Centre for Pharmacoeconomics; NHS EED, National Health Service Economic Evaluation Database; NICE, National Institute for Health and Care Excellence; QA, quality assessment; ScHARRHUD, University of

Sheffield School of Health and Related Research Health Utilities Database; SIGN, Scottish Intercollegiate Guidelines Network; SLR, systematic literature review; SMC, Scottish Medicines Consortium.

The SLR identified a total of 2,247 records with 1,281 retrieved from electronic databases and 981 identified through supplementary searches. Of this a total of 41 publications from 24 unique studies were included in the SLR as being relevant to one or more of the three types of evidence the process aimed to identify. This included: 27 cost-effectiveness papers (17 unique studies), 19 HRQoL papers (11 unique studies) and 8 cost papers (3 unique studies). Only primary publications were extracted.

The EAG notes that eight of the 17 unique cost-effectiveness studies considered the NHS perspective, four were NICE TAs in migraine prevention (TA260, TA764/TA631, TA659 and TA682) and none included rimegepant as a preventative treatment.[14, 25-27] The most common time horizon used was 10-years, with a range of 1- to 3-month cycles. The hybrid decision-tree plus Markov model structure described by Mahon *et al.* 2021[91] was designed based on expert consultation and systematic review of clinical practice guidelines and has been adopted in prior TAs in migraine prevention. The company deemed this structure to be the most relevant to the current decision problem and used it to inform the economic model of rimegepant in migraine prevention. The key differences between these modelling assumptions and the company's modelling assumptions are discussed further in Sections 4.2.4.2 and 4.2.5.2.

Of the 10 extracted (nine provided as Batty *et al*. 2013[92] is missing) and unique HRQoL studies, two reported EQ-5D values data directly, one collected data from the Health Utilities Index (HUI)-3 and reported values mapped to the EQ-5D, one elicited utility values using a time trade-off (TTO) task and five reported EQ-5D values mapped from the MSQ or Headache Impact Test (HIT)-6. These studies were not used to inform the base case as the company elicited MSQv2 data from the key clinical trial of rimegepant (study BHV3000-305). Please refer to Section 4.2.11.2 for further details on the HRQoL data applied in the model.

The company considered the cost and resource use data in the recent NICE appraisals for migraine prevention to be more appropriate to inform the economic analysis than the three included cost papers. Please refer to Section 4.2.12.2 for further details on the cost and resource use data applied in the model.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 36 summarises the EAG's appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base-case analysis, with reference to the NICE final scope outlined in Section 2.3.

Table 36. NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission	
		Acute migraine	Migraine prevention
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes.	Yes.
Perspective on costs	NHS and PSS	Yes.	Yes. Lost productivity costs considered in sensitivity analysis.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes.	Yes.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The company used a 20-year time horizon. The EAG considers the company's long-term modelling assumptions regarding reductions in MMD to be too uncertain to accurately capture the costs and consequences over a 20-year time horizon. Shorter time horizons (2 years) have been adopted in other economic evaluations for the treatment of acute migraines.	Yes (20 years).
Synthesis of evidence on health effects	Based on systematic review	Yes.	Yes.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Health effects were expressed in QALYs. Study BHV3000-201 included MSQv2 responses from patients which the company mapped to EQ-5D utilities, to inform the baseline utility. HSUVs by migraine pain severity were obtained from the	Health effects were expressed in QALYs. The EQ-5D does not appear to be appropriate to measure HRQol in this population as patients may not have a migraine when they complete the EQ-5D. The

		literature and patients completed the EQ-5D-3L in these studies.	MSQ is preferred as it has a 4-week recall period. Study BHV3000-305 included MSQv2 responses from patients which the company mapped to EQ-5D utilities.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes.	Yes.
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Yes. MSQv2 was mapped to EQ-5D-3L utilities using a validated algorithm developed by Gillard *et al.* 2012, which uses a UK valuation set.[93] HSUVs from Stafford *et al*. 2012 were also valued using a UK tariff.[86]	Yes. MSQv2 was mapped to EQ-5D-3L utilities using a validated algorithm developed by Gillard *et al.* 2012, which uses a UK valuation set.[93]
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.	Yes.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	The company estimated HCRU from a retrospective study of patients from France, Germany, Italy, Spain, and the UK included in the NHWS (Vo *et al.* 2018[94]). This study was used to inform the fremanezumab submission (TA631/TA764[26]). Unit costs were derived from the BNF, PSSRU and NHS References Costs.[95-97]	The company utilised HCRU estimates accepted in previous NICE appraisals in migraine prevention (TA631/TA764[26] and TA682[25]), these estimates were obtained from the NHWS. Unit costs were derived from the BNF, PSSRU and NHS References Costs.[95-97]
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes	Yes.

Abbreviations: BNF, British National Formulary; EAG, External Assessment Group; HCRU, healthcare resource use; HRQoL, health-related quality of life; HSUVs, health state utility values; MSQ, Migraine Specific Questionnaire; NHS, national health service; NHWS, National Health and Wellness Survey; PSS, personal social services; QALY, quality adjusted life year

4.2.2 Population

The population considered in the NICE final scope consists of adults with migraine.[49] The company focuses on two specific patient populations within this, which will be referred to briefly as "acute migraine" and "migraine prevention". The proposed target populations are narrower than the NICE final scope and marketing authorisation because of their relevance to NHS clinical practice. These two target populations are described in turn below.

4.2.2.1 Acute migraine treatment

The economic analysis considers adults with migraine who have had inadequate symptom relief after trials of at least 2 triptans or in whom triptans are contraindicated or not tolerated; and have inadequate pain relief with NSAIDs and paracetamol. This population is narrower than the marketing authorisation which considers the acute treatment of migraine with or without aura in adults. However, the EAG and the EAG's clinical experts consider the narrower population to be reasonable, particularly as it is a group with high unmet need as other treatment options have been exhausted.

To inform the economic analysis, the company used clinical effectiveness data from three acute randomised controlled trials (RCTs) (study BHV3000-301, -302, and -303) and a long-term safety study (BHV3000-201). The three acute RCTs were pooled and informed response (pain relief at 2 hours) and pain trajectories, while the long-term safety study informed the baseline patient characteristics (including the baseline utility and baseline MMD distribution), and long-term outcomes (treatment discontinuation and the frequency of MMDs with rimegepant).

All of these studies enrolled a mix of patients with and without triptan failure and the company originally used clinical effectiveness data from the subgroup of patients with at least 2 triptans failures to inform the economic analysis. However, only 9.3% (325/3,507) and [redacted] had discontinued at least 2 triptans in the three acute pooled RCTs and long-term safety study, respectively.

As discussed in Section 2.3.1.1, the EAG considers the full trial population to be more relevant and more robust than the subgroup of patients who previously failed 2 triptans in the trials. Moreover, the results demonstrate no large differences in results for most outcomes between subgroups and the mITT analyses. Therefore, during clarification, the EAG requested that the company used the clinical effectiveness data from the mITT population to inform the economic analysis. The company

updated their economic analysis to include results from the mITT population but maintained the subgroup of patients with at least 2 triptan failures as their base case.

Based on the mITT population, the company reported an ICER of £16,312 for rimegepant vs BSC, which is less than the base case ICER based on the subgroup with at least 2 triptan failures (£17,160). The EAG notes that even though response in the mITT population (pain relief at 2 hours) [redacted] of rimegepant vs BSC (mean percentage points difference of [redacted] in the mITT population vs [redacted] in the subgroup with at least 2 triptan failures) the ICER does not increase given that the patient characteristics in the mITT population (technically the "all-comer" population based on study BHV3000-201) lead to a [redacted] per 48-hour cycle for rimegepant ([redacted] in the mITT population vs [redacted] in the subgroup with at least 2 triptan failures).

The EAG also requested the company to provide results including a fourth acute RCT; study BHV3000-310, which is like the other acute RCTs but focuses on Chinese and Korean patients and is a second study (alongside BHV3000-303) using the ODT formulation of rimegepant. As explained in Section 3.1.2, the EAG did not agree that it being in an Asian population was a reason for exclusion from the company's original analysis. When this study was added to the company's analysis, the ICER for rimegepant vs BSC in the mITT population increased from £16,312 to £19,285 (triptan failure status not recorded in study BHV3000-310). Given that the mean percentage points difference in pain relief at 2 hours between rimegepant and BSC is [redacted] when study BHV3000-310 is included ([redacted] including study BHV3000-310 vs [redacted] excluding study BHV3000-310), the EAG suspects the increase in the ICER is due to the [redacted] pain trajectories observed in BSC non-responders when study BHV3000-310 is included. Baseline patient characteristics are still based on study BHV3000-201 and therefore the reduction in MMD frequency per 48-hour cycle for rimegepant is [redacted], whether study BHV3000-310 is included or excluded. However, further clarification from the company to explain the direction of the ICER would be helpful.

Detailed cost-effectiveness results arising from these scenarios are provided in Table 37.

Table 37. Results of scenario analysis provided by the company at the clarification stage changing the population informing the acute model

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)
Company's revised base case (subgroup with at least 2 triptan failures)					

BSC	£2,396	7.72	-	-	-
Rimegepant	£9,704	8.14	£7,307	0.43	£17,160
mITT population excluding study BHV3000-310					
BSC	£2,206	8.41	-	-	-
Rimegepant	£6,360	8.67	£4,154	0.25	£16,312
mITT population including study BHV3000-310					
BSC	£2,018	8.55	-	-	-
Rimegepant	£6,368	8.78	£4,350	0.23	£19,285

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; mITT, modified intention-to-treat; QALYs, quality-adjusted life years.

Throughout the remainder of this report, the EAG will report inputs and results for the company's base case population (subgroup of patients with at least 2 triptans failures) and the EAG's preferred population (mITT population including study BHV3000-310).

The baseline patient characteristics included in the economic analysis are given in Table 38. Values applied in the revised base case are highlighted in bold. During the clarification stage, the company explained that the long-term study should be used to inform the baseline patient characteristics in the economic analysis as it includes a broader inclusion criterion and likely reflects a population more similar to the real-world migraine population eligible for rimegepant than the acute RCTs.

The EAG notes that the long-term open-label study is similar to the acute pooled RCTs in terms of inclusion criteria but there was one notable difference; patients with a higher number of moderate to severe migraine attacks per month could be included (2 to 14 rather than 2 to 8 in the RCTs). The EAG also notes that the SmPC[1] for rimegepant is not limited to the acute treatment of episodic migraines (EMs) despite the three acute RCTs only including patients with less than 15 monthly headache days. The implications of this are discussed further in Section 4.2.6.2.

In the economic analysis, age and sex were used to calculate all-cause mortality (see Section 4.2.10). Baseline migraine attacks per month, number of triptan failures, prior prophylactic use and the proportion of moderate baseline pain (vs severe) were included in the regression model to calculate the frequency of migraine attacks with rimegepant (see Section 4.2.7.1.3). Age, sex, baseline migraine attacks per month and the number of triptan failures were included in the regression model to estimate baseline utility (see Section 4.2.11.1). Baseline migraine attacks per month and the proportion of moderate baseline pain (vs severe) were included in the quality-adjusted life hour (QALH) regression analysis (see Section 4.2.11.1).

Table 38. Baseline patient characteristics included in the revised acute model

Patient characteristic	Study BHV3000-201		Pooled acute RCTs	
	mITT population ("all-comers")	Subgroup with at least 2 triptan failures	mITT population including study BHV3000-310	Subgroup with at least 2 triptan failures
Age (years)	[redacted]	[redacted]	[redacted]	[redacted]
Sex (% female)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline migraine attacks per month (mean)	[redacted]	[redacted]	[redacted]	[redacted]
Proportion with prior prophylactic use	[redacted]	[redacted]	NR	NR
Proportion of moderate baseline pain (vs severe)	NR	NR	[redacted]	[redacted]
Proportion with one triptan failure	[redacted]	[redacted]	[redacted]	[redacted]
Proportion with at least 2 triptan failures	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: mITT, modified intention-to-treat; NR, not reported; RCT, randomised controlled trial
Values applied in the revised base case are highlighted in bold.

Cost-effectiveness results were not presented for any subgroups. However, the EAG does not consider this to be an issue given that a consistent treatment effect was observed in the subgroups and that the only factor that was stratified at randomisation was use of preventative migraine treatment. Based on the limited subgroup results available from each trial for prophylactic use vs no prophylactic medication provided to the EAG at the clarification stage (pain freedom at 2 hours and freedom from MBS at 2 hours), the EAG is not concerned that one of these subgroups should be favoured and that use of the full population is appropriate. For a detailed discussion of the subgroups presented by the company, see Sections 2.3.1.5 and 3.1.3.7.

4.2.2.2 Migraine prevention

The economic analysis considers adults with EM who have at least four migraine days per month but fewer than 15 headache days per month, and have failed three or more conventional preventive therapies. This target population is narrower than the marketing authorisation, which considers adults with EM who have at least four migraine attacks per month.

The EAG considers it important to note that one migraine attack can last up to 72 hours, thus, one migraine attack per month could equal up to three MMDs. As such, the population specified in the decision problem (based on MMDs) may therefore be slightly broader than the marketing authorisation (based on migraine attacks). This is highlighted as a key issue in Section 1.3.2. Aside

from this, the EAG and the EAG's clinical experts consider the narrower population to be reasonable, particularly as there is greater unmet need for patients who fail to respond to conventional preventive therapies. The company's target population is also consistent with the BASH guidelines[98] and recent NICE recommendations for the comparator treatments (monoclonal antibody [mAb] calcitonin gene-related peptide [CGRP] antagonists – erenumab 140 mg [TA682], galcanezumab [TA659] and fremanezumab [TA631/TA764]).[25-27]

The company used clinical effectiveness data for rimegepant from the mITT population of study BHV3000-305 to inform the economic analysis, alongside the results of a network meta-analysis (NMA). Study BHV3000-305 was used to inform baseline characteristics, MMD distribution at baseline, MMD distribution over the assessment period, utility values, and long-term outcomes (treatment discontinuation and MMD distribution after the assessment period), while the NMA was used to inform response at 9-12 weeks. The response rate for the baseline treatment in the NMA (rimegepant) was also taken from study BHV3000-305.

A key difference between study BHV3000-305 and the marketing authorisation and target population is the inclusion of patients with chronic migraine (CM) (23%). According to the company, it was not possible to restrict the analysis to the episodic-only subgroup without breaking randomisation, as this was not a pre-specified stratification factor for randomisation in study BHV3000-305. However, as noted in Section 2.3.2.1, the EAG's clinical experts consider CMs more difficult to treat that than EMs due to secondary sensitisation and medication overuse. To address these concerns, the company provided a within-trial analysis at the clarification stage. As discussed in Section 2.3.2.1,

[redacted]. Baseline characteristics between the two groups were [redacted]. The company subsequently concluded that they did not anticipate having a full episodic population to an impact on the cost-effectiveness results and the EAG is generally in agreement with the company.

An additional and related area of concern is that the means MMDs in the observation period and number of moderate to severe attacks per month are higher than what would be seen for episodic patients in UK practice due to the inclusion of some patients with CM. As such, study BHV3000-305

represents a population with a higher migraine burden compared to EM patients, which may subsequently affect cost-effectiveness results (see Section 4.2.6.2).

The EAG also notes that [redacted] and [redacted] of rimegepant patients included in study BHV3000-305 were receiving concurrent preventative treatment at randomisation and prior to enrolment, respectively. Nevertheless, data specific to the number of treatment failures is not available from the trial (as described as a limitation in Section 1.3.2). The EAG, therefore, considers the mITT population to be appropriate to estimate cost-effectiveness. The EAG's clinical experts also advised that if patients are offered a new class of treatment (rimegepant) then the number of prior failures would only have a nominal impact in the results.

However, if migraines do not respond to multiple classes of preventative drugs, the EAG's clinical experts have noted that this may indicate refractory migraine, which may be more difficult to treat with new drug classes such as rimegepant.

[redacted]. However, in the absence of data comparing refractory and non-refractory rimegepant patients, the EAG is unable to predict what impact including patients with refractory migraine would have on the cost-effectiveness results with certainty. For further discussion of this issue, see Section 2.3.2.1.

The baseline age (mean 41 years) and sex (82.5% female) inputs in the economic analysis were taken from study BHV3000-305 and used to calculate all-cause mortality (see Section 4.2.10). The distribution of MMD at baseline (mean 10.046) is discussed in Section 4.2.6.2.

Cost-effectiveness results were not presented for any subgroups. As noted in Sections 2.3.2.5 and 3.2.3.6, the only factor that was stratified at randomisation was use of preventative migraine treatment. However, the subgroup using a preventative migraine treatment at randomisation was [redacted] (≥50% reduction in baseline MMD outcome), which makes it difficult to draw any meaningful conclusions. For a greater discussion of the subgroups presented by the company, see Section 2.3.2.5 and 3.2.3.6.

4.2.3 Interventions and comparators

4.2.3.1 Acute migraine treatment

4.2.3.1.1 Intervention

The economic analysis investigates the cost-effectiveness of rimegepant (VYDURA®) 75 mg *pro re nata* (PRN, as needed); a small molecule, orally administered CGRP antagonist. As per the SmPC, rimegepant is indicated for the acute treatment of migraine.[1]

The phase III, BHV3000-303 study assessed the safety and efficacy of the rimegepant orally dispersible tablet (ODT) formulation, while the two phase III, BHV3000-301 and BHV3000-302 studies assessed the safety and efficacy of the rimegepant oral tablet formulation. These studies offered a single dose of rimegepant 75 mg to treat a migraine attack of moderate or severe intensity. The long-term, open-label, safety study, BHV3000-201, assessed the safety and tolerability of the rimegepant 75 mg oral tablet. In this study, rimegepant was offered to patients in two PRN groups at onset of mild, moderate or severe migraine; patients could take up to 1 tablet per day for up to 52 weeks.

According to the company, the ODT formulation is bioequivalent to the oral tablet formulation,[56] and the ODT formulation can be advantageous for patients who want quick relief and/or have nausea or vomiting and do not want to drink liquids or would otherwise prefer to avoid swallowing a tablet. During the clarification stage, the company confirmed, if recommended, it would be the ODT formulation of rimegepant that is available to patients (and the tablet formulation is not planned to be made available).

EAG comment

The EAG consulted with its clinical experts who advised that the efficacy may differ with different formulations of rimegepant, as can be observed for other acute migraine treatments in clinical practice. To address this concern, the company was asked, for the mITT population, to provide pooled results from trials using the ODT formulation only and to comment on whether these are comparable to when all trials, regardless of formulation, are included. As discussed in Sections 2.3.1.2, 3.1.2 and 3.1.3, the company found that the ODT formulation may have contributed to a slightly higher percentage of patients receiving pain relief at 2 hours than compared to the combined tablet and ODT formulation pooled analysis. However, when the ODT formulation results were applied in the economic analysis, the ICER in the mITT population (including studies BHV3000-

303 and 310) was £22,645, which is higher than the ICER in the mITT population including all acute RCTs (£19,285). The total costs and QALYs resulting from these analyses are provided in Table 39.

The EAG suspects the increase in the ICER is due to smaller additional benefits in pain trajectories from rimegepant vs BSC observed in the ODT studies and the resulting QALH regression. Baseline patient characteristics are still based on study BHV3000-201 and therefore the reduction in MMD frequency per 48-hour cycle for rimegepant is [redacted], whether the tablet formulation is included or excluded. However, clarification from the company would be helpful to better understand the direction of the ICER.

Table 39. Results of scenario analysis provided by the company at the clarification stage regarding the formulation of rimegepant informing the acute model

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)
mITT population including study BHV3000-310 (combined tablet and ODT formulation pooled analysis)					
BSC	£2,018	8.55	-	-	-
Rimegepant	£6,368	8.78	£4,350	0.23	£19,285
mITT population including studies BHV3000-310 and -303 (ODT formulation studies only)					
BSC	£2,204	8.77	-	-	-
Rimegepant	£6,702	8.97	£4,499	0.20	£22,645

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; mITT, modified intention-to-treat; ODT, orally dispersible tablet; QALYs, quality-adjusted life years.

4.2.3.1.2 Comparator

The comparators listed in the NICE final scope[49] are:

- Paracetamol, with or without an anti-emetic;
- An NSAID, with or without an anti-emetic;
- An oral or non-oral triptan, with or without an anti-emetic;
- Paracetamol with an oral or non-oral triptan, with or without an anti-emetic;
- An NSAID with a triptan, with or without an anti-emetic; and,
- Best supportive care (BSC).

However, the company based their analysis of rimegepant against a comparison of BSC only given that the target population for rimegepant is in those who have exhausted all available acute treatment options (triptans, NSAIDs, paracetamol, and combinations thereof), thus leaving BSC as

the only relevant comparator. The company used the placebo arms in the pooled acute RCTs to approximate BSC (matching placebo with rescue medication permitted after 2 hours; rescue medication was paracetamol, aspirin, ibuprofen, NSAIDs, antiemetics or baclofen).

EAG comment

The EAG's clinical experts affirmed that the placebo arms were generally representative of BSC and the EAG agrees with the company that BSC is the appropriate comparator for the economic analysis.

As noted in Section 4.2.12.1.1, no acquisition costs are incurred by patients receiving BSC, and the EAG considers this to be conservative assumption.

4.2.3.2 Migraine prevention

4.2.3.2.1 Intervention

The economic analysis investigates the cost-effectiveness of rimegepant (VYDURA®) 75 mg every other calendar day (EOD); a small molecule, orally administered CGRP antagonist. As per the SmPC, rimegepant is indicated for the preventative treatment of EM.[1]

The phase II/III BHV3000-305 study assessed the safety and efficacy of the rimegepant 75 mg oral tablet formulation. In this study, rimegepant was offered EOD during a 12-week double-blind treatment phase and a 52-week open-label extension (OLE) phase. During the OLE phase, participants were instructed to take 1 tablet of rimegepant 75 mg EOD. If participants had a migraine on a day that they were not scheduled to dose with rimegepant, they could take 1 tablet of rimegepant 75 mg on that calendar day to treat a migraine. Therefore, during the OLE phase, participants could take a maximum of 1 rimegepant 75 mg tablet per calendar day for this 52-week period.

EAG comment

The EAG notes that although the marketing authorisation and submission is focused on the ODT formulation, the only included trial for the preventive setting is study BHV3000-305, which is based on a tablet formulation. Although the EAG's clinical experts raised this as a possible issue in terms of assessing efficacy for the acute treatment setting (where efficacy was measured at a time-point of 2 hours), there was less concern about the effect on outcomes in the preventive setting given outcomes are measured over a longer time period in this setting to determine efficacy. Furthermore,

based on the subgroup results conducted by the company on the acute RCTs (see Section 4.2.2.1), the EAG is satisfied that using efficacy data on the tablet formulation will not introduce bias in favour of rimegepant.

4.2.3.2.2 Comparator

The comparators listed in the NICE final scope[49] are:

- Oral preventive treatments (such as topiramate, propranolol, amitriptyline);
- Erenumab (4 or more migraine days per month and after at least 3 preventive drug treatments have failed);
- Galcanezumab (4 or more migraine days per month and after at least 3 preventive drug treatments have failed);
- Fremanezumab (in CM and after at least 3 preventive drug treatments have failed);
- Botulinum toxin type A (in CM that has not responded to at least 3 prior pharmacological prophylaxis therapies); and,
- BSC.

The company excluded botulinum toxin type A as a comparator, as the NICE recommendation is limited to CM (TA260).[14] The company also excluded BSC, as the target population would be eligible to receive one of the injectable mAbs recommended by NICE.

In February 2022, NICE updated their guidance on fremanezumab (TA764) to align the with the recommendation for erenumab and galcanezumab (i.e. 4 or more migraine days per month and after at least 3 preventive drug treatments have failed).[26] Following this, the company considered fremanezumab, erenumab and galcanezumab to be relevant comparators in the preventative setting. These three comparators are injectable mAb CGRP antagonists. Rimegepant is a next-generation, oral, selective, and potent small molecule CGRP receptor antagonist. These differences are important when making class-specific assumptions to inform the economic analysis.

Two regimens of fremanezumab are recommended by NICE: 225 mg monthly and 775 mg every three months (quarterly). Both regimens were included in the company's NMA, but the company adopted the results using the 225 mg monthly regimen in the economic analysis. According to the company, the 225 mg monthly regimen is more frequently prescribed and its NMA estimate numerically favours fremanezumab (odds ratio for the proportion achieving 50% reduction from baseline MMD reported in the CS: 225 mg vs rimegepant and 675 mg vs rimegepant, [redacted] and [redacted],

respectively). Monthly dosing also allows consistency of dosing across the mAbs in the economic analysis.

For erenumab, the modelled dose reflected the dose recommended by NICE in TA682 (140 mg).[25] For galcanezumab, the modelled dose reflected the dose recommended in the BNF (120 mg monthly dose after a 240 mg initial loading dose), which aligns with clinical trial evidence informing TA659.[27, 97] The EAG also notes that these doses reflect the clinical trials informing the NMA.

EAG comment

The EAG agrees that, in the preventive setting, the population rimegepant is positioned for use in (EM with ≥4 MMDs that have failed on at least three oral preventives) rules out oral preventive treatments and botulinum toxin type A as comparators. The EAG's clinical experts have also advised that there is not a large group within the specified population that would be ineligible for mAbs but eligible for rimegepant. Based on this, the EAG agrees that BSC is not a relevant comparator for the appraisal and if recommended, rimegepant is an option only where mAbs would also be considered.

The EAG heard from its clinical experts that the decision to offer 225 mg monthly and 775 mg quarterly is usually a commissioning decision. However, if both doses were available to clinicians, the 225 mg monthly regimen may be more frequently prescribed at the beginning of treatment to monitor adverse events. The EAG's clinical experts also supported the company's view that the two regimens are equally effective. The EAG also notes that both regimens incur the same quarterly acquisition cost as both regimens require three 225 mg injections (3 x £450 = £1,350). However, 10% of patients are assumed not to self-administer and incur a cost for nurse time at every administration (£2.10). As such, the company has assigned a higher administration cost to fremanezumab by modelling the more frequent regimen (£6.30 per quarter vs £2.10 per quarter). Nevertheless, the EAG considers the difference in administration cost and response between the two regimens to have a negligible impact on the cost effectiveness results.

Overall, the EAG considers the comparators included in the economic analysis to be appropriate.

4.2.4 Modelling approach and model structure

The company provided two economic models in their submission as some outcomes differed between the two target populations. The modelling approach and model structure applied to each of these populations is described in turn below.

4.2.4.1 Acute migraine treatment

The company developed a *de novo* cost-effectiveness model in Microsoft Excel to evaluate the incremental cost-utility of rimegepant versus BSC, in the acute treatment of adults with migraine. The company stated that the structure of the model is consistent with the proposed clinical care pathway for rimegepant and was informed by the ICER evidence report. ICER assessed the cost-effectiveness of novel acute therapies in migraine in the USA (rimegepant, lasmiditan and ubrogepant).[52] A key difference in this model compared to the ICER model, is the incorporation of potential reduction in migraine frequency of acute treatment with rimegepant.

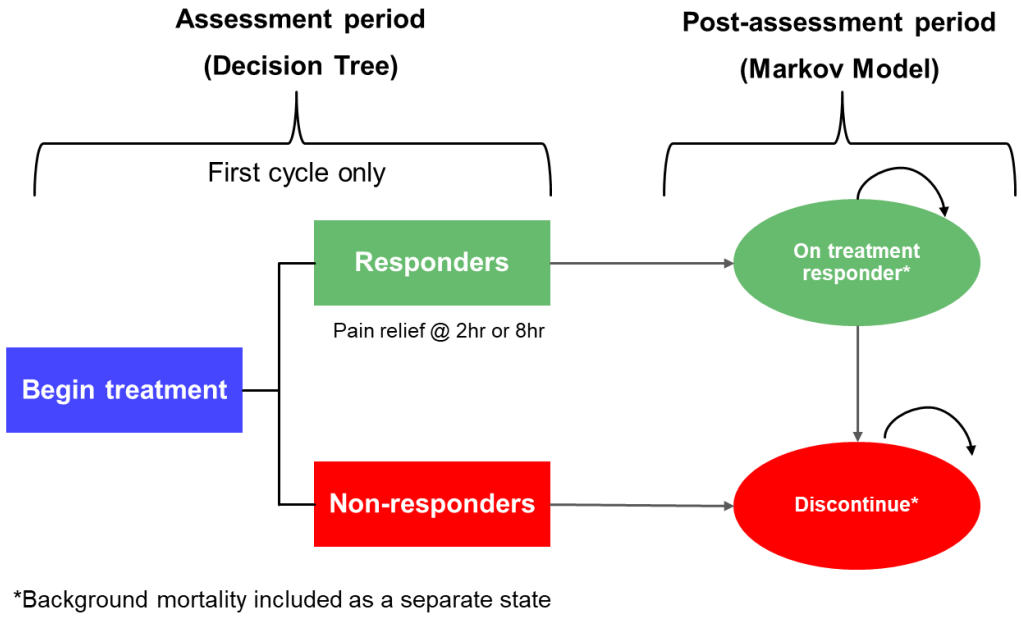
The model developed by the company includes a short-term (2 hours) decision tree component, to capture the response to the first migraine attack, followed by a long-term Markov model, to capture the impact of subsequent migraine attacks.

Within the model, the impact of migraine is captured by severity; the pain intensity level (none, mild, moderate and severe) is characterised over the 48-hour migraine period (see Section 4.2.7.1.1). The impact of migraine is also captured by frequency; the probability of experiencing a migraine in each 48-hour cycle (see Section 4.2.7.1.3).

Assessment period

All patients who enter the model (decision tree) experience their first migraine attack in the first model cycle. All patients treat this attack with either rimegepant or BSC, depending on the treatment arm. Patients are then assessed for response at 2 hours (see Section 4.2.7.1.1). Patients who respond, stay on treatment (to treat acute events), and experience the pain trajectories observed for responders, while those who do not respond, discontinue treatment, and experience the pain trajectories of BSC non-responders. In other words, the first migraine event is used to determine whether patients remain on or discontinue treatment in the model. Patients then continue to the post-assessment period (Markov model). The model structure is presented in Figure 4. The model also includes a health state for background mortality; however, this did not differ across the treatment arms.

Figure 4. Overview of the model structure for acute treatment of migraine (reproduced from Figure 14 of the CS)



Post-assessment period

In the Markov model, the probability of experiencing migraine is calculated for each 48-hour model cycle, based on baseline number of migraine attacks per month (see Section 4.2.6.1).

Non-responders to rimegepant or BSC at 2 hours enter the Markov model in the off-treatment (discontinue) health state and experience the outcomes of a BSC non-responder.

Responders to rimegepant at 2 hours enter the Markov model in the on-treatment responder health state. The company assumed these patients continue to respond to subsequent migraine attacks. Patients who discontinue rimegepant during the post-assessment period are assumed to achieve the benefits of BSC responders for 1 year, before immediately transitioning to the outcomes of a BSC non-responder. As rimegepant patients discontinue at different time points over the time horizon, and the memoryless property of a Markov model, this adjustment is achieved by a one-off application of the associated QALYs at the time of discontinuation, adjusted for mortality and any relevant time horizon cap over the subsequent 12 months.

During the clarification stage, the company was asked to explain why no adjustment was made for HCRU. The company explained that "*Due to the complexity of the one-off calculation, and the relative low impact of HCRU in ICER results, the conservative assumption was made to not adjust for HCRU in the discontinuation calculation. HCRU represents <10% of total costs and excluding HCRU*

from the model altogether results in approximately £1K difference in the ICER; thus the impact of this adjustment is expected to be negligible".

Responders to BSC at 2 hours are assumed to see the treatment effect dissipate after 1 year, consistent with previous NICE appraisals in migraine prevention (TA764/TA631, TA659 and TA682).[25-27] The company also assumed that responders to BSC would dissipate to the pain trajectories of a BSC non-responder immediately.

As touched upon above, the company did not consider gradual transitions from BSC responder pain trajectories to non-responder pain trajectories, they were immediate. In response to a clarification question, the company explained that because the exact definition of return to baseline is unknown, a viable approach for "gradual return" was not identified, and as an acknowledged area of uncertainty this was explored in scenario analyses within the CS (see Section 5.1.3). Immediately reverting rimegepant discontinuers to BSC non-responders at discontinuation (CS scenario 12) increased the ICER by around £1,000 and varying the time point at which benefit was lost between 6 and 18 months (base case 12 months) (CS scenario 13) had a minimal impact on the ICER (less than £100).

EAG comment

The EAG's clinical experts disagreed with the company's assumption that all patients who initially respond to rimegepant, then discontinue rimegepant, would respond to BSC for 12-months. The EAG considered that a more appropriate assumption would be to use the proportion of patients experiencing pain relief at 2-hours from BSC in the acute pooled RCTs ([redacted] and [redacted] in the subgroup with at least 2 triptan failures and mITT population including study BHV3000-310, respectively), and subsequently suggested this to the company at the clarification stage.

In response, the company provided an alternative scenario where rimegepant responder discontinuers were allocated the pain trajectory of BSC allcomers for 12 months, to reflect a mix of responders and non-responders to BSC. Pain trajectories from all-comers are compared with responders and non-responders in Table 40. This scenario increased the ICER for rimegepant vs BSC from £17,160 to £17,769 in the subgroup with at least 2 triptan failures. The company did not provide cost-effectiveness results for this scenario in the mITT population including study BHV3000-310.

Table 40. Pain hours per migraine event for the population with two or more triptan failures in pooled acute RCTs (BSC arm)

Pain intensity level	All-comers (scenario)		Responders (2-hour)		Non-Responders (2-hour)	
	Mean	SE	Mean	SE	Mean	SE
Subgroup with at least 2 triptan failures (company base case)						
None	[redacted]					
Mild	[redacted]					
Moderate	[redacted]					
Severe	[redacted]					
mITT population including study BHV3000-310						
None	[redacted]					
Mild	[redacted]					
Moderate	[redacted]					
Severe	[redacted]					

Abbreviations: BSC, best supportive care; mITT, modified intention-to-treat; RCT, randomised controlled trial; SE, standard error

In their response, the company also explained that initial response status to rimegepant was assumed to be informative of subsequent response, with rimegepant responders assumed to be analogous to placebo responders and non-responders to placebo non-responders. Additionally, if rimegepant patients who discontinued were to transition directly to placebo non-responder status it would paradoxically create a situation where patients who initially responded to rimegepant and discontinued would then have poorer outcomes than patients who responded to placebo and didn't initiate an active treatment. As such, the 12-month response for rimegepant is defined to be consistent with the placebo assumptions, with equivalent benefits observed post-discontinuation as are assumed for placebo patients.

The EAG considers that the company has provided no evidence to suggest rimegepant responders are analogous to placebo responders. However, the EAG considers the scenario analysis provided by the company a more realistic representation of response to BSC following rimegepant and therefore includes this scenario in its preferred base case.

An additional and related area of concern raised by the EAG's clinical experts is the assumption that all responders to BSC wane back to baseline efficacy over 1 year. Based on their clinical experience, a small proportion of patients will maintain a response to BSC, and for one patient that loses response another may gain response. However, they were unable to suggest what proportion will maintain a response to BSC. The EAG considers that consistency with previous NICE appraisals in migraine

(TA764/TA631, TA659 and TA682)[25-27] should be applied unless there is long-term clinical evidence or a numerical estimate based on clinical expert consensus for BSC that allows such a scenario to be reliably modelled.

The EAG has one more key issue with the company's modelling approach in the acute model, which is the appropriateness of using treatment response to the first migraine attack to inform whether a patient stays on treatment or discontinues treatment. Clinical experts advising the EAG affirmed that this does not reflect how treatment is trialled in clinical practice and noted that their preference would be to trial a new treatment for two or three attacks before it is stopped. Additionally, no stopping rule is included in the SmPC[1] for rimegepant or in the modelling for the ICER evidence report on acute treatments in migraine (rimegepant, lasmiditan and ubrogepant).[52] For these reasons, the company was asked to comment on the appropriateness of using treatment response to the first migraine attack as a stopping rule.

In their response, the company noted that NICE recommendations from prior appraisals for the mAbs have included stopping rules to focus long term treatment on those patients who benefit the most. Additionally, clinical experts indicated to the company that rimegepant would only be continued long term in those patients achieving sufficient symptom relief, with pain relief at 2-hours considered most reflective of response. This is consistent with *post-hoc* analyses of preference data from BHV3000-303 that indicated a greater preference for continuing rimegepant amongst patients that achieved 2-hour pain relief.

The EAG considered a scenario where the stopping rule is removed but was then faced with making an additional assumption of what it could be replaced with (i.e., when would a treatment be considered a failure). Thus, in the absence of clinical data indicating how many patients would respond after taking rimegepant to treat a second or third migraine, who did not respond during their first episode, the EAG considers this to be an unresolvable area of uncertainty. The EAG also notes that the company's approach may be considered conservative if more initial non-responders to rimegepant responded on the second or third attack than initial non-responders to BSC.

4.2.4.2 Migraine prevention

The company developed a *de novo* cost-effectiveness model in Microsoft Excel to evaluate the incremental cost-utility of rimegepant versus erenumab, fremanezumab, and galcanezumab, in adults with EM. The model included a short-term (12-week) decision tree component, to capture the

assessment period, followed by a long-term Markov model, to capture the post-assessment period. Within both components of the model, the impact of migraine is captured by 29 health states representing the frequency of migraines (0, 1, 2, 3….28) per 28-day cycle.

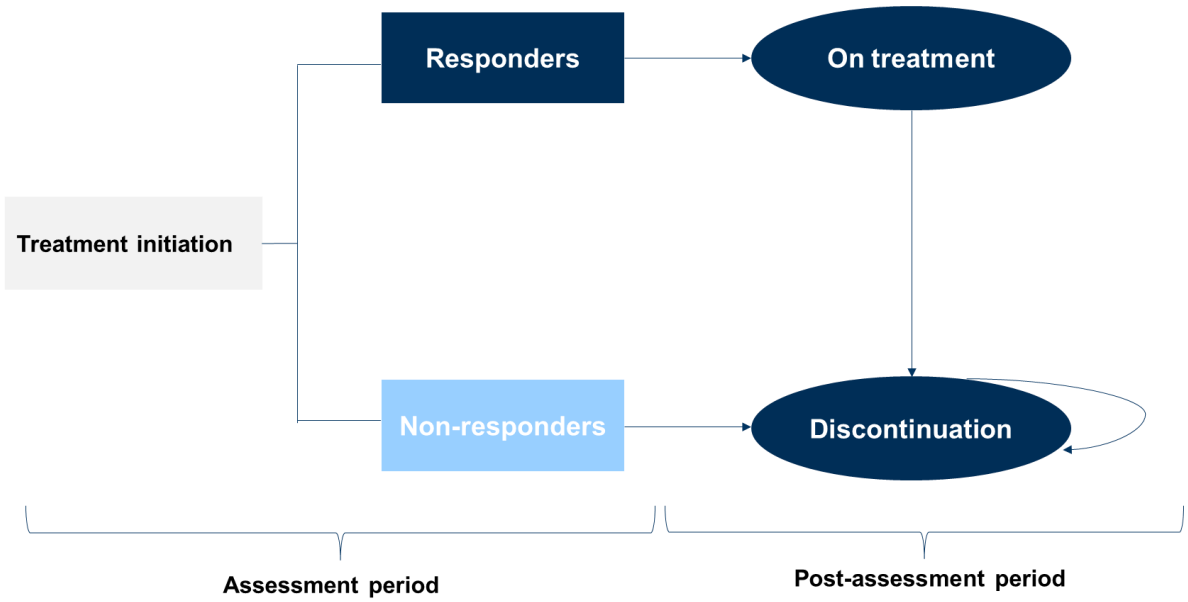
Assessment period

At the start of the model, patients initiate treatment on rimegepant, erenumab, fremanezumab, or galcanezumab for a period of 12 weeks. Response is then assessed after the 12-week trial period and defined as a ≥50% MMD reduction from baseline (see Section 4.2.7.2). The company explained that this approach is consistent with the previous NICE appraisals in migraine prevention (TA764/TA631, TA659 and TA682)[25-27] and that the response criteria of 50% is consistent with the International Headache Society (IHS) guidelines, which consider a ≥50% MMD reduction from baseline to be a clinically meaningful reduction in EM and recommend the use of this endpoint in prevention clinical trials.[99]

Within the assessment period, there are three cycles: Cycle 1, for Weeks 1 to 4; Cycle 2, for Weeks 5 to 8; and, Cycle 3, for Weeks 9 to 12. In Cycles 1 and 2, the distribution of MMD is conditional on treatment arm. In Cycle 3, the distribution of MMD is conditional on treatment arm and response. To estimate the distribution of MMD, count models were fit to the individual patient-level data from study BHV3000-305. For a detailed description of MMD distributions, see Section 4.2.6.2.

Non-responders immediately discontinue treatment at 12 weeks, consistent with previous NICE appraisals in migraine prevention (TA764/TA631, TA659 and TA682). Non-responders enter the Markov model in the off-treatment (discontinuation) health states and responders continue treatment and enter the Markov model in the on-treatment health states. The model structure is presented in Figure 5. The model also includes a health state for background mortality; however, this does not differ across treatment arms.

Figure 5. Overview of the decision tree plus Markov model for migraine prevention (reproduced from Figure 15 of the CS)



Post-assessment period

In the Markov model, non-responders at 12 weeks revert to the distribution of baseline MMD over a period of 12 months (for a detailed description of MMD distributions, see Section 4.2.6.2). Responders at 12 weeks remain on treatment and maintain the predicted distribution of responder MMDs, consistent with previous NICE appraisals in migraine prevention (TA764/TA631, TA659 and TA682). Patients who discontinue over the longer term (i.e., after initially being assessed as responders), are assumed to immediately return to the baseline distribution of MMD.

EAG comment

The EAG considers the company's model structure and modelling approach to be generally in line with those accepted in previous NICE appraisals in migraine prevention (TA764/TA631, TA659 and TA682).

Some subtle differences in the long-term modelling assumptions (treatment waning) were identified and these are outlined Table 41, based on committee preferences reported in the final appraisal determination documents.

Table 41. Treatment waning assumptions in previous NICE migraine prevention TAs accepted at the final ACM

TA	Non-responders to BSC	Responders to BSC	Non-responders to active treatment at 12-weeks	Responders to active treatment who stay on treatment	Responders to active treatment who discontinue treatment
Company	NA	NA	Wane back to baseline MMDs over 12 months	Treatment effect maintained	Return to baseline MMDs immediately
Erenumab TA682 (FAD Section 3.17 and 3.21)	Return to baseline MMDs immediately	Return to baseline MMDs at the end of year 1 immediately	Return to baseline MMDs immediately	Treatment effect maintained	Return to baseline MMDs immediately
Fremanezumab TA764/TA631 (FAD Section 3.16)	Return to baseline MMDs immediately*	Wane back to baseline MMDs over 12 months	Wane back to baseline MMDs over 12 months	Treatment effect maintained	Wane back to baseline MMDs over 12 months
Galcanezumab TA659 (Technical report, Issue 5)	Return to baseline MMDs immediately*	Wane back to baseline MMDs over 12 months	Wane back to baseline MMDs over 12 months (treatment-specific waning)*	Treatment effect maintained	Wane back to baseline MMDs over 12 months (treatment-specific waning)

Abbreviations: ACM, appraisal committee meeting; BSC, best supportive care; MMDs, monthly migraine days; NA, not applicable; NICE, National Institute for Health and Care Excellence; TAs, technology appraisals

*This assumption is not explicitly stated but could be inferred

As highlighted in Table 41, the company's assumptions regarding reversions to baseline MMD, are inconsistent. During the assessment period, the reversion to baseline takes 12 months, but after the assessment period, the reversion to baseline is immediate. This approach favours the least effective treatment (rimegepant) as these patients will maintain benefits for longer after discontinuation than patients who initially respond then discontinue. As shown in the company's scenario analysis, assuming an immediate reversion to baseline in both periods reduce the ICERs for each mAb vs rimegepant by around £10,000, favouring the comparators. Due to time constraints, the EAG has been unable to explore a scenario where the reversion to baseline takes 12 months for both periods. The EAG would consider this scenario to be more plausible than assuming an immediate reversion to baseline MMD. Nevertheless, the EAG would expect both scenarios to have a similar impact on the results. The EAG also includes the assumption of immediate reversion to baseline in both periods in its preferred base case.

It has been accepted in previous appraisals, that all responders to BSC wane back to baseline efficacy over 1 year (immediately or gradually, depending on the TA). However, as per the acute model, the EAG's clinical experts strongly disagreed with this assumption as a small proportion of patients will

maintain their response, and for one patient that loses response another may gain response. However, they were unable to suggest what proportion will maintain a response to BSC. The EAG considers that consistency should be applied unless there is long-term clinical evidence, or a numerical estimate based on clinical expert consensus for BSC that allows such a scenario to be reliably modelled.

4.2.5 Perspective, time horizon and discounting

4.2.5.1 Acute migraine treatment

The acute model was conducted from the perspective of the UK NHS and Personal Social Services (PSS), in line with the NICE reference case.[100] However, the company explained that migraine is most prevalent in a younger working-age population and migraine-related disability contributes to substantial economic and societal burden.[7, 101, 102] As such, sensitivity analysis was conducted from the societal perspective, in which costs associated with lost productivity were included (see Section 4.2.12.1.4).

The time horizon of the model was 20 years and the company considered this to cover a lifetime time horizon. The company then noted that the time horizon was capped at 20 years given that migraine frequency tends to decline with older age and a negligible proportion of patients would be modelled to continue on any treatment beyond 20 years. Based on a starting age of [redacted] years, patients would be [redacted] years old at the end of the time horizon. In scenario analysis, the company considered time horizons of 2, 5 and 10 years.

The cycle length in the model was 48 hours to align with the typical trial length in studies of acute migraine therapies. No half cycle correction was applied. However, given the short cycle length of 48 hours, the impact of a half-cycle correction was assumed to be negligible.

Finally, an annual discount rate of 3.5% was applied to both costs and benefits, in line with the NICE reference case. In scenario analysis, an annual discount rate of 1.5% was applied.

EAG comment

As noted in Section 4.1.1, three of the included cost-effectiveness studies identified in the SLR (Atlas *et al.* 2020 [ICER evidence report][52], Johnston *et al.* 2021[54] and Touchette *et al*. 2020[53]) assessed rimegepant and considered cycle lengths of 48 hours and a time horizon of two years.

A cycle length of 48 hours is consistent with the model developed by the company. However, the company's modelled time horizon is substantially longer (20 years vs 2 years). The ICER evidence report justify a 2-year time horizon as migraine onset is rapid, resolution occurs quickly, and costs are incurred with each treatment and benefits are observed immediately.[52] As shown in the company's scenario analysis (in the subgroup with at least 2 triptan failures), the ICER for rimegepant vs BSC in increases with shorter time horizons and increases from £17,160 to £20,560 when the time horizon is reduced from 20 years to 2 years.

The EAG agrees that a 2-year time horizon would be insufficient to capture the costs and consequences associated with reductions in MMD. However, as noted in Section 4.2.7.1.3, the EAG considers the modelled reductions in MMD to be based on weak evidence.

4.2.5.2 Migraine prevention

The prevention model was conducted from the perspective of the UK NHS and PSS, in line with the NICE reference case.[100]

The time horizon of the model was 20 years. Based on a starting age of 41 years, patients would be 61 years old at the end of the time horizon. In scenario analysis, the company considered time horizons of 5 and 40 years. The company acknowledged that in previous appraisals for migraine prevention (TA764/TA631, TA659 and TA682) EAGs have noted that a time horizon less than lifetime may not be sufficient to capture all relevant costs and outcomes associated with the intervention.[25-27] The company then highlighted a statement in the CS for galcanezumab to contradict this, "*migraine affects predominately women and the natural course of disease suggests that prevalence of migraine reduces significantly after menopause*". The company then explained that a time horizon shorter than lifetime may be appropriate given that migraine frequency tends to decline with older age, the anticipated (high) rates of discontinuation from treatment, and as there is no mortality or other prognostic implication of migraine prevention.

The cycle length in the model was 28 days to align with the schedule of MMD reporting in the BHV3000-305 study. No half cycle correction was applied. However, given the short cycle length of 28 days, the impact of a half-cycle correction was assumed to be negligible.

Finally, an annual discount rate of 3.5% was applied to both costs and benefits, in line with the NICE reference case. In scenario analysis, an annual discount rate of 1.5% was applied.

EAG comment

At the end of the 20-year time horizon, less than 1% of patients remain on the most effective treatment (galcanezumab). For this reason, the EAG agrees with the company that extending the time horizon will have no meaningful impact on the results.

The EAG also notes that the company extended the time horizon to 40 years in scenario analysis. However, this cannot be considered equivalent to a lifetime time horizon as only [redacted] of patients had died in each treatment arm by the end of the time horizon. To align with committee preferences in previous NICE appraisals in migraine prevention (TA764/TA631, TA659 and TA682), the company was asked to perform a scenario using a lifetime time horizon during the clarification. Nevertheless, the impact on the ICERs for each mAb vs rimegepant was negligible (impact of less than £100). The EAG also notes that this scenario is potentially unreliable given that longer time horizons exacerbate an issue with the company's approach to model mortality (i.e., qx vs mx); noted in Section 4.2.10.

4.2.6 Monthly migraine day (MMD) distributions

4.2.6.1 Acute migraine treatment

In the original CS, the EAG found that the company obtained migraine attacks per month from the studies and treated these as MMDs. This assumption is important because one migraine attack can last up to 72 hours, thus, one migraine attack per month could equal up to three MMDs. In response to a clarification question, the company revised their analysis to generate 0 to 14 migraine attacks per month rather than 0 to 28 MMDs per month. This involved converting migraine attacks to MMDs using the proportion of migraine attacks lasting >24 hours (Table 42). For example, in study BHV3000-201, [redacted] of migraines lasted less than 1 day, and so the number of MMDs per migraine attack was estimated to be [redacted]. All migraine attacks were capped at 2 MMDs given that pain trajectories data were only available for 48 hours per migraine attack. The company acknowledged that migraines may last up to 72 hours and considered their approach to be conservative as it limits the potential benefits for migraine improvement beyond 48 hours.

Table 42. Distribution of migraine attack durations (mITT populations)

Migraine duration	Study BHV3000-201 (PRN groups) (company base case)		Pooled acute RCTs (BHV3000-301, -302 and 303)*	
	N	%	N	%
4 to 24 hours	[redacted]	[redacted]	[redacted]	[redacted]
25 to 48 hours	[redacted]	[redacted]	[redacted]	[redacted]

49 to 72 hours	[redacted]	[redacted]	[redacted]	[redacted]
73 to 96 hours	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: mITT, modified intention-to-treat; PRN, pro re nata; RCT, randomised controlled trial
*Data including study BHV3000-310 not reported

To generate cost-effectiveness results, the company used the distribution of migraine attacks per month from study BHV3000-201 in their base case analysis, which included patients with 2 to 14 migraine attacks per month. The distribution approach involved generating costs and QALYs for each number of migraine attacks per month (0, 1, 2, 3… 14), then taking a weighted average of these values according to the distribution. A parametric distribution was not applied to the observed data.

The company preferred the distribution of attacks per month from study BHV3000-201 to the acute RCTs as the acute RCTs restricted inclusion to 2 to 8 migraine attacks per month, which, according to the company, doesn't provide a natural distribution of the full range potentially observed in the UK population for the acute treatment of migraine. The company also noted that they preferred to generate results using the distribution rather than the mean as the mean cannot fully account for patients with high-frequency migraine episodes, which have the potential to have a reduction in frequency with rimegepant.

In response to a clarification question, the company confirmed that [redacted] patients from the acute pooled RCTs were also included in study BHV3000-201 (N=1,514) and these patients contributed to the distribution of migraine attacks per month.

For the mean number of baseline attacks per month observed in study BHV3000-201 and the pooled acute RCTs, see Table 43.

Table 43. Mean baseline attacks per month (obtained by the EAG from the revised model)

	Study BHV3000-201		Pooled acute RCTs	
	mITT population ("all-comers")	Subgroup with at least 2 triptan failures (company base case)	mITT population including study BHV3000- 310	Subgroup with at least 2 triptan failures
Mean baseline attacks per month	[redacted]	[redacted]	[redacted]	[redacted]
Number of MMDs per event	[redacted]	[redacted]	[redacted]	[redacted]
MMDs	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; MMD, monthly migraine days; mITT, modified intention to treat; RCT, randomised controlled trial

*Based on the mITT population

EAG comment

According to the company's one-way sensitivity analysis (OWSA), the baseline MMD is a key model driver, with a higher baseline MMD leading to a lower ICER for rimegepant vs BSC. Thus, it is paramount to ensure that the most appropriate evidence is used to inform the baseline MMD in the model.

The EAG highlights that the ICER evidence report[52] for acute treatment used a mean of 4.8 MMDs at baseline which is closer to the MMDs estimated from the acute pooled RCTs than study BHV3000-201. The EAG's clinical experts also advised that they would expect a larger proportion of patients to experience between 2 and 8 moderate-to-severe migraine attacks per month than 9 or more a month. Based on the mITT population ("all-comer" population) in study BHV3000-201, [redacted] of patients experienced more than 9 migraine attacks per month, which would be within the range clinical experts suggested to the EAG.

The EAG also notes that the acute pooled RCTs were used to inform the pain trajectories (severity) per migraine in the economic analysis, while study BHV3000-201 was used to inform the baseline MMD, which implicitly assumes that the number of migraine attacks per month does not impact the severity of each migraine. Following this, the EAG considered if there was an important mismatch in using the pain trajectories from the acute pooled RCTs and the baseline MMD from study BHV3000-201. The EAG sought clinical expert feedback who advised the EAG that the number of MMDs should be independent of pain trajectories if a patient is experiencing less than nine migraine attacks per month. Given that [redacted] of patients in study BHV3000-201 experienced more than 9 migraine attacks per month, the assumption that pain trajectories are independent of migraine frequency cannot be satisfied.

Furthermore, as discussed in Section 2.3.1.1, the acute RCTs excluded those with CM by only including those with <15 monthly headache days, meaning it is unclear whether similar efficacy would apply to those with CM. For these reasons, the EAG would prefer baseline patient characteristics such as MMDs to be informed by the acute pooled RCTs to ensure consistency between sources used for pain relief, pain trajectories and baseline MMDs.

Subsequently, the company was requested to provide a scenario using the acute pooled RCTs to inform the distribution of MMD at baseline during the clarification stage. The company did not provide the requested scenario as they did not think it was an appropriate distribution to consider. The EAG asks that the company reconsiders this at technical engagement. In the meantime, the EAG considers a scenario using the acute pooled trials to inform the mean approach (as opposed to the distributional approach in the absence of data). For results of the EAG's analysis, see Section 6.

During the clarification stage, the company was also asked why a parametric distribution was not used to estimate the distribution of MMD at baseline. In their response, the company provided scenarios employing the negative binomial and Poisson distributions but still considered the observed data from study BHV3000-201 to be most appropriate to inform the base case analysis. The Poisson distribution had the largest impact on the ICER (increased from £17,160 to £17,729 in the subgroup with at least 2 triptan failures). The company did not provide any figures comparing the parametric distributions versus the observed distribution and goodness of fit statistics in their response or explain why other distributions like the normal distribution were not considered.

For completeness, the EAG compared the observed data to the Poisson distribution (

Figure 6). The EAG considers the observed data sporadic and the Poisson distribution more in line with the distribution observed for migraine prevention (see Figure 9) and would therefore prefer the Poisson distribution to inform the economic analysis if study BHV3000-201 is employed.

Figure 6. Distribution of migraine events per month for the population with two or more triptan failures in study BHV3000-201 (generated by the EAG)

4.2.6.2 Migraine prevention

Baseline MMD distribution

To inform the baseline MMD distribution the company used the data from the efficacy evaluable population in study BHV3000-305, which provided a baseline mean MMD of 10.046. The company fitted a normal distribution to this data (Figure 7), which provided a baseline mean MMD of 10.546.

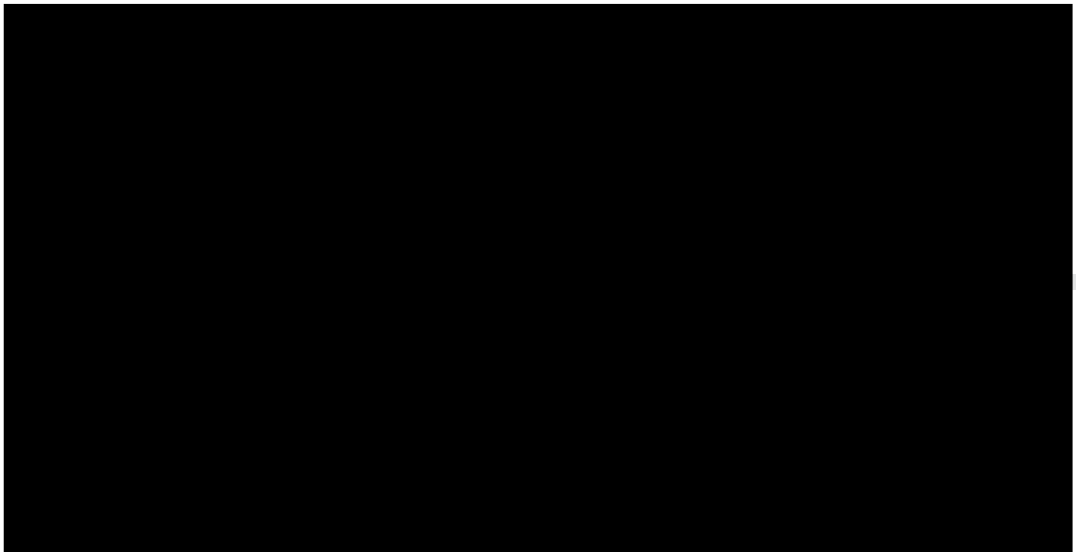


Figure 7. Baseline MMD in study BHV3000-305 (reproduced from Figure 22 of the CS)

MMD distribution during the 12-week assessment period

To estimate the distribution of MMD during the 12-week assessment period, count models were fit to the individual patient-level data from study BHV3000-305. These included the beta-binomial, zero-inflated negative binomial, negative binomial, and Poisson. Analysis of the patient-level data allowed the proportion of patients experiencing a given MMD frequency to be captured by treatment group in BHV3000-305 (rimegepant or placebo), at different timepoints in the study (Week 4, Week 8, or Week 12), and according to response at 12-weeks. The regression parameters for each model are provided in Table 81 of Appendix P. Based on both AIC (Table 82 in Appendix P) and visual assessment (Figure 1 in Appendix N) the zero-inflated negative binomial appeared to provide the better fit to the study data and was selected in the base case analysis. The beta-binomial, negative binomial, and Poisson distributions, and a non-parametric distribution were explored by the company in scenario analysis. As shown in Section 5.2.3, alternative distributions had a small impact on the ICER.

As patient-level data were not available to fit equivalent distributions for the three mAbs, the company assumed that the three mAbs were associated with the same MMD distribution as rimegepant. This means that, from Cycle 3 (Weeks 9 to 12), the difference in effectiveness (difference in the distribution of MMD) between rimegepant and the three mAbs is modelled solely as the difference in the proportion of patients achieving 50% MMD reduction. For the predicted mean MMD associated with rimegepant and the three mAbs, see Table 44.

Table 44. Predicted mean MMD for rimegepant, erenumab, fremanezumab, and galcanezumab observed in the company's base case analysis when fitting the ZI NB model to the rimegepant arm in study BHV3000-305

Assessment	Predicted mean MMD
Baseline*	[redacted]

Assessment	Predicted mean MMD
Week 4 (cycle 1)	[redacted]
Week 8 (cycle 2)	[redacted]
Week 12 non-response (cycle 3+)	[redacted]
Week 12 response (cycle 3+)	[redacted]

Abbreviations: CS, company submission; MMD, monthly migraine days; ZI NB, zero-inflated negative binomial

Note: the baseline mean is a parameter in the regression model used to predict the distribution of MMD at Weeks 4, 8 and 12. The baseline mean is taken from the parametric distribution in the revised model, not the observed data

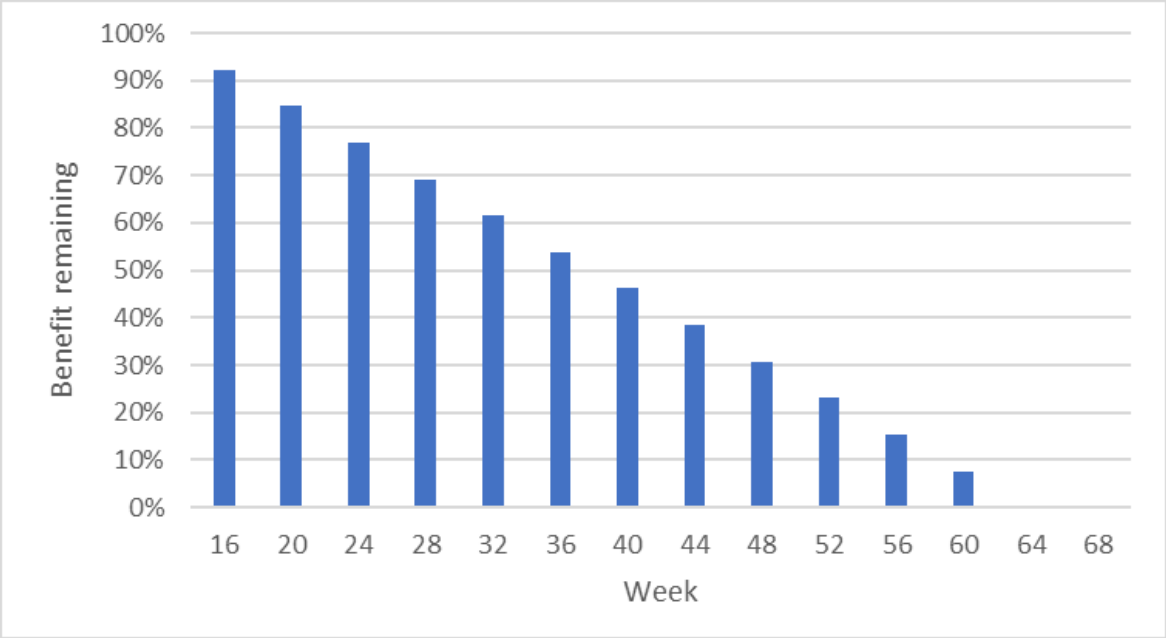
MMD distribution during the post-assessment period

As touched upon in Section 4.2.4.2, the company made three key assumptions when modelling the distribution of MMD during the post-assessment period.

Firstly, the company assumed that those on treatment maintained the improved number of MMD achieved when response is established at Week 12, i.e., the distribution of MMD by responder status estimated at Week 12 will be maintained over the full post-assessment period for rimegepant, erenumab, fremanezumab, and galcanezumab. The company noted that this assumption is aligned with prior NICE TAs in migraine prevention (TA764, TA659 and TA682)[25-27] and supported by the results from the OLE of study BHV3000-305, where the efficacy was maintained over the long-term (see Figure 7 in the CS).

Secondly, it was assumed that non-responders at 12 weeks reverted to the distribution of baseline MMD over a period of 12 months. In Figure 8 the proportion of change from baseline retained at each cycle up to Month 16 assuming a full linear attenuation of effect after model Week 12 is presented, as applied in the base case. An option to apply an exponential revision was added to the model at the clarification stage (a more immediate reversion to baseline).

Figure 8. Reversion to baseline (off-treatment at 12 weeks) (reproduced from Figure 21 of the CS)



Thirdly, patients who discontinue over the longer term (i.e., after initially being assessed as responders), are assumed to immediately return to the baseline distribution of MMD.

EAG comment

During the clarification stage, the company was asked to clarify if a number of parametric distributions were assessed to estimate the distribution of MMD at baseline. In their response, the company explained that alternative parametric distributions were not considered, and that the normal distribution was chosen as it appeared this had been favoured in a previous appraisal. The company also provided Figure 9 and goodness of fit statistics using the Poisson, beta-binomial and normal distributions. According to the Akaike information criterion (AIC), the Poisson and beta-binomial distributions appears to provide a slightly better fit (AIC 3505 and 3518, respectively) than the normal distribution (AIC 3538), with results similar to those when using the observed baseline MMD data. In consequence, the company added these options to the model. When the EAG employed the Poisson distribution in the model the ICERs for each mAb vs rimegepant increased by around £4,000, favouring rimegepant. Thus, the company's decision to use a normal distribution may be considered conservative. Nevertheless, given that the Poisson distribution has a better statistical and visual fit than the company's base case distribution, the EAG will employ a Poisson distribution in its preferred base case.

Figure 9. Alternative parametric distributions to represent the baseline MMD observed in study BHV3000-305 (reproduced from the company's clarification response)

[redacted]

As noted in Section 4.2.2.2, the inclusion of some patients with CM means MMDs in the observation period and number of moderate-to-severe attacks per month are higher than what would be seen for episodic patients in UK practice. As such, study BHV3000-305 represents a population with a higher migraine burden compared to EM patients, which may subsequently affect efficacy. An additional and related area of concern is that the distribution of baseline MMD does not match the company's target position of at least four MMDs but fewer than 15 headache days per month. During the clarification stage, the company noted that the baseline MMD reflects the natural tendency for there to be some variability outside this range in an EM population. However, an option to truncate the baseline MMD from 4 to 14 was included by the company in their revised model. When the truncation is applied, the ICERs for the mAbs vs rimegepant decreased by around £5,000, favouring the comparators. Given that no stopping rules are included in the model (i.e. patients will not discontinue treatment if their EMs progress from episodic to chronic) and patients are unlikely to worsen and experience more MMDs on treatment, ([redacted]) the EAG is not hugely concerned that no further outcomes are adjusted when the baseline distribution of MMD is truncated.

Finally, as discussed in Section 4.2.5.2, the EAG finds the company's assumptions regarding reversions to baseline MMD, once treatment is discontinued, inconsistent.

4.2.7 Treatment effectiveness

4.2.7.1 Acute migraine treatment

4.2.7.1.1 Response

Pain relief at 2 hours (a secondary endpoint in the studies) was selected as the base case definition of response. The company explained that pain freedom at 2 hours (the primary endpoint in the studies) was not used because a treatment that can decrease pain intensity from moderate or severe to mild or no pain, (i.e., definition of pain relief), would be considered a success in clinical practice. Additionally, it is unlikely that patients will discontinue their treatment if they achieve an improvement of their pain intensity. This was supported by expert feedback from two advisory boards.[50] The company also explained that pain relief at 8 hours was not used as patients would reasonably expect a therapy to have some pain relief outcome within 2 hours to be considered effective, and that this can be considered a proxy for binary treatment effect; by 8 hours and longer, a greater proportion of patients have experienced pain relief, and treatment effects cannot be fully disentangled from spontaneous improvement that some patients may experience by an 8 hour time point (which is less relevant at 2 hours). This was also supported by expert feedback from two advisory boards.[50] For completeness, the company provided a scenario analysis using pain relief at 8 hours. The response probabilities included in the economic analysis are summarised in Table 45.

Table 45. Response (pain relief) probabilities used to inform the acute model

Response	Subgroup with at least 2 triptan failures (company base case)		mITT population including study BHV3000-310	
	Rimegepant	BSC	Rimegepant	BSC
N	148	177	2,415	2,432
2 hours (base case)	[redacted]	[redacted]	[redacted]	[redacted]
8 hours (scenario)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; mITT, modified intention-to-treat

4.2.7.1.2 Modelling pain hours

To incorporate the experience of pain trajectories per migraine event, the company characterised the pain intensity level (none, mild, moderate, severe) over a 48-hour migraine period, using patient-level data from the acute pooled RCTs (BHV3000-301, -302, and -303).

As noted in Section 4.2.2.1, the acute RCTs recruited patients with 2 to 8 moderate-to-severe migraine attacks per month. The distributions of pain severity across the patients included in these RCTs at time 0 is reported in Table 46, according to treatment arm and population. During the clarification stage the company noted that the regression-based approach used to estimate QALH values for rimegepant and BSC, described in Section 4.2.11.1, adjusts for any imbalances in severity at baseline (i.e., severity as a covariate) and includes a common value for both treatment arms.

Table 46. Distribution of pain severity at baseline

Pain intensity level	Rimegepant	BSC	Moderate baseline pain (vs severe)*
Subgroup with at least 2 triptan failures (company base case)			
Moderate pain	[redacted]	[redacted]	[redacted]
Severe pain	[redacted]	[redacted]	
mITT population including study BHV3000-310			
Moderate pain	NR	NR	[redacted]
Severe pain	NR	NR	

Abbreviations: BSC, best supportive care; NR, not reported; mITT, modified intention-to-treat; RCT, randomised controlled trial

*the severity covariate included in the regression-based approach

The pain hour distributions (none, mild, moderate, severe) over the 48-hour migraine period, applied in the company's base case (subgroup with two or more triptan failures), according to treatment arm and response (measured at 2-hours), are reported in Table 47. These pain distributions are based on the percentage of patients in each pain state and the average time spent in these states. For pain hour distributions in the mITT population including study BHV3000-310, see Table 48.

Table 47. Pain hours per migraine event for the population with two or more triptan failures in pooled acute RCTs (adapted from Table 53 of the CS)

Pain intensity level	Responders		Non-Responders	
Rimegepant	**Mean**	**SE**	**Mean**	**SE**
No pain	[redacted]	[redacted]	[redacted]	[redacted]
Mild pain	[redacted]	[redacted]	[redacted]	[redacted]
Moderate pain	[redacted]	[redacted]	[redacted]	[redacted]
Severe pain	[redacted]	[redacted]	[redacted]	[redacted]
Total	48.0	-	48.0	-
BSC	**Mean**	**SE**	**Mean**	**SE**
No pain	[redacted]	[redacted]	[redacted]	[redacted]

Mild pain	[redacted]	[redacted]	[redacted]	[redacted]
Moderate pain	[redacted]	[redacted]	[redacted]	[redacted]
Severe pain	[redacted]	[redacted]	[redacted]	[redacted]
Total	48.0	-	48.0	-

Abbreviations: BSC, best supportive care; RCT, randomised controlled trial; SE, standard error

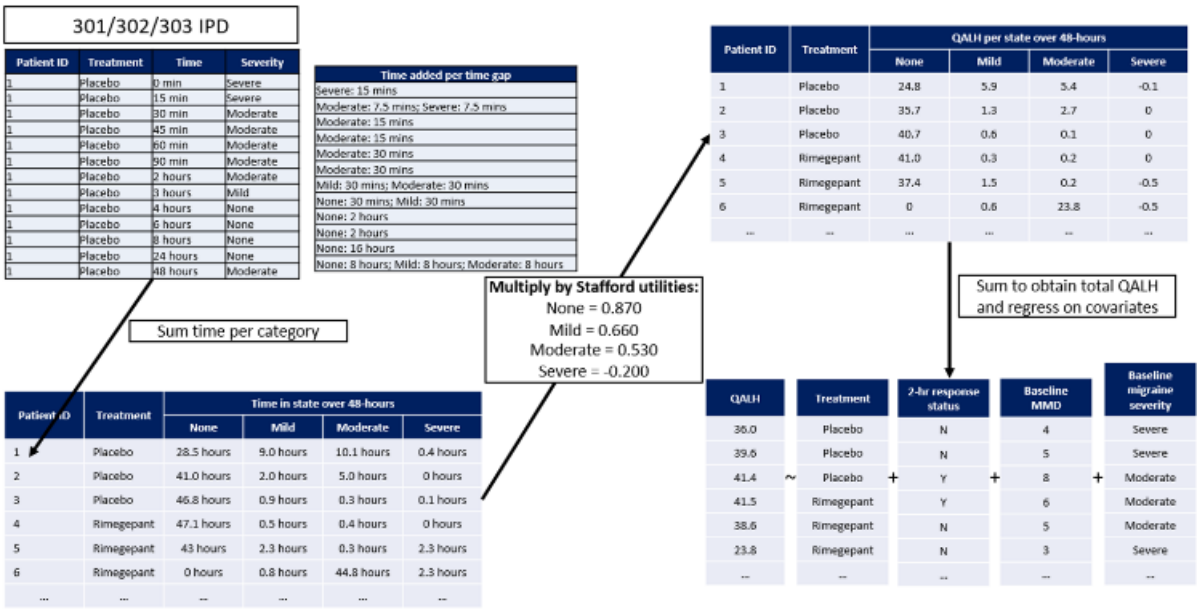
Table 48. Pain hours per migraine event for the mITT population including study BHV3000-310

Pain intensity level	Responders		Non-Responders	
Rimegepant	**Mean**	**SE**	**Mean**	**SE**
No pain	[redacted]	[redacted]	[redacted]	[redacted]
Mild pain	[redacted]	[redacted]	[redacted]	[redacted]
Moderate pain	[redacted]	[redacted]	[redacted]	[redacted]
Severe pain	[redacted]	[redacted]	[redacted]	[redacted]
Total	48.0	-	48.0	-
BSC	**Mean**	**SE**	**Mean**	**SE**
No pain	[redacted]	[redacted]	[redacted]	[redacted]
Mild pain	[redacted]	[redacted]	[redacted]	[redacted]
Moderate pain	[redacted]	[redacted]	[redacted]	[redacted]
Severe pain	[redacted]	[redacted]	[redacted]	[redacted]
Total	48.0	-	48.0	-

Abbreviations: BSC, best supportive care; RCT, randomised controlled trial; SE, standard error

The company then used an area-under-the curve (AUC) approach to apply health state utilities by pain intensity level and estimate the cumulative quality-adjusted time spent by treatment arm. A flow diagram outlining the methods used to calculate quality-adjusted life hours (QALHs) from pain trajectories in the pooled acute RCTs is presented in Figure 10. The utility values used to inform this approach are discussed in Section 4.2.11.1.

Figure 10. Flow diagram outlining the methods used to calculate quality-adjusted life hours from pain trajectories (reproduced from Figure 10 of Appendix O)



4.2.7.1.3 Probability of experiencing subsequent migraines

From Cycle 2, the average probability of experiencing migraine during a 48-hour migraine cycle was calculated based on the baseline MMD.

Then, based on a *post-hoc* analysis of study BHV3000-201, which evaluated the reduction in MMD observed with rimegepant PRN, the company assumed that rimegepant PRN could result in reductions in MMD over time. Briefly, the analysis was conducted in the 1,044 participants with six or more MMD at baseline and changes were non-linear with greater reductions in the first weeks of treatment, followed by a stable rate over the remainder of the follow up period (Figure 3 in L'Italien *et al.* 2022).[103]

To predict MMD reductions for given cohort characteristics, the company performed a regression analysis using patient-level data from the PRN dosing groups in study BHV3000-201. The following four points were taken into consideration when selecting regression covariates:

1. Clinical significance of a covariate;
2. Statistical significance of a covariate in both univariate and multivariate regression analyses;
3. Alignment with the population of interest (subgroup with at least 2 triptan failures); and,
4. Alignment with adjustments made in the primary outcome of Study BHV3000-305.

The covariates included by the company in the regression model are detailed in Table 49. The company also noted that linear time, non-linear time, presence of the subject in a previous rimegepant single-event acute trial (BHV3000-301, -302, or -303), age, and sex were considered but did not meet any of the considerations for inclusion. Additionally, after an initial drop in MMD, change in baseline in MMD were relatively stable throughout the 52-week period. This led to the justification on not including a time covariate in the final model, but still accounting for repeated measurements.

During the clarification stage, the company confirmed that a stepwise approach was used to inform the model (no further details were provided). The company also noted that models were comparable with and without the (statistically insignificant) Proph_mig_meds covariate.

Table 49. Decisions on the inclusion/exclusion of specific covariates for the change from baseline in MMD associated with acute PRN rimegepant treatment over time

Covariate	Consideration			
	1	2	3	4
Proph_mig_meds [Yes, No (reference)]: Whether the patient used prophylactic migraine medication throughout the trial period while on rimegepant.	✓	-	-	✓
trip_lines [0 (reference), 1, 2+]: Number of prior refractory triptan lines of therapy	-	✓	✓	-
pills_per_migraine: The total number of rimegepant pills taken per migraine within each given 4-week time interval.	-	✓	-	-
BL_MMD: Baseline monthly migraine days	✓	✓	-	-

Abbreviations: BL, baseline; MMD, monthly migraine day; PRN, pro re nata (as needed)

The final regression model is outlined in Table 50 and the resulting reduction in MMD for rimegepant using the base case patient characteristics is given in Table 51. The company concluded that the results from the regression indicate that higher frequencies of MMD (and so rimegepant administration) are associated with greater MMD reduction. The company also noted that when base case patient characteristics are applied to the regression, a reduction in MMD is predicted for a BL_MMD of at least nine. If the BL_MMD is below this, the predicted frequency of MMD in rimegepant and BSC patients is equal.

The probability of experiencing subsequent migraines is summarised in

Table 52 for the company's revised base case (subgroup with at least 2 triptan failures). For the probability in the mITT population including study BHV3000-310, see Table 53.

Table 50. Regression analysis for the change from baseline in MMD associated with acute PRN rimegepant treatment over time (adapted from Table 54 of the CS)

Term	Estimate	Standard error	Lower bound of 95% CI	Upper bound of 95% CI	p-value
(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BL_MMD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
trip_lines1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
trip_lines2+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
pills_per_migraine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proph_mig_meds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BL, baseline; CI, confidence interval; CS, company submission; MMD, monthly migraine days; PRN, pro re nata; trip_lines [0 (reference), 1, 2+]: Number of prior refractory triptan lines of therapy proph_mig_meds, prophylactic migraine medications

Table 51. Resulting reduction in MMD for rimegepant using base case patient characteristics

Term	Estimate	Subgroup with at least 2 triptan failures (company base case)		mITT population including study BHV3000-310	
		Base case patient characteristics	Resulting reduction in MMD for rimegepant	Base case patient characteristics	Resulting reduction in MMD for rimegepant
(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BL_MMD	[redacted]	[redacted]		[redacted]	
trip_lines1	[redacted]	[redacted]		[redacted]	
trip_lines2+	[redacted]	[redacted]		[redacted]	
pills_per_migraine	[redacted]	[redacted]		[redacted]	
Proph_mig_medsYes	[redacted]	[redacted]		[redacted]	

Abbreviations: BL, baseline; CI, confidence interval; MMD, monthly migraine days; trip_lines [0 (reference), 1, 2+]: Number of prior refractory triptan lines of therapy proph_mig_meds, prophylactic migraine medications

* This is an assumption, based on alignment with the model in which the cost of one rimegepant tablet is added for each migraine attack

Table 52. Probability of experiencing subsequent migraines (company's revised base case in the subgroup with at least 2 triptan failures)

Based on the regression analysis (responders on rimegepant)		Based on the baseline MMD in study BHV3000-201 in the subgroup with at least 2 triptan failures	
MMDs for treated patients	Treated probability of experiencing a migraine during each 48-hour cycle	MMDs for untreated patients	Untreated probability of experiencing a migraine during each 48-hour cycle
[redacted]	[redacted]	[redacted]	[redacted]

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

[redacted]

Table 53. Probability of experiencing subsequent migraines (mITT population including study BHV3000-310)

Based on the regression analysis (responders on rimegepant)		Based on the baseline MMD in the mITT population including study BHV3000-310	
MMDs for treated patients	Treated probability of experiencing a migraine during each 48-hour cycle	MMDs for untreated patients	Untreated probability of experiencing a migraine during each 48-hour cycle
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; mITT, modified intention-to-treat; MMDs, monthly migraine days
[redacted]

4.2.7.1.4 EAG comment

The EAG considers the long-term reductions in MMD with PRN rimegepant to be highly uncertain as this is based on a *post-hoc* analysis of the long-term safety study which may suffer from confounding (including but not limited to a possible placebo effect). Also, compared to the model time horizon (20 years), the long-term reductions in MMD with PRN rimegepant are based on a relatively short follow-up period (1 year), and small numbers at risk during the last few weeks of follow-up (see **Error! Reference source not found.**).

Moreover, the ICER evidence report assumed that acute treatment of migraine with lasmiditan, rimegepant, ubrogepant, and triptans does not affect migraine frequency as studies evaluating new migraine therapies were either short-term single episode studies or non-controlled open label studies and were not designed to demonstrate changes in migraine frequency with treatment.[52] They also note that longer-term, uncontrolled, open-label studies suffer from a possible placebo effect and a high likelihood that regression to the mean may affect the study's results.

For these reasons, the company was asked to identify comparative evidence to inform a more robust estimate of treatment effectiveness. In their response, the company acknowledged that the lack of a comparator arm in the study design of 201 is a limitation, and argued that *post-hoc* analyses of these data, showing the long-term reductions in MMD, are available in a number of peer reviewed publications that collectively support the effect using a variety of outcomes and analytical approaches.[103-105] The EAG notes that these publications are not based on any new data.

The EAG is aware that clinical expert feedback to the company was supportive of including reductions in MMD by PRN rimegepant in the model. However, in the absence of long-term comparative evidence, the EAG considers it more appropriate to remove reductions in MMD by PRN

rimegepant from the base case analysis and include them in scenario analysis. As shown in Section 5.1.3, removing reductions in MMD by PRN rimegepant increases the ICER from £17,160 to £22,529 in the subgroup of patients with at least 2 triptan failures. If the time horizon is also reduced to 2 years, like the ICER evidence report, increases the ICER from £17,160 to £27,851.

Finally, as noted in Section 4.2.7.1.2, the EAG was concerned that there were imbalances in pain severity between the treatment arms at baseline. Although the company affirmed that the QALH regression adjusted for these differences, the EAG still considers the imbalances to potentially bias the patient population in favour of rimegepant. The EAG subsequently considered the other outcomes from these trials that were modelled by the company; the company modelled pain relief (a decrease in pain intensity from moderate or severe to mild or no pain). If the company had modelled pain freedom (a decrease in pain intensity from moderate or severe to no pain), this would introduce major bias in favour of rimegepant as a larger proportion of patients in the BSC arm would need pain severity to reduce by two increments (severe pain to no pain). Overall, it is unclear how much bias this imbalance introduces for the pain relief outcome, but it is thought to be lower than if the pain freedom outcome had been used to inform the economic analysis.

4.2.7.2 Migraine prevention

In the prevention model, the treatment effect is modelled according to the proportion of patients achieving a 50% reduction in MMD from baseline, consistent with previous NICE appraisals in EM prevention (TA764/TA631, TA659 and TA682).[25-27] The probabilities for achieving response were derived from a NMA and results were expressed in terms of odds ratios (ORs).

As noted in Section 3.2.4.2, the company observed heterogeneity among the included trials, in the methods used to calculate response. Some studies reported the 50% responder endpoint as calculated from the observation period to Weeks 9 to 12 ("at 12-weeks"), while others calculated the 50% responder endpoint from the observation period as averaged over Weeks 1-12, or the entire DBT period ("average over 12-weeks"). The company chose the latter definition for the NMA as it was the most frequently reported endpoint.

The ORs obtained from the NMA and used to inform the model are summarised in Table 54, these are the updated NMA results, provided to the EAG at the clarification stage. Results from the fixed-effects baseline risk adjusted model were used to inform the company's revised base case (based on deviance information criterion [DIC]) and results from the random effects baseline risk adjusted

model were explored in scenario analysis. One key difference between the original NMA and revised NMA is that the original was based on moderate-to-severe migraine attacks, while the revised NMA is based on mild-to-severe attacks. For a greater discussion of the company's NMAs, see Section 3.2.4.

During the clarification stage the company explained that median ORs were used to inform the model as a converged symmetrical posterior distribution means there should not be much difference in taking the median compared to the mean. When the EAG validated the NMA, the means and medians were very similar.

Rimegepant was used as the baseline treatment in the economic analysis (i.e., the treatment ORs are compared to). The response probability for rimegepant was calculated from the observation period to Weeks 9-12 ("at 12-weeks") in BHV3000-305 (171/348 = 0.491). The resulting response probabilities for the comparators are given in Table 54. As noted in Section 4.2.6.2, these response probabilities were used to inform MMD distributions in the model from Cycle 3 (Weeks 9 to 12).

Table 54. ORs for response ("average over 12-weeks") and corresponding probabilities applied in the revised base case

Treatment	Fixed-effects baseline risk adjusted model (base case)		Random-effects baseline risk adjusted model (scenario)	
	OR (95% CrI)	Response probability	OR (95% CrI)	Response probability
Rimegepant	1	0.491	1	0.491
Erenumab 140 mg	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 225 mg	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab 675 mg*	[redacted]	[redacted]	[redacted]	[redacted]
Galcanezumab 120 mg	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CrI, credible interval; OR, odds ratio (treatment vs rimegepant)

*The NMA estimated effects separately for fremanezumab 225 mg and 675 mg, but only the 225 mg estimate was used to inform the base case, for the reasons outlined in Section 4.2.3.2.

EAG comment

The EAG considers the rimegepant response probability (49.1%) to be inconsistent with the outcome included in the NMA for two reasons. Firstly, the rimegepant response probability is based on the outcome "at 12-weeks" while the NMA is based on the "average over 12-weeks". Secondly, the rimegepant response probability is based on patients with moderate-to-severe migraine attacks while the NMA is based on mild-to-severe attacks.

To address the first issue, the company was asked to provide a scenario using the rimegepant response probability based on the "average over 12-weeks". At the clarification stage the company provided this, on top of their revised NMA, using a probability of [redacted]. The impact on the cost-effectiveness results was large and reduced the ICERs for the mAbs vs rimegepant by around £12,000, favouring the comparators. Given that this probability is also based on patients with mild-to-severe migraine attacks, the EAG considers this scenario to resolve both issues and therefore includes the scenario as part of the EAG preferred base case.

Furthermore, as discussed in Section 3.2.4.4, the EAG considers the random-effects NMA to be more appropriate than the fixed-effects NMA given the large amount of heterogeneity between the clinical trials informing the NMA. The EAG is also of the opinion that the phase II studies should be included in the NMA as the baseline characteristics of these additional studies was similar and there were no additional concerns about heterogeneity with these included. The EAG therefore includes the random-effects baseline risk adjusted NMA including the phase II studies, in its preferred base case (Table 55).

Table 55. ORs for response ("average over 12-weeks") and corresponding probabilities from the phase II sensitivity analysis, random-effects baseline risk adjusted NMA, applied in the EAG's preferred base case

Treatment	OR (95% CrI)	Response probability
Rimegepant	1	0.385**
Erenumab 140 mg	[redacted]	[redacted]
Fremanezumab 225 mg	[redacted]	[redacted]
Fremanezumab 675 mg*	[redacted]	[redacted]
Galcanezumab 120 mg	[redacted]	[redacted]

Abbreviations: CrI, credible interval; EAG, External Assessment Group; OR, odds ratio (treatment vs rimegepant)

*The NMA estimated effects separately for fremanezumab 225 mg and 675 mg, but only the 225 mg estimate was used to inform the base case, for the reasons outlined in Section 4.2.3.2.

**Using the EAG's preferred response probability for rimegepant

Given that response in the NMA was assessed as the "average over 12-weeks" and not "at 12-weeks", the EAG considers that the results from the NMA should be implemented in the economic analysis from Cycle 1 (Weeks 1 to 4) rather than from Cycle 3 (Weeks 9 to 12). During the clarification stage, the company was asked to provide a scenario to address this. The company did not provide the scenario because, "*All patients are modelled to remain on treatment through 12 weeks. Consequently, distinguishing between responders and non-responders in these earlier cycles is unnecessary as the model reflects the overall effect in the total population (both responders and non-*

responders). In contrast the post 12-week period relies on separate estimates for those who are responders and continue on treatment and non-responders who will not."

Based on the clinical data reported in the comparator trials, the EAG considers there to be evidence to suggest patients exhibit a significant response in the first month of treatment, with significant effects maintained in subsequent months.[57, 73, 74, 77, 81] Furthermore, the EAG is still of the opinion that it is inconsistent to apply results based on an average at the end of the observation period. As such, the EAG would urge the company to provide a scenario at technical engagement where the NMA results (and Week 12 MMD distributions according to response) are applied from Cycle 1 (Weeks 1 to 4) and patients stay on treatment until the end of the assessment period (Week 12).

Finally, the EAG has a potential issue, which has not been raised in previous migraines prevention appraisals. This is regards to using the response at 12 weeks as a negative stopping rule in the economic analysis (patients discontinue treatment if they do not respond at 12 weeks). In clinical practice, stopping rates depend not only on lack of efficacy but also other factors such as adverse events, patient preference, or physician preference. As such, using the response at 12 weeks alone could overestimate the proportion of patients that remain on treatment. However, the EAG is unable to predict the direction or magnitude of bias in the absence of complete data for all treatments.

4.2.8 Long-term discontinuation

4.2.8.1 Acute migraine treatment

Long-term discontinuation in the post-assessment period was informed by the subset of patients from the pooled acute RCTs (BHV3000-301, -302 and 303) who continued into the long-term safety study (BHV3000-201) and received rimegepant 75 mg PRN for 52-weeks. During the clarification stage, the company confirmed that these patients responded to treatment at 2 hours. Discontinuation rates over one-year were applied based on observed discontinuations due to adverse events, lack of efficacy, or withdrawal by participant (Table 56).

Table 56. Long-term discontinuation rates applied in the acute model

Subgroup with at least 2 triptan failures	mITT population*
[redacted]	[redacted]

Abbreviations: mITT, modified-intention-to treat
*Excluding study BHV3000-310

EAG comment

During the clarification stage the company provided the annual rate of discontinuation according to the reason for discontinuation in those enrolled in studies BHV3000-301, -302 and -303 and who continued into the BHV3000-201 study (Table 57). The EAG suspects the value of [redacted] in Table 57 differs to the value of [redacted] reported for the mITT population in Table 56 as the company has taken annual rates from the KM graph rather than calculating it based on the raw data, as was confirmed by the company for migraine prevention in Section 4.2.8.2. The EAG also assumes this was a *post-hoc* analysis for the model as the data are not reported in the CSR.

Table 57. Reasons for discontinuation in study BHV3000-201 used to inform the long-term discontinuation rate in the acute model

Reason	Count (N=239)	Percentage
Adverse event	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]
Withdrawal by subject	[redacted]	[redacted]
Total	[redacted]	[redacted]

4.2.8.2 Migraine prevention

Following the 12-week assessment (from Cycle 4 [Weeks 13 to 16]), patients are at risk of discontinuation. This was based on the OLE study for BHV3000-305. Of the 185 rimegepant treated patients who responded to treatment and continued into the OLE study, [redacted] of these remained on treatment after 1 year. As such, the company assumed an annual probability of [redacted] (equal to a 28-day cycle probability of [redacted]). The company also used this rate to inform the three mAbs, in the absence of evidence for differing rates of discontinuation.

EAG comment

During the clarification stage the company provided the annual rate of discontinuation according to the reason for discontinuation (Table 58) and noted that this was a *post-hoc* analysis for the model and is not reported in the CSR. The EAG was unclear why the company used an annual rate of [redacted] and not [redacted], but the company clarified at the factual accuracy stage that an annual rate of 23.0% was decided on as it was derived from patient-level data facilitating the running of the KM curve rather than a proportionate value. The value at year 1 from the KM curve was used rather than the raw proportion. Although the raw proportion would be preferred by the EAG, amending the annual rate from [redacted] to [redacted] will have a minimal impact on the cost-effectiveness results in favour of

the comparators, as demonstrated by the company's OWSA (see Section 5.2.2) and EAG's additional analysis (ICER reduces by £246 to £711, depending on the comparator).

Table 58. Reasons for discontinuation in the OLE study used to inform the long-term discontinuation rate in the economic analysis

Reason	Count (N=185)	Percentage
Adverse event	[redacted]	[redacted]
Death	[redacted]	[redacted]
Non-compliance	[redacted]	[redacted]
Other	[redacted]	[redacted]
Physician decision	[redacted]	[redacted]
Pregnancy	[redacted]	[redacted]
Withdrawal by subject	[redacted]	[redacted]
Total	[redacted]	[redacted]

The EAG has two other key comments to make on the company's approach to model discontinuations in the prevention model. These include the company's assumption that the long-term discontinuation rate for the three mAbs is equal to rimegepant and the omission of discontinuations during the 12-week assessment period for reasons other than response.

Firstly, the EAG's clinical experts disagreed with the company's assumption that the three mAbs would have a discontinuation rate equal to rimegepant as they have different mechanisms of action. However, they were unable to suggest if rimegepant would be associated with a lower or higher rate than the mAbs because it is a new treatment. To address these concerns, the company was asked to perform a NMA of treatment discontinuation, which can be used to inform treatment-specific long-term discontinuation rates, or a class-based discontinuation rate for the injectable mAbs vs rimegepant if data are not available to inform a NMA. In their response, the company explained that data for the comparator trials is not publicly available to inform this. Based on the EAG's targeted searches, the EAG found that erenumab may be associated with a long-term all-cause discontinuation rate of 2.38% per 12-week cycle according to the TA682 FAD and ongoing OLE study of a phase II trial of erenumab.[106] This rate is notably [redacted] than the annual rate of discontinuation estimated by the company for rimegepant ([redacted]). However, it is unclear if the discontinuation rate for erenumab is conditional on patients initially responding to treatment and if response was measured using a ≥50% reduction in baseline MMD. As such, the EAG performed an exploratory analysis using a long-term all-cause discontinuation rate of 2.38% per 12

weeks for the mAbs and retained the company's base case assumption in the EAG preferred base case.

Secondly, the EAG notes that the company did not consider discontinuation during the 12-week assessment period. One reason for discontinuation (discontinuation due to adverse events), prior to the assessment of response, was modelled in TA682 (0.8% over 12 weeks for erenumab based on STRIVE, ARISE and LIBERTY for EM, Table 53 on page 199 of 696 of the committee papers) and TA659 (redacted for galcanezumab based on EVOLVE-2 for EM).[25, 27] In study BHV3000-305, 7 of 370 (1.9%) rimegepant subjects discontinued treatment during the 12-week DBT phase due to adverse events. However, given that these are small numbers, the EAG does not consider excluding discontinuations due to adverse events during the 12-week assessment period to be a major issue.

4.2.9 Adverse events

The company did not include adverse events in either model (acute treatment or migraine prevention) given the small proportion of patients experiencing serious adverse events (<2% in either treatment arm) in the phase III acute treatment studies (BHV3000-301,-302 and -303), BHV3000-201 study and BHV3000-305 study. The company also considered this to be a conservative assumption for migraine prevention given the potential for injection site reactions, constipation and hypersensitivity reactions with mAbs.

EAG comment

The EAG heard from its clinical experts that rimegepant is a new treatment and therefore the threshold for reporting adverse events is lower (as indicated by the SmPC black triangle[1]). They were also unaware of any specific serious adverse events associated with rimegepant. The EAG's clinical experts disagreed with the company's assumption that it would be conservative to exclude adverse events for migraine prevention. This is because rimegepant and the mAbs have different mechanisms of action. However, they could not say if the adverse events associated with rimegepant would be more severe or frequent than those associated with the mAbs as rimegepant is a new treatment.

Overall, the EAG accepts the company's decision to omit adverse events from the model as including the costs and consequences associated with the adverse events observed in the rimegepant studies is likely to have a negligible impact on the results.

4.2.10 Mortality

In both models, the company only included all-cause mortality, as per prior NICE TAs in migraine prevention (TA764, TA659 and TA682).[25-27] To further support this approach, the company referred to a published meta-analysis, which found no association between migraine and all-cause mortality.[107]

The company obtained all-cause general population mortality from UK national life tables provided by the Office of National Statistics (ONS).[108] Data from Years 2017 to 2019 were used to inform the models, not Years 2018 to 2020 as stated in the CS. These probabilities were age and sex adjusted according to the baseline patient characteristics in the rimegepant studies.

EAG comment

The EAG found that the company, in the prevention model, used mx in the life tables (the central rate of mortality, defined as the number of deaths at age x last birthday in the three-year period to which the National Life Table relates divided by the average population at that age over the same period) to estimate the probability of mortality in the model. The EAG considers qx in the life tables (the mortality rate between age x and [x +1], that is the probability that a person aged x exact will die before reaching age [x +1]) to better reflect the annual probability of mortality. However, at the end of the modelled time horizon (61 years of age) the mx and qx are very similar (males 0.00835 vs 0.00831 and females 0.00551 vs 0.00549 for mx and qx, respectively). The EAG would have also preferred the company to use the most recent life tables provided by the ONS (Years 2018-2020). However, these amendments are expected to have a minimal impact on the cost-effectiveness results.

4.2.11 Health-related quality of life

4.2.11.1 Acute migraine treatment

4.2.11.1.1 Baseline utility data from BHV3000-201

In the acute model, the company derived a baseline utility value for patients not experiencing a migraine attack in every 48-hour cycle by mapping MSQv2 values from the BHV3000-201 trial data (PRN groups) to the EQ-5D. Mapping was carried out using the episodic migraine regression in Gillard *et al* 2012.[93]

The company then explored regression models of EQ-5D. Models were considered using baseline only data (using baseline MMD), post-baseline only data (using either absolute MMD or change from baseline [CFB] in MMD as a covariate), and baseline + post-baseline data (using absolute MMD as a covariate). According to the company, the latter model performed well and was best suited for incorporating into the economic analysis. This model included age, sex, prior triptan lines and MMD as covariates (Table 59) and resulted in a more favourable baseline utility for rimegepant due to the MMD reduction associated with rimegepant (each MMD averted is associated with an increment of 0.0054 to utility).

Table 59. EQ-5D regression coefficients and standard errors, acute model

Term	Coefficient	SE	conf.low	conf.high	p-value	Base case patient characteristics	
						Subgroup with at least 2 triptan failure (company base case)	mITT population including study BHV3000-310
(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex = Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
trip_lines1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
trip_lines2+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: mITT, modified intention-to-treat; MMD, monthly migraine day; SE, standard error

[redacted]

This regression led to a baseline utility of 0.687 for the subgroup with at least 2 triptan failures (the company base case) and a utility of 0.719 for the mITT population including study BHV3000-310.

4.2.11.1.2 Health state utility data according to pain severity

The company considered two studies identified in the SLR to inform the health state utility values (HSUVs) by migraine pain severity; Stafford *et al.* 2012[86] and Xu *et al.* 2011.[87] The EAG notes that Xu *et al.* 2011 was used to inform HSUVs the ICER evidence report.[52]

In the base case analysis, the company used the values from Stafford *et al.* 2012 as they were more relevant to the UK population than Xu *et al.* 2011; the "Pain free" utility in Stafford *et al.* 2012 was much closer to the UK population age-adjusted utility norms than Xu *et al.* 2011 and Stafford *et al.*

enrolled patients with migraines from the UK and used the UK scoring algorithm, while Xu *et al.* 2011 enrolled patients with migraines from the USA and used the USA scoring algorithm.

Furthermore, to test the face validity of the findings by Xu *et al.* 2011, the company set the pain dimension of the UK EQ-5D value set to the most severe level and assumed perfect health in the other four dimensions of the EQ-5D. This resulted in a utility of 0.264, which is substantially lower than the severe pain utility reported by Xu *et al.* 2011 of 0.44, which indicates 0.44 is implausibly high.

In Stafford *et al.* 2012, the utility value for severe pain was estimated at -0.20, a negative number indicating a state worse than death. In scenario analysis, the company set this utility to 0. The company did not consider a negative utility to be a major issue given that over the 48-hour observation period in the rimegepant pooled acute trials, the time spent on the highest pain intensity "severe pain" is relatively short compared to the three other categories. The EAG also considers a state worse than death to be plausible when considering a few hours of time.

However, the company argued that the "pain free" utility in Stafford *et al.* 2012 (0.87) was relatively high compared to the interictal baseline value predicted from the study BHV3000-201 (reported as 0.72 in the CS and 0.687 in the company's revised base case). Thus, the HSUVs from Stafford *et al.* 2012 were adjusted to retain the differences across pain categories, while reflecting the expectation that time periods without a migraine will have better HRQoL than time periods with a migraine. To do this, the company considered multiplicative and additive approaches, shown below in Table 60. The multiplicative approach was taken in the base case though the additive was run as a scenario.

Table 60. Stafford *et al.* 2012 utility by migraine severity and company adjustments (adapted from Figure 12 in Appendix O)

Health state	Unadjusted Stafford Utility	Multiplicative approach (company base case)	Multiplicative values (company base case)	Additive approach	Additive values
Severe pain	-0.20	*(U_0/0.870)	-0.158	-($0.870-U_0$)	-0.383
Moderate pain	0.53		0.418		0.347
Mild pain	0.66		0.521		0.477
Pain free	0.87		0.687		0.687

Abbreviations: U_0, baseline utility (values in this table use a baseline utility of 0.687, as per the company's revised base case)

4.2.11.1.3 HRQoL data applied in the model (QALH regression)

The time per pain category (none, mild, moderate, severe) was multiplied by health state utilities derived from Stafford *et al*. 2012[86] and then summed over the 48-hour study period to generate QALHs over 48 hours. A regression analysis was then fitted to describe QALH outcomes adjusted for treatment arm, two-hour response status, baseline MMD, and baseline migraine severity. Table 61 shows the regression applied in the company's base case analysis in the subgroup of patients with at least 2 triptan failures. Table 62 shows the regression fitted to the QALH outcomes based on the mITT population including study BHV3000-310.

Table 61. QALH regression analyses fit to pain-hour trajectories for base case parameters (subgroup with at least 2 triptan failures)

Term	Coefficient	SE	conf.low	conf.high	p-value
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BL_severity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BL, baseline; MMD, monthly migraine days; QALH, quality-adjusted life hour; SE, standard error

Table 62. QALH regression analyses fit to pain-hour trajectories in the mITT population including study BHV3000-310

Term	Coefficient	SE
Intercept	[redacted]	[redacted]
Treatment	[redacted]	[redacted]
Responder	[redacted]	[redacted]
MMD	[redacted]	[redacted]
BL_severity	[redacted]	[redacted]

Abbreviations: BL, baseline; mITT, modified intention-to-treat; MMD, monthly migraine days; QALH, quality-adjusted life hour; SE, standard error.

Note, no conf.low, conf.high or p-value reported for this regression.

The model also allows a user to run the economic analysis using raw QALH data (pain-hours multiplied by HSUVs, without any QALH regression) as an alternative to the aforementioned regression. In response to a clarification question, the company explained that the regression was chosen for the base case to adjust for differences in baseline characteristics between treatment arms, particularly differences in baseline severity. The company also noted that, "*the primary advantage of the raw QALH calculation option within the model is that it allows for testing alternative utility values by pain category; due to the nature of the data, these utilities must be pre-*

specified in order to fit the regression models outside of Excel and imported into the model and thus the regression method is not amenable to ad-hoc *adjustments to utility values. Furthermore, use of regression analysis was found to be a conservative approach in scenario 7*".

Finally, during the clarification stage, the company added age-related utility decrements to the acute model, using Ara and Brazier 2010,[109] to align with the prevention model.

4.2.11.1.4 EAG comment

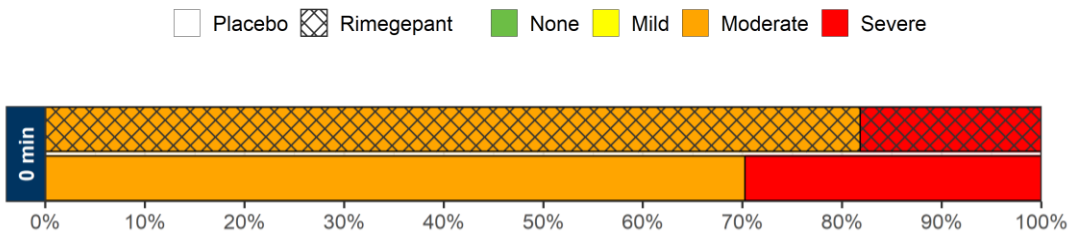
Response to CQ on BL_severity appears to contradict the CS and model

The BL_severity coefficient in the QALH regression is negative ([redacted]). In response to CQ B21 the company stated that, "*The BL_severity coefficient represents the proportion of severe migraines at baseline (vs. moderate), i.e. higher proportion reflects greater severity… the negative relationship with QALH is to be expected as it reflects decreased QALH for greater severity".*

However, in cells H42:H46 of the 'Params' worksheet, the BL_severity coefficient (H51) is multiplied by modpain_live (H24). The modpain_live label is described as the "*Proportion of moderate baseline pain (vs. severe)*" in both the 'Params' worksheet and 'Settings' worksheet. Furthermore, Figure 11 of Appendix O in the CS shows that modpain_live value ([redacted] in the company's base case) is likely referring to the proportion of moderate migraines rather than the proportion of severe migraines. The relevant part of this diagram has been extracted in Figure 11 below.

As such, the EAG considers the company's current modpain_live value to be erroneously inverted and will therefore correct the company's base case so the proportion of severe migraines at baseline (vs moderate) is [redacted] rather than [redacted]. For corrected company results, see Section 6.

Figure 11. Patient baseline pain trajectory for mITT patients treated with placebo and rimegepant in pooled acute trials, two or more triptan failures (adapted from Figure 11 of Appendix O in the CS)



Baseline utility value for patients not experiencing a migraine attack every 48-hour cycle

As mentioned earlier, the MSQv2 has a 4-week recall period and is therefore a useful tool for breaking down patient utility by MMD. In previous submissions, and the prevention model within this submission, the EQ-5D responses mapped from the MSQv2 have been used to represent the average utility of patients over the course of one month (some of these days will include migraines). Therefore, including the baseline utility from study BHV3000-201 as the non-migraine utility and then including an additional utility for patients experiencing migraines will likely result in double counting, as acknowledged by the company's response CQ B23. However, the company also explained in that this is unlikely to impact results, as the overall utilities would be shifted up or down analogously for both treatment arms.

The EAG somewhat agrees with the company but only given certain changes to the model. The difference between rimegepant and BSC utility is driven in the regression by a reduction in average MMDs for rimegepant and is intended to represent the interictal benefit of a reduction in migraine frequency (less stress, easier ability to plan). However, as established, the utility difference driven by reduced MMDs will be an average over the month, meaning it will not just include improvements in the interictal period but also the improvement from not having those additional migraines. Given the EAG does not accept the difference in MMDs between BSC and rimegepant, no action is required to change this as there would likely be little to no impact on results.

The EAG also considered alternative approaches to estimate the non-migraine utility, which do not involve the MSQ or require as many steps or assumptions to estimate. The EAG then reviewed the approach in the ICER evidence report[52] and found that the "pain free" utility from Xu *et al.* 2011 was used for patients without migraine. During the clarification stage, the EAG asked the company to consider using the "pain free" utility value from Stafford *et al*. 2012 (or Xu *et al.* 2011 when HSUVs from Xu *et al.* 2011 are used in place of Stafford *et al.* 2012) or general population norms to inform the non-migraine utility.[86,87] In their response, the company explained that these suggestions were inappropriate as the "pain free" utility is focussed on experience of migraine pain only and does not incorporate other elements of interictal burden or social or emotional impact of migraine. The company also felt that UK population norms are inappropriate, given the reduction in utility associated with migraine (including interictal periods). Nevertheless, the company provided scenarios exploring these suggestions. When the EAG reviewed how these were implemented, it was noticed that the QALH regression was replaced with the raw QALH calculation. Given that the raw QALH calculation cannot adjust for differences in baseline severity between treatment arms, the EAG considers these scenarios to be of limited use.

Overall, the EAG is satisfied with the company's argument that study BHV3000-201 should be used to inform baseline utility value for patients not experiencing a migraine attack in every 48-hour cycle and that HSUVs according to pain severity (Stafford *et al.* 2012) should be adjusted for this baseline using the multiplicative approach.

4.2.11.2 Migraine prevention

Study BHV3000-305 collected MSQv2 data at baseline and Week 12. The company mapped these values to the EQ-5D using algorithms from Gillard *et al*. 2012[93] and noted that this is consistent with the methods used in previous NICE appraisals in migraine prevention.

Mapped EQ-5D data from the end of week 12 was used as the dependent variable in a regression with MMD and 'on treatment' being used as independent variables (Table 63). This regression was then used to get the fixed 'on treatment' benefit and the utility by MMD. The 'on treatment' benefit value was applied to both rimegepant and the comparator mAbs as the company assumed the benefit from rimegepant was equivalent to comparator treatments. The company justified this in CQ B45 by stating that rimegepant has a similar method of action to the mAbs. The company also noted that their approach may be conservative as the utility for rimegepant could be higher due to the differentiated oral nature of the drug. A summary of utility values by MMD used in the economic analysis is presented in Table 78 of the CS.

Age-related utility decrements were included in the prevention model based on the algorithms reported in Ara and Brazier 2010.[109]

Table 63. Regression models for mapped EQ-5D-3L utility (adapted from Table 77 of the CS)

Term	Coefficient	SE	p-value	95% CI	
				lower	upper
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; CS, company submission; MMD, monthly migraine days; SE, standard error

4.2.11.2.1 EAG comment

During the clarification stage, the company was asked to explain how regression model covariates were selected as this was not provided in the CS. In their response, the company said, "*An effect of*

MMD is expected, and the coefficient for treatment, adjusting for MMD, was also statistically significant. Further covariates were not considered. This is consistent with previous appraisals of erenumab and fremanezumab". The EAG agrees that the covariates match the appraisal of erenumab, but not fremanezumab as the regression model covariates and values in that submission were redacted.

The EAG also notes that the baseline mapped EQ-5D scores from study BHV3000-305 were not provided by the company in their submission. Given that patients were randomised in this study, the EAG would expect them to be similar in both treatment arms. However, if they are dissimilar, this would call into question the appropriateness of the treatment covariate in the regression as a difference between arms at baseline may be persisting at Week 12 (the regression is based on mapped EQ-5D scores collected at Week-12). To reduce this uncertainty, the company should provide the baseline mapped EQ-5D scores from study BHV3000-305 according to treatment arm and include them in the regression if any imbalances are observed. This is potentially an important issue as the covariates in the regression had large impacts on the ICER in the company's OWSA.

4.2.12 Resource use and costs

4.2.12.1 Acute migraine treatment

4.2.12.1.1 Drug acquisition and administration costs

Rimegepant is given as a 75 mg tablet, self-administered by patients, as and when an acute migraine attack occurs (*pro re nata* [PRN]). According to the company, the list price of rimegepant is £160.00 for a pack of eight 75 mg tablets, which is equivalent to £20.00 per dose. No patient access scheme (PAS) is in place for rimegepant. During the clarification stage, the company affirmed that the list price applies to the ODT formulation or rimegepant and that the tablet formulation has not been included in the MHRA marketing authorisation and SmPC.

In the first model cycle, the company assumed that patients who do not respond to their first migraine attack discontinue treatment, but still incur the cost of one 8-pack of tablets (£160.00). In the CS, the company suggests this assumption was made to account for the fact that patients would trial a treatment for two or three migraine attacks before stopping treatment.

For subsequent migraine attacks, responders incur the cost of a single tablet until they discontinue treatment, which means drug wastage is not incorporated beyond the first pack.

No treatment costs were considered for the comparator (BSC), which the EAG accepts as a conservative assumption.

4.2.12.1.2 Treatment monitoring costs

No treatment specific monitoring cost were included and no justification for this was provided in the CS. The company has since stated in response to clarification that this decision was taken as no monitoring requirements were outlined in the SmPC for rimegepant.[1]

4.2.12.1.3 Health care resource use cost per migraine

As the company identified no relevant sources in their SLR to inform HCRU, the company reviewed previous NICE appraisals for migraines and identified a study by Vo *et al*. 2018[94] in the fremanezumab submission (TA631/TA764)[26]. This study used data from the National Health and Wellness Survey (NHWS), which included patients from France, Germany, Italy, Spain, and the UK. Health care resource utilisation in this study was compared between migraine respondents suffering from ≥4 monthly headache days (n=218) and non-migraine controls (n=218). The company included three types of HCRU from this study in the economic analysis: hospitalisations, emergency department (ED) visits, and General Practitioner (GP) visits. The company did not consider the other types of HCRU reported in this study (neurologist visits and psychiatrist visits). However, the EAG and its clinical experts do not consider this to be an important omission for a population receiving acute treatment.

Vo *et al.* 2018[94] reported the probability of HCRU per six months for EMs in two groups: 4 to 7 MMDs (n=106) and 8 to 14 MMDs (n=49). The company then converted the six-month probabilities into a per-migraine probability of HCRU by dividing by the midpoint of each migraine frequency group. A weighted average of the two frequency groups was then derived using baseline data for 4 to 7 vs 8 to 14 MMDs from the subgroup of patients with at least 2 triptan failures in study BHV3000-201. The company did not allow this to be varied according to the selected population. The final HCRU probabilities and costs applied in the model are summarised in Table 64. More detail on these calculations can be found in Table 59 of the CS (note that the utilisation of ED visits per six months for 4 to 7 MMDs in this table should be 0.27 rather than 0.37, this error is not contained in the model).

Table 64. Probability and cost of health care resource use per migraine event

Drug	Probability of HCRU per migraine event			Unit cost	
	Mean	SE	Source	Unit cost	Source
Hospitalisation	0.003	0.001	Weighted average from Vo *et al.* 2018 using baseline MMD data in the subgroup of patients with at least 2 triptan failures in study BHV3000-201	£643.29	NHS Reference Costs 2019/20[95]: weighted average of AA31C, AA31D, and AA31E
ED visit	0.010*	0.003		£188.07	NHS Reference Costs 2019/20[95]: VB09Z, as per TA260[14]
GP visit	0.066	0.009		£39.23	PSSRU[96]: cost per patient contact lasting 9.22 minutes

Abbreviations: ED, emergency department; GP, General Practitioner; HCRU, healthcare resource use; MMD, monthly migraine day; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; SE, standard error

*0.009 in the economic analysis

The company only applied these HCRU values to patients experiencing severe events (one at which pain was still moderate or severe at 24 hours), as per the ICER evidence report.[52] The proportion of patients experiencing severe events is given in Table 65 and was taken from the acute pooled RCTs (BHV3000-301, -302, and -303).

Table 65. Proportion of patients with severe events, by response status at 2 hours

Treatment	Subgroup with at least 2 triptan failures		ITT population*	
	Responder	Non-responder	Responder	Non-responder
Rimegepant	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ITT, intention-to-treat

*Excluding study BHV3000-310

4.2.12.1.4 Productivity costs (sensitivity analysis only)

In a scenario, the company included lost productivity costs. The EAG found that the lost productivity cost values reported in Table 62 of the CS did not match the values in the model (Table 66). During the clarification stage, the company clarified that the correct values were those stated in the CS and revised the model accordingly.

Table 66. Lost productivity unit costs, UK employment and labour market statistics

Parameter	Value in CS (correct)	Value in model (incorrect)	Source
Median hourly wage	£16.29	£21.54	ONS 2021[110]
Cost of missed workday (7.5 hour working day)	£122.20	£161.55	ONS 2021[110]

Employment rate	75.6%	92.5%	ONS 2022[111]
Abbreviations: CS, company submission; ONS, Office for National Statistics			

4.2.12.1.5 EAG comment

Omission of treatment specific monitoring costs

In response to a clarification question, the company argued that no monitoring requirements were outlined in the SmPC for rimegepant.[1] However, the EAG notes that the black triangle in the SmPC states, "*This medicinal product is subject to additional monitoring*". As such, the EAG sought clinical expert opinion that revealed that the black triangle is likely to lead to additional administrative work (as the threshold for reporting adverse events is lower) rather than additional patient contact. The clinical experts also noted that they would expect rimegepant to be prescribed by hospital specialists at least initially, possibly moving to primary care over time. In consequence, the EAG considers it important to include the cost of the initial visit with a specialist in its preferred base case.

Omission of drug wastage costs

Non-responders in the first cycle who discontinue treatment incur the cost of a whole pack. For subsequent migraine attacks, tablets are costed individually (that is, there is no pack wastage). During the clarification stage, the EAG requested the company conduct analysis including pack wastage. In their response, the company explained that incorporating wastage would add unnecessarily complexity to the model. The EAG considers that the company could explore this uncertainty by implementing a simple assumption - assume on average, half a pack is wasted when patients discontinue rimegepant. For the EAG's results employing this assumption, see Section 6.3.1.

Limitations of the source used to inform HCRU (Vo et al. 2018)

The EAG verified the company's HCRU estimates with its clinical experts. They advised that the hospitalisation rate would be notably lower in clinical practice. Following this, the EAG reviewed the source used to inform HCRU (Vo *et al.* 2018)[94] and found that the non-migraine control group vs the 4 to 7 EM and 8 to 14 EM groups was not considered statistically significant for hospitalisations (though it was for CM). In response to a clarification question the company explained that hospitalisations were included in the economic analysis to align with the prevention model and previous TAs in migraine. For completeness, the EAG explored a scenario setting the frequency of

hospitalisations per migraine to zero; the ICER increased by around £500 in the subgroup of patients experiencing at least 2 triptan failures.

The EAG also considers the results from the 'Non-migraine' control group to be important as the HCRU estimates in the control group, 4 to 7 EM group and 8 to 14 EM group may not be attributable to migraine related healthcare needs. In response to a clarification question, the company stated that the control group was not taken into account when considering which HCRUs to include and that this is consistent with previous NICE TAs. However, the EAG notes that these TAs included HCRU rates for patients with 0 MMDs.

The EAG does not consider this to be a major issue given that none of the HCRU estimates or unit costs associated with them are key model drivers according to the company's OWSA. However, the company's current approach is likely leading to systemic bias in HCRU by overestimating HCRU for above average MMD rates and underestimating below average MMD rates. The EAG has produced estimates by graphing the 6 monthly Vo *et al*. 2018 HCRU estimates for the non-migraine control group as 0 and the midpoints for the 4 to 7 and 8 to 14 MMD groups. The EAG also employed a linear equation, like the linear assumption made by the company. These graphs are shown below, adjusted to monthly rates, and shown in comparison to the company's estimates (Figure 12,

Figure 13 and

Figure 14). As such, the EAG would urge the company to reassess the data taken from Vo *et al.* 2018 at technical engagement by utilising the control group.

Figure 12. Monthly hospitalisation rate by MMD

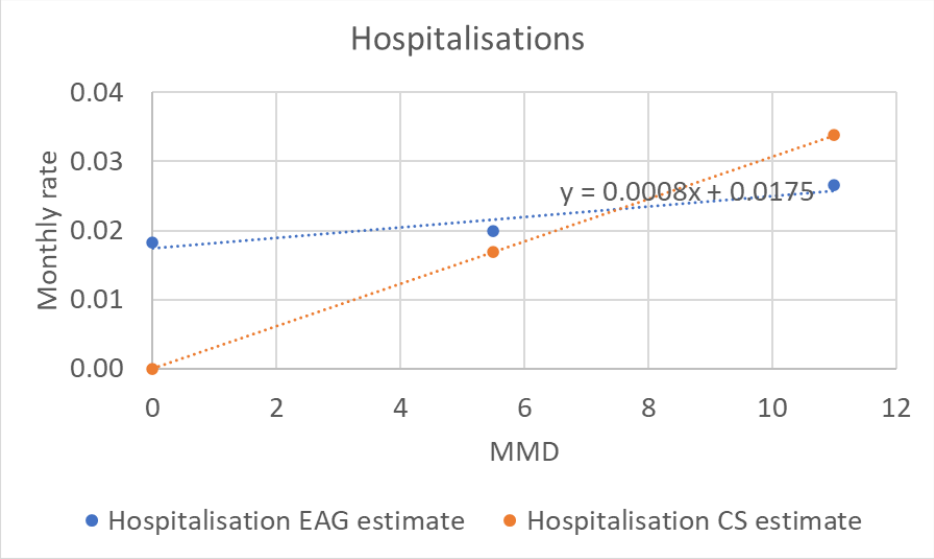


Figure 13. Monthly ED visit rate by MMD

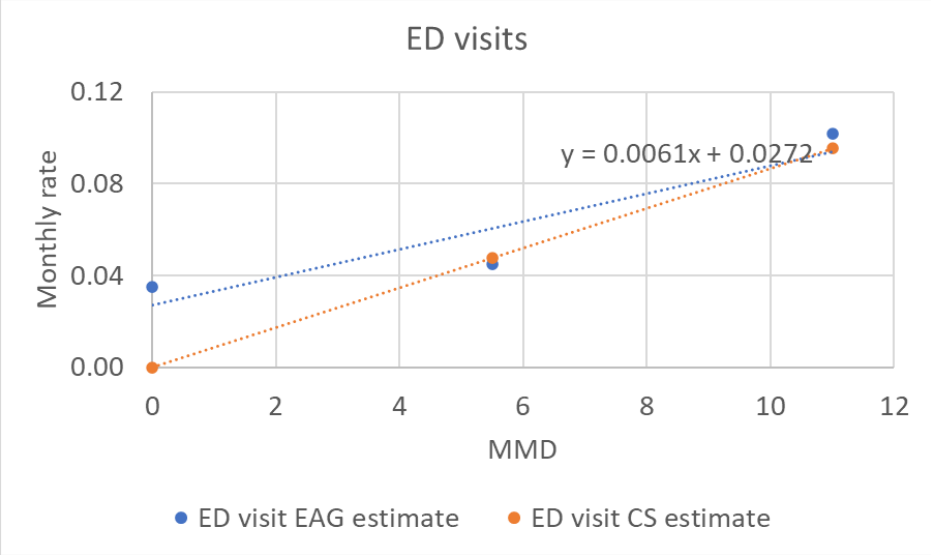
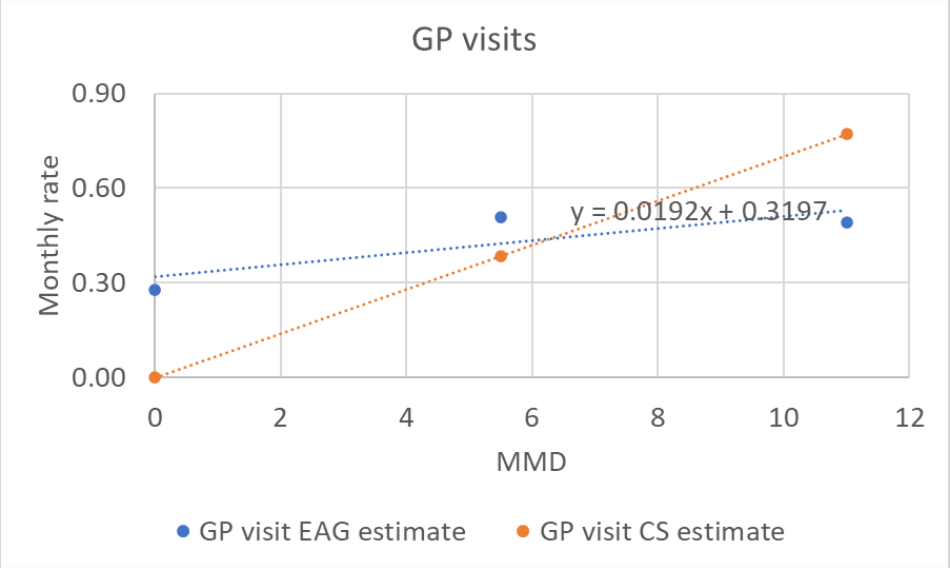


Figure 14. Monthly GP visit rate by MMD



The EAG also considers it important to highlight that the estimates in Vo *et al.* 2018 were based on patients experiencing headaches and not migraines. However, the EAG does not consider this to be a major issue given that this limitation was acknowledged and accepted by committee when appraising fremanezumab (TA631/764)[26]. The EAG's clinical experts also considered the HCRU estimates, except for hospitalisations, to be a reasonable representation of MMDs.

Finally, the company was asked to justify why only severe migraines were costed when Vo *et al.* 2018 did not single out severe migraines (headaches) as the only migraines incurring HCRU. In their response, the company acknowledged that this is a limitation to the current evidence base and that they were unable to account for potential increases in resource use that would arise from migraine with lower pain severity at 24 hours. The company also reiterated that their assumption to cost severe migraines only is in line with the ICER evidence report.[52] Given that the EAG's clinical experts support the view that mild migraine attacks would be unlikely to incur additional health care resources, the EAG does not consider this to be a major issue.

Alternative HCRU source (Doane et al. 2020)

The EAG considers that Doane *et al*. 2020[112] may be a more appropriate source of HCRU evidence than Vo *et al.* 2018[94] because it uses a more recent release of the NHWS data (2017 instead of 2016) and includes four categories of monthly headache days (1 to 3, 4 to 7, 8 to 14, and 15 or more), rather than two (4 to 7 and 8 to 14). However, a key advantage of Vo *et al.* 2018 is that it includes

non-migraine control group (though as previously stated this is not currently incorporated into the model) and has been used in previous NICE appraisals in migraine prevention (TA631/TA764).[26]

4.2.12.2 Migraine prevention

4.2.12.2.1 Drug acquisition and administration costs

Rimegepant is given as a 75 mg tablet, self-administered by patients, every other day (EOD) for migraine prevention. As noted previously, the list price of rimegepant (ODT formulation) is £160.00 for a pack of eight 75 mg tablets, which is equivalent to £20.00 per dose. The dosing schedule in Study BHV3000-305[68] during the 12-week double-blind phase was 1 tablet of rimegepant 75 mg EOD. The modelled dose reflects this schedule as 14 tablets were utilised every 28 days.

Acquisition costs for the comparators (erenumab, fremanezumab and galcanezumab) were obtained from the BNF.[97] However, these treatments are subject to PAS discounts and results including these discounts can be found in the confidential appendix. As noted in Section 4.2.3.2, the modelled doses for the comparators were obtained from the BNF and/or previous NICE appraisals, and these doses reflect the clinical trials informing the NMA.

The acquisition cost of rimegepant and each mAb, per 28-day cycle, using list prices, is summarised in Table 67. The initial 28-day cost for each mAb appears to be based on using a whole vial whereas the ongoing 28-day costs are adjusted down from 1 month (30.4 days) to 28 days. Rimegepant is the exception, with the initial and ongoing costs based on the same number of days and packs (1.75 packs, equivalent to 14 tablets per 28-day cycle).

As for administration costs, the company assumed that 10% of patients receiving mAbs require 30 minutes of nurse time to administer the treatment (£2.10 per 28-day cycle), consistent with the assumption accepted in previous NICE appraisals in migraine prevention (TA764/TA631, TA659 and TA682).[25-27]

Table 67. Treatment costs for prevention (adapted from Table 79 of the CS)

Treatment	Dose	Cost per pack or vial	28-day initial treatment cost	28-day ongoing treatment cost
Rimegepant	75 mg taken EOD	£160.00	£280.00	£280.00
Erenumab	140 mg taken monthly	£386.50	£386.50	£355.50
Fremanezumab	225 mg taken monthly	£450.00	£450.00*	£414.00
Galcanezumab	120 mg taken monthly with 240 mg initial dose	£450.00	£900.00*	£414.00

Abbreviations: CS, company submission; EOD, every other day
*These numbers were erroneously switched in Table 79 of the CS; the correct cost is reported.

4.2.12.2.2 Treatment monitoring costs

No treatment specific monitoring cost were included and no justification for this was provided in the CS. The company has since stated in response to clarification that this decision was taken as no monitoring requirements were outlined in the SmPC for rimegepant.[1]

4.2.12.2.3 Health care resource use cost per migraine

As the company identified no relevant sources in their SLR to inform HCRU, the company reviewed previous NICE appraisals for migraines. The company then used HCRU estimates from the erenumab submission (TA682[25]), according to MMDs. The estimates from TA682[25] were based on the NHWS, but this is not equivalent to the data reported in Vo *et al.* 2018[94] (the study used to inform HCRU in the acute model using the NHWS) as these data were analysed directly from the NHWS 2017 as opposed to being indirectly taken from Vo *et al.* 2018,[94] which reports estimates based on the NHWS 2016.

In the original CS, the company obtained resource use for acute medication from the fremanezumab submission (TA764[26]). At the clarification stage, the company obtained these from the erenumab submission (TA682[25]), which were based on the erenumab trials (STRIVE, ATISE and LIBERTY).

The HCRU quantities and total costs applied in revised model are listed in Table 68. For a list of the unit costs associated with each type of HCRU, see

Table 69.

Table 68. HCRU by MMD used applied in the revised base case

Migraine days	Mean resource use per migraine day category							Total HCRU cost*
	Physician visits	ED visits	Hospital stays	Nurse practitioner visits	Specialist consultation	Triptan	Other medication	
0	0.605	0.090	0.070	0.010	0.190	0.000	3.323	£96.51
1	0.865	0.200	0.125	0.045	0.305	0.886	3.972	£174.74
2	0.865	0.200	0.125	0.045	0.305	2.368	4.621	£175.28
3	0.865	0.200	0.125	0.045	0.305	3.850	5.270	£175.83
4	1.240	0.175	0.120	0.040	0.525	5.332	5.919	£191.45
5	1.240	0.175	0.120	0.040	0.525	6.814	6.568	£191.99
6	1.240	0.175	0.120	0.040	0.525	8.296	7.216	£192.54

7	1.240	0.175	0.120	0.040	0.525	9.778	7.865	£193.08
8	1.660	0.275	0.120	0.115	0.145	11.260	8.514	£227.37
9	1.660	0.275	0.120	0.115	0.145	12.742	9.163	£227.92
10	1.660	0.275	0.120	0.115	0.145	14.224	9.812	£228.46
11	1.660	0.275	0.120	0.115	0.145	15.706	10.461	£229.01
12	1.660	0.275	0.120	0.115	0.145	17.188	11.109	£229.55
13	1.660	0.275	0.120	0.115	0.145	18.670	11.578	£230.05
14	1.660	0.275	0.120	0.115	0.145	20.152	12.407	£230.64
15	1.755	0.350	0.155	0.220	0.380	21.634	13.056	£301.59
16	1.755	0.350	0.155	0.220	0.380	23.116	13.705	£302.14
17	1.755	0.350	0.155	0.220	0.380	24.598	14.354	£302.68
18	1.755	0.350	0.155	0.220	0.380	26.080	15.003	£303.23
19	1.755	0.350	0.155	0.220	0.380	27.562	15.651	£303.77
20	1.755	0.350	0.155	0.220	0.380	29.044	16.300	£304.32
21	1.755	0.350	0.155	0.220	0.380	30.526	16.949	£304.87
22	1.755	0.350	0.155	0.220	0.380	32.008	17.598	£305.41
23	1.755	0.350	0.155	0.220	0.380	33.490	18.247	£305.96
24	1.755	0.350	0.155	0.220	0.380	34.972	18.896	£306.50
25	1.755	0.350	0.155	0.220	0.380	36.454	19.544	£307.05
26	1.755	0.350	0.155	0.220	0.380	37.935	20.193	£307.59
27	1.755	0.350	0.155	0.220	0.380	39.417	20.842	£308.14
28	1.755	0.350	0.155	0.220	0.380	40.899	21.491	£308.69

Abbreviations: ED, emergency department; HCRU, healthcare resource use; MMD, monthly migraine days; NHWS, National Health and Wellbeing Survey

*In the original CS, acute medication costs were omitted, but the company corrected this and included them at the clarification stage.

Table 69. List of resource use and associated costs used in the prevention economic model

Resource	Unit cost	Description	Source
GP visit	£39.23	Based on cost per patient contact lasting 9.22 minutes	PSSRU[96]
Neurologist visit	£192.24	Consultant led neurology visit (service code 400) unit cost	NHS Reference Costs 2019/20[95]
ED visit	£188.07	HRG code VB08Z	NHS Reference Costs 2019/20[95]
Hospitalisation	£643.28	Weighted average of HRG codes AA31C, AA31D, and AA31E	NHS Reference Costs 2019/20[95]
Nurse practitioner	£42.00	One hour of working time for Band 5 nurse	PSSRU[96]
Triptan use	£0.25*	1.3 sumatriptan tablet	BNF[97]

Other medication**	£0.28	Assumption based on the erenumab submission (TA682[25]), inflated to 2020/21 prices

Abbreviations: BNF, British National Formulary; ED, emergency department; GP, general practitioner; HRG, healthcare resource group; NHS, National Health Service; PSSRU, Personal Social Services Research Unit

*£0.19 reported in the CS, and 1 sumatriptan tablet reported in the model reference, the values applied in the model calculations are reported

**Added to the model by the company at the clarification stage, this was not included in the original CS

4.2.12.2.4 EAG comment

Omission of treatment specific monitoring costs

Within Section 1.3.3.2 of the CS the company states that, "*Patients should be reviewed every six months to assess a need for continuation of prophylaxis*", which would suggest there should be some monitoring cost for all preventative treatments. Previous NICE appraisals in migraine prevention (TA764/TA631, TA659 and TA682)[25-27] have also noted that mAbs need monitoring at regular intervals. The committee for TA659 concluded that additional monitoring costs for galcanezumab should be included in the model to account for an appointment with a consultant every 6 months and the CS for fremanezumab (TA631) included a 15-minute appointment with a medical consultant every 6 months. Despite this, the company included no treatment specific monitoring costs in the prevention model.

Clinical experts have also advised the EAG that as rimegepant is a new technology, it is likely to be prescribed and monitored by a specialist, and in line with where the mAbs are prescribed. However, as rimegepant is an oral drug it may move to primary care in time.

During the clarification stage, the company was asked to clarify why no treatment specific monitoring costs were included in the prevention model. In response, the company stated that no monitoring requirements were outlined in the SmPC[1] for rimegepant. As noted in Section 4.2.12.1.5, the black triangle in the SmPC suggests additional monitoring is required, but this will lead to additional administrative work rather than additional patient contact.

Overall, the EAG considers it conservative of the company to exclude treatment specific monitoring costs from the prevention model given these are likely to be incurred by more mAb patients than rimegepant patients (rimegepant is the least effective treatment which means patients discontinue rimegepant sooner than mAbs, and rimegepant may move from being monitored in secondary care to primary care in time). Furthermore, it could be argued that treatment specific monitoring costs

are already incorporated as part of the HCRU costs as some costs are incurred when patients experience 0 MMDs.

Inconsistent method to model drug acquisition costs

For the mAb treatments, the company applied different acquisition costs in the initial 28-day cycle and subsequent 28-day cycles. In the initial 28-day cycle, the company costed the whole vial, but in subsequent cycles, the cost of a vial is adjusted so that it reflects 28 days rather than one month (30.4 days). As such, the initial 28-day cycle is more expensive than subsequent 28-day cycles. For rimegepant, both the initial 28-day cycle and subsequent 28-day cycles are costed assuming 28 days. The EAG can find no rationale for applying a 30.4-day cost to the mAbs in the initial 28-day cycle and therefore implements a 28-day cost to these cycles in its preferred base case (while maintaining the loading dose for galcanezumab).

The EAG also found that the BNF reports a slightly different regimen for erenumab than fremanezumab and galcanezumab: erenumab should be offered every 28 days while fremanezumab and galcanezumab should be offered every month (30.4 days). The company has assumed all mAbs are offered every month (30.4 days). Following this, the EAG sought clinical expert feedback on how important these differences are in clinical practice. They advised that these differences will not be observed in clinical practice as offering a mAb every 28 days or 30.4 days will not impact efficacy. They also noted that the recommended doses in the BNF may need to reflect the treatment regimens in the trials which informed the marketing authorisations. Nevertheless, the EAG considers it important to align dosing with marketing authorisations and will therefore adopt the 28-day regimen for erenumab in its preferred base case.

Inconsistent HCRU sources

According to the NICE guide to the methods of TA, eMIT[113] should be used to cost generic drugs. Thus, the cost per migraine based on triptan use should be £0.22 (1.03/6*1.3) rather than £0.25 (1.17/6*1.3). The EAG also identified a few discrepancies with the triptan costs and assumptions applied in the model and CS, however these would have a negligible impact on the cost-effectiveness results given that sumatriptan is relatively inexpensive.

Finally, as mentioned in Section 4.2.12.1.5, Vo *et al.* 2018[94] was based on MHDs and not MMDs but the EAG does not consider this to be a major issue given that the values were accepted by committee in TA682.

5 Cost effectiveness results

The results included in this section are based on list prices. Results including comparator patient access scheme (PAS) discounts can be found in the confidential appendix. As noted in Section 4.2.12, no PAS is in place for rimegepant.

5.1 Acute migraine treatment

During the clarification stage, the company revised their base case analyses. The changes made by the company include:

- Converting migraine attacks per month into monthly migraine days (MMDs);
- Adding age-adjusted utilities;
- Amending the discontinuation rate per cycle calculation;
- Updating lost productivity parameters.

All results in this section include these changes.

To generate cost-effectiveness results, the company used the distribution of migraine attacks per month from study BHV3000-201. This distribution-based approach involves generating costs and quality-adjusted life years (QALYs) for each number of migraine attacks per month (0, 1, 2, 3… 14), then taking a weighted average of these values according to the distribution. The company preferred to generate results using the distribution rather than the mean as the mean doesn't fully account for patients with high-frequency migraine episodes, which have the potential to have a reduction in frequency with rimegepant. Results using the mean approach are provided in scenario analysis (see Section 5.1.3).

5.1.1 Company's base case results

5.1.1.1 Deterministic results

The company's deterministic base case results are given in Table 70. In the company's base case, rimegepant is associated with higher costs and higher QALYs compared to best supportive care (BSC), resulting in an incremental cost-effectiveness ratio (ICER) of £17,160 per QALY gained.

Table 70. Company's revised deterministic base case results (acute treatment) (adapted from Table 65 of the company's clarification response)

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)
BSC	£2,396	7.72	-	-	-
Rimegepant	£9,704	8.14	£7,307	0.43	£17,160

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

5.1.1.2 Probabilistic results

The company performed probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around base case results. Generally, probabilities were varied using a beta distribution and regressions using a Cholesky decomposition, except for the regression to predict reductions in MMD by *pro re nata* (PRN) rimegepant, which was not varied. Utilities for no pain, mild pain and moderate pain were varied using a beta distribution, while the utility for severe pain was varied using a normal distribution (as the mean severe pain utility was negative). The only baseline characteristic that was varied in PSA was the number of migraine attacks, using a normal distribution. The EAG also notes that no unit costs or pain trajectories were varied. Most of these parameters were also omitted from the company's one-way sensitivity analysis (OWSA). The EAG would not expect drug costs to be varied as these are fixed but would expect non-drug costs to be varied using +/-20% of the mean value in the absence of any reported variation. The EAG is also unclear how utilities can be varied in PSA as this would require the quality-adjusted life hour (QALH) regression to be remodelled for every variation in utility. Overall, although the EAG considers the distributions assigned to the parameters reasonable, the EAG considers the varied parameters to be somewhat incomplete.

The PSA results provided by the company, arising from 1,000 simulations, are reproduced in Table 71. The company did not provide any additional results from their PSA at clarification (i.e., a PSA scatter plot or cost-effectiveness acceptability curve [CEAC]). Although the EAG is satisfied that the deterministic and probabilities results are similar, the EAG has been unable to replicate the

company's PSA given that it takes several hours to run (the model also includes a pop-up with this warning, and a note that the previous run took 493.9 minutes). Moreover, the model provided to the EAG at the clarification stage did not include the PSA results generated by the company, the model was saved on a PSA run on 9 June 2022 (prior to the company's revisions).

Table 71. Company's revised probabilistic base case results (acute treatment) (adapted from Table 66 of the company's clarification response)

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)
BSC	£2,387	7.72	-	-	-
Rimegepant	£9,700	8.14	£7,313	0.43	£17,187

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

5.1.2 *Company's one-way sensitivity analyses*

The company carried out OWSA to assess the impact of varying the key parameters between the upper and lower 95% confidence interval (CI) of the mean value. Where 95% CIs were not available, the company varied the mean value by +/-20%. The 10 most influential parameters resulting from the OWSA are reported in Table 72. The ICER was most sensitive to the adherence to the parameters in the quality-adjusted life hour (QALH) regression and the baseline number of migraine attacks per month.

Table 72. Results of the deterministic sensitivity analysis for rimegepant vs BSC (acute treatment) (adapted from Table 67 of the company's clarification response)

Parameters	Parameter input		ICER (£/QALY)		
	Base case	(lower, upper)	Lower	Upper	Max difference from base case
Responder Yes parameter QALH regression	6.466	(4.1, 8.82)	21,398	14,324	4,237
Rimegepant parameter QALH regression	2.74	(0.46, 5.03)	21,159	14,433	3,999
MMD parameter QALH regression	-0.68	(-1.27, -0.1)	15,927	18,601	1,440
Baseline migraine attacks	7.33	(5.86, 8.8)	18,523	16,941	1,362
Intercept QALH regression	34.05	(30.55, 37.54)	16,471	17,910	749
Age	45.7	(18, 65)	17,737	16,857	576
Mod/sev 24 hr per migraine Usual care- non-responder	0.28	(0.2, 0.37)	17,659	16,615	546
EQ-5D regression: (Intercept)	0.71	(0.7, 0.73)	17,624	16,720	464
Rimegepant discontinuation per year	0.097	(0.0226, 0.2168)	17,551	16,704	456

Parameters	Parameter input		ICER (£/QALY)		
	Base case	(lower, upper)	Lower	Upper	Max difference from base case
EQ-5D regression: age covariate	0.001	(0.0006, 0.0014)	17,616	16,728	456

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; MMD, monthly migraine day; QALH, quality-adjusted life hour

5.1.3 *Company's scenario analyses*

The company undertook a series of scenario analyses to assess the impact of applying alternative assumptions to key model parameters. These scenarios are presented in Table 73. The largest increases in the ICER were observed for an assumption of no reduction in MMD frequency among frequent PRN user (£22,529) and for a two-year time horizon (£20,560). No other scenarios led to an ICER above £20,000 per QALY. The largest decrease in the ICER was observed for a responder definition of pain relief at 8 hours (£10,044). Assuming a societal perspective switched the direction of the ICER (rimegepant dominates BSC).

The company also conducted several scenario analyses requested by the EAG, which are outlined in Section 6.3.1.

In the CS, the company inferred that they would conduct a scenario employing the HSUVs from Xu *et al.* 2011 instead of Stafford *et al.* 2012.[86, 87] When the EAG reviewed the company's scenarios, the EAG found that this scenario was missing. Given that the QALH regressions are only available using HSUVs from Stafford *et al.* 2012, the EAG is unable to run the scenario adjusting for differences in baseline characteristics, which is particularly important given the differences in baseline severity between the treatment arms. The EAG would therefore urge the company to provide a scenario where the HSUVs and QALH regression are informed by Xu *et al.* 2011 at technical engagement, to help inform committee should they prefer Xu *et al.* 2011 to Stafford *et al.* 2012.

Table 73. Scenario analysis: rimegepant vs BSC (using Study BHV3000-201 MMD distribution option) acute treatment of migraine (adapted from Table 68 of the company's clarification response)

#	Description	Base case	Value in scenario	Inc. costs	Inc. QALYs	ICER (£/QALY)
1	Base case	-	-	£7,307	0.43	17,160
2	Adopt societal perspective	NHS and PSS	-	-16,602	0.43	Rimegepant dominant

#	Description	Base case	Value in scenario	Inc. costs	Inc. QALYs	ICER (£/QALY)
3	Discount rate	3.5%	1.5%	8,140	0.48	17,076
4	Time horizon	20 years	2 years	1,961	0.10	20,560
		20 years	5 years	3,952	0.22	17,998
		20 years	10 years	5,880	0.34	17,351
5	Responder definition	Pain relief at 2-hours	Pain relief at 8-hours	6,784	0.68	10,044
6	Reduction of MMD frequency among frequent PRN rimegepant users	Include	Exclude	8,505	0.38	22,529
7	QALH utility	From regression	Raw data: Pain intensity x hour	7,307	0.45	16,282
8	Event utility regression	Multiplicative adjustment	Additive adjustment	7,307	0.55	13,302
9	Migraine event utility values Pain intensity x hour	Stafford *et al.* as published	Set severe utility to 0 instead of negative value	7,307	0.41	17,975
10	Patient population from pooled rimegepant acute trials	≥2 triptan failure	mITT (responder, pain trajectory), baseline characteristics = 201 all comers.	4,154	0.25	16,312
			mITT (responder, pain trajectory, and baseline characteristics)	4,241	0.25	16,821
11	Rimegepant discontinuation annual rate	Use discontinuation due to adverse events, lack of efficacy, or withdrawal by participant from Study BHV3000-201 (██% annually)	Use “all cause” discontinuation to inform the model (20% annually) from Study BHV3000-201	4,182	0.25	16,760
12	Response following rimegepant discontinuation	Assumed to revert to placebo non-responders after one year at placebo responder rate	Immediately revert to BSC non-responders at discontinuation	7,307	0.40	18,141

#	Description	Base case	Value in scenario	Inc. costs	Inc. QALYs	ICER (£/QALY)
13	BSC waning effect (time period before BSC responders transition to BSC non-responder trajectories)	12 months	6 months	7,285	0.42	17,168
		12 months	18 months	7,329	0.43	17,141
14	MMD approach to generate results	Weighted across migraine event distribution observed in Study BHV3000-201	Mean	7,681	0.41	18,570

Abbreviations: BSC, best supportive care; CQ, clarification question; ICER, incremental cost-effectiveness ratio; mITT, modified intention to treat; PRN, pro re nata (as needed); QALYs, quality adjusted life year

5.1.4 Model validation and face validity check

In the CS, the company stated that extensive technical validation was undertaken by a third-party. This involved a detailed review of programming and extreme value testing. The cost-effectiveness model was quality-assured using the internal processes of the health economists who built the model. Additionally, the model was also quality checked and validated by an external health economist not involved with the original programming of the model. Further, extreme value testing has been performed to investigate and ensure robustness of model behaviours for wide range of input parameter values.

Despite these checks, the EAG identified a few errors that were corrected by the company at the clarification stage. For example, the company erroneously interpreted migraine attacks per month as MMDs (see Section 4.2.6.1). The EAG also identified an error after the clarification stage regarding the proportion of moderate vs severe migraine attacks at baseline (see Section 4.2.11.1.4). Results including this correction can be found in Section 6.

The company also noted that two virtual consultation meetings were held in March 2022 with 19 UK experts consisting of a broad range of consultants from primary, secondary and tertiary care, including general practitioners (GPs), GPs with special interest (GPwSI), neurologists, pharmacists, nurse specialists, pain specialists, and health economists to validate the model structure and assumptions.[50] The EAG's clinical experts were generally in agreement with the items that were discussed at the company's consultation meetings, particularly that it is generally recommended to

try a particular treatment on two or three episodes before abandoning it and that pain relief at 2 hours is a reasonable and pragmatic measure to determine response to treatment.

However, it is unclear if the company asked its experts at these consultation meetings if they considered the distribution of baseline migraine attacks per month from study BHV3000-201 or the acute pooled RCTs to better reflect the range potentially observed in the UK population for the acute treatment of migraine (see Section 4.2.6.1). The model is sensitive to this assumption and therefore additional clinical expert input but would be helpful to inform it.

5.2 Migraine prevention

During the clarification stage, the company revised their base case analyses. The changes made by the company include:

- Updating the network meta-analysis (NMA);
- Replacing the health care resource use (HCRU) estimates from the fremanezumab submission with the erenumab submission;
- Using the exact HCRU values from the erenumab submission (no rounding);
- Using CODA from the updated NMA to inform the probabilistic analysis.

All results in this section include these changes.

5.2.1 Company's base case results

5.2.1.1 Deterministic results

Table 74 shows the company's deterministic base case resulting comparing each of the three monoclonal antibodies (mAbs) to rimegepant. As shown in Table 74, the mAbs are associated with higher costs and higher QALYs than rimegepant (i.e., a north-east quadrant ICER). Based on willingness-to-pay (WTP) thresholds of £20,000 or £30,000 per QALY, rimegepant would be considered cost-effective compared to each mAb as the ICERs are above these WTP thresholds and the incremental net monetary benefits (NMBs) are negative. The company's fully incremental results are provided in Table 75.

If the company compared rimegepant to the three mAbs, rimegepant would be associated with lower costs and lower QALYs than the mAbs (i.e., a south-west quadrant ICER). Given that

rimegepant is the treatment that is being appraised, the EAG considers it more intuitive to present results in this way and will therefore present the EAG's results like this in Section 6.

Table 74. Company's revised pairwise deterministic base case results (migraine prevention) (adapted from Table 84 of the company's clarification response)

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)	Inc. NMB (£20,000/ QALY WTP threshold)	Inc. NMB (£30,000/ QALY WTP threshold)
Rimegepant	£19,925	9.033	-	-	-	-	-
Erenumab	£23,134	9.068	£3,209	0.044	£92,671	-£2,516	-£2,170
Rimegepant	£19,925	9.033	-	-	-	-	-
Fremanezumab	£25,201	9.077	£5,276	0.035	£118,883	-£4,388	-£3,945
Rimegepant	£19,925	9.033	-	-	-	-	-
Galcanezumab	£25,987	9.086	£6,062	0.053	£115,211	-£5,010	-£4,484

Abbreviations: ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

Table 75. Company's revised fully incremental deterministic base case results (migraine prevention) (adapted from Table 84 of the company's clarification response)

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)
Galcanezumab	£25,987	9.086	2,853	0.018	£158,591**
Fremanezumab	£25,201	9.077	2,067	0.009	Dominated*
Erenumab	£23,134	9.068	3,209	0.035	£92,671
Rimegepant	£19,925	9.033	-	-	-

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

*Extendedly dominated

**ICER for galcanezumab vs erenumab

5.2.1.2 Probabilistic results

The company performed PSA to assess the joint parameter uncertainty around base case results. Generally, probabilities were varied using a beta distribution and regressions using a Cholesky decomposition (utilities were included in a regression). The company also varied the odds ratios obtained from the NMA using CODA. No unit costs or baseline characteristics (except MMDs) were varied in PSA, but the EAG does not consider this to be an issue given that they were varied in the

company's OWSA. Overall, the EAG considers the parameters and chosen distributions to be generally sound.

The PSA results provided by the company, arising from 1,000 simulations, are reproduced in Table 76. The EAG considers these results to be similar to the company's deterministic results. However, the company did not provide any additional results from their PSA at clarification (i.e., a PSA scatter plot or CEAC). When the EAG re-ran the company's PSA, to see if it could generate similar results to the company, these were generated. The EAG's ICERs are reported alongside the company's ICERs in Table 76. For scatter plots, see Figure 15 to Figure 17 and for CEACs, see Figure 18. The scatter plots in the model are generated comparing rimegepant to the mAbs. As a result, most simulations lie in the south-west quadrant where rimegepant is cheaper and less effective than the mAb. According to the CEACs, rimegepant is the most cost-effective option at all tested WTP thresholds.

Table 76. Company's revised probabilistic base case results (migraine prevention) (adapted from Table 68 of the company's clarification response)

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)	EAG ICER (£/QALY)
Rimegepant	£19,916	9.041	-	-	-	
Erenumab	£23,146	9.075	£3,230	0.034	£94,366	£94,198
Rimegepant	£19,916	9.041	-	-	-	
Fremanezumab	£25,288	9.086	£5,372	0.045	£119,098	£118,559
Rimegepant	£19,916	9.041	-	-	-	
Galcanezumab	£26,038	9.093	£6,122	0.052	£116,629	£116,394

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Figure 15. Scatter plot for rimegepant vs galcanezumab (generated by the EAG)

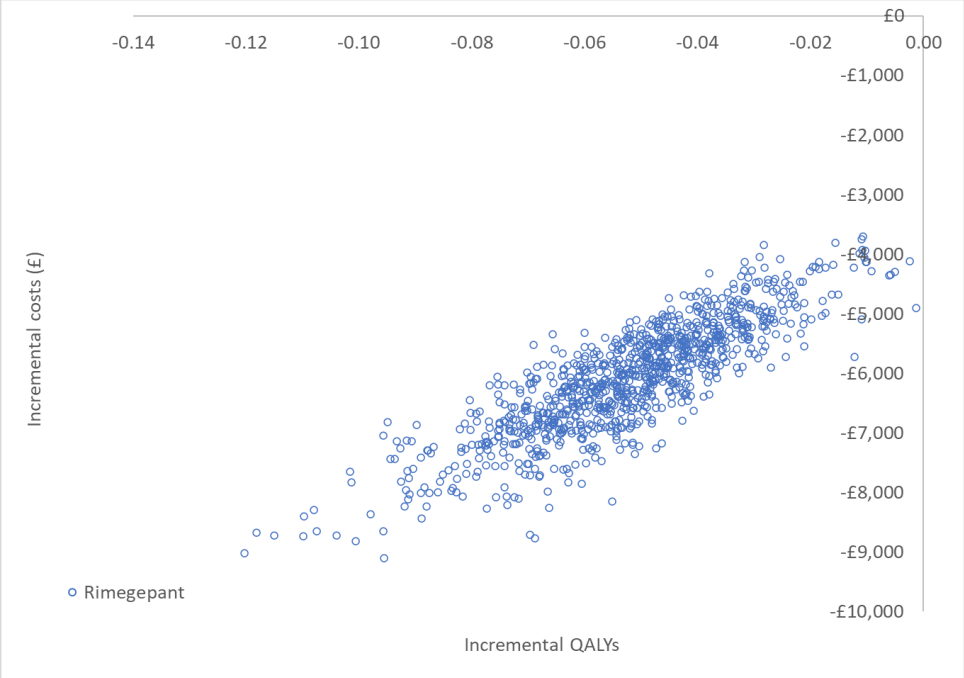


Figure 16. Scatter for rimegepant vs fremanezumab (generated by the EAG)

Figure 17. Scatter plot for rimegepant vs erenumab (generated by the EAG)

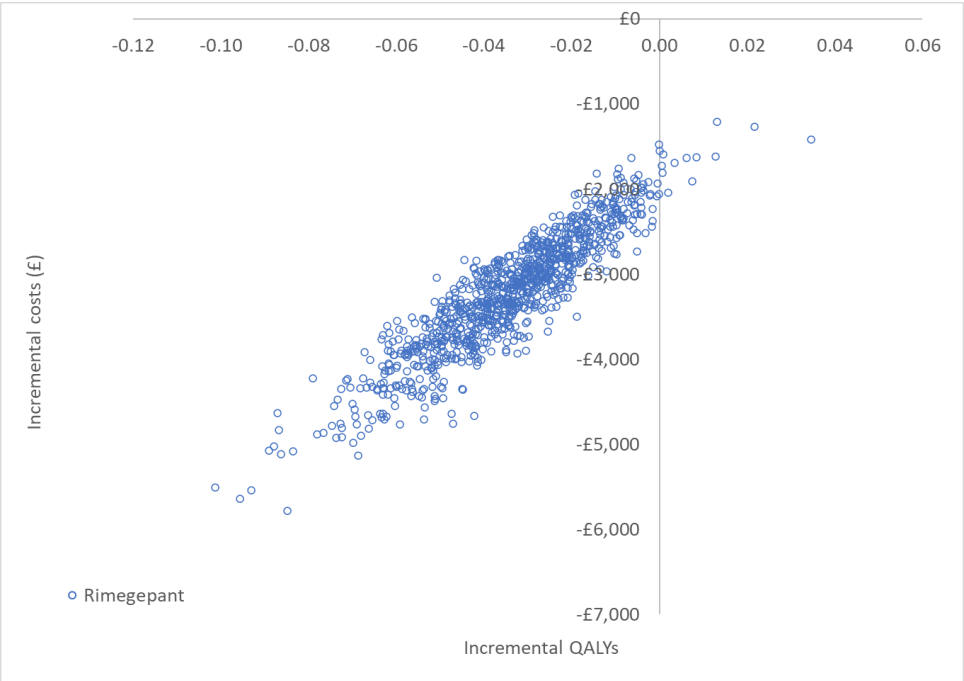
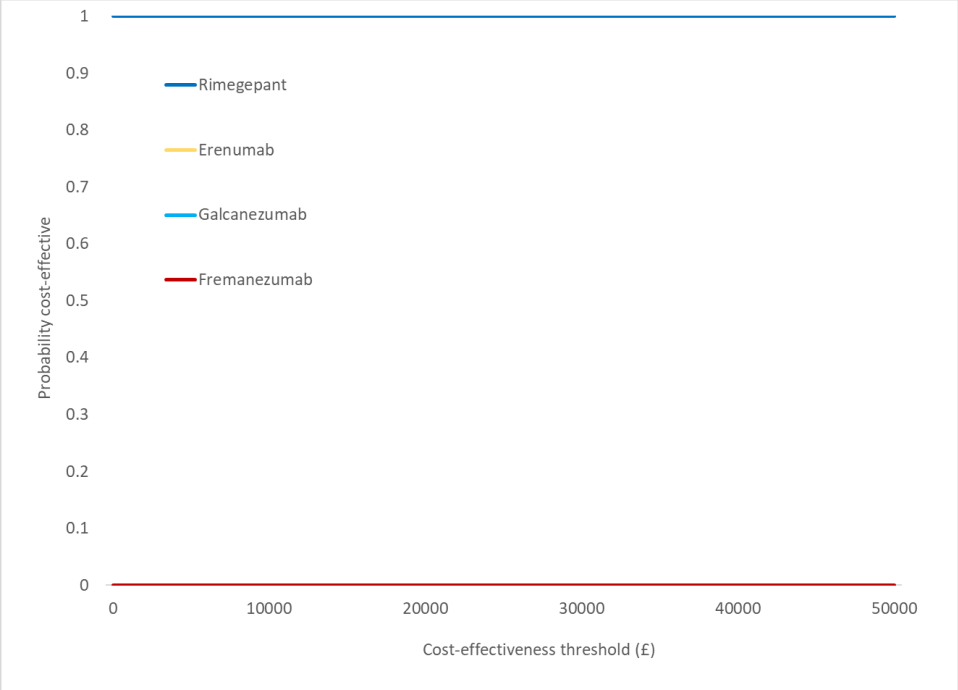


Figure 18. CEAC (migraine prevention) generated by the EAG



5.2.2 Company's one-way sensitivity analyses

The company carried out OWSAs to assess the impact of varying the key parameters between the upper and lower 95% CI of the mean value. In the CS, the company noted that resource use by MMD adopted the lower and upper bounds across the spectrum of MMD, based on +/-20% of the mean and unit costs by +/-10% of the mean. The EAG also notes that odds ratios for response were varied using their 95% credible intervals (CrI).

The 10 most influential parameters resulting from the OWSA, comparing galcanezumab with rimegepant, are reported in Table 77. The company selected galcanezumab on the basis of it having the highest QALY gain among the three mAbs. The company also noted that similar patterns are expected across the two other mAbs.

As shown in Table 77, the ICER was most sensitive to response at 12 weeks and the parameters in the EQ-5D regression.

Table 77. Results of the deterministic sensitivity analysis for galcanezumab vs rimegepant (migraine prevention) (adapted from Table 87 of the company's clarification response)

Parameter	Parameter input		ICER (£/QALY)		
	Base case	(lower, upper)	Lower	Upper	Difference (lower – upper)
Odds ratios (response) – galcanezumab	1.642	(1.215, 2.223)	227,649	88,344	139,305
EQ-5D - rimegepant	0.022	(0.003, 0.041)	135,517	100,198	35,319
EQ-5D - MMD	-0.013	(-0.015, -0.011)	101,028	134,028	33,001
Rimegepant response probability	0.491	(0.439, 0.544)	108,412	123,935	15,523
Discontinuation rate	0.230	(0.172, 0.293)	112,285	118,332	6,047
Rate of reversion to baseline	0.077	(0.011, 0.2)	117,562	113,685	3,877
Zero inflated - arm	-0.104	(-0.168, -0.04)	113,530	117,055	3,526
Baseline age	41	(18, 65)	114,407	116,721	2,313
MMD related resource use	97	(62, 138)	115,987	114,270	1,717
Unit cost – nurse, per hour	£42	(£34, £51)	114,820	115,642	822

Abbreviations: ICER, incremental cost-effectiveness ratio; MMD, monthly migraine day

5.2.3 Company's scenario analyses

The company undertook a series of scenario analyses to assess the impact of applying alternative assumptions to key model parameters. These scenarios are presented in Table 78. The largest

increases in the ICER (favoring rimegepant) were seen using the observed data from study BHV3000-305 to inform the distribution of MMD at baseline and using a beta-binomial distribution to inform the MMD distribution in subsequent timepoints. However, these increases are relatively small compared to the base case ICER.

The largest decrease in the ICER (favoring the mAbs) was observed for an assumption of immediate return to baseline MMDs. Assuming the mAbs had the same 12-week response as rimegepant switched the direction of the ICER (rimegepant dominates).

The company also reported the incremental NMB for rimegepant compared to the mAbs using a WTP of £30,000 per QALY. As shown in Table 78 the incremental NMB was positive for every scenario indicating rimegepant is cost-effective and that the results are robust to alternative assumptions.

Additionally, the company conducted several scenario analyses requested by the EAG, which are outlined in Section 6.3.2.

Table 78. Pairwise ICERs and NMB (rimegepant vs mAbs) for scenario analyses (adapted from Table 88 of the company's clarification response)

#	Scenario description	Erenumab		Galcanezumab		Fremanezumab	
		ICER	NMB*	ICER	NMB*	ICER	NMB*
-	Base Case	92,671	2,170	115,211	4,484	118,883	3,945
1	Time horizon set to 5 years	94,051	1,709	119,069	3,611	120,551	3,096
2	Time horizon set to 40 years	92,676	2,176	115,199	4,494	118,890	3,955
3	Discounting - 1.5% for costs & outcomes	92,367	2,291	114,424	4,712	118,513	4,167
4	MMD baseline - observed	96,532	2,213	119,997	4,549	123,819	4,000
5	MMD distribution - Beta-binomial	96,635	2,220	120,068	4,559	123,885	4,008
6	MMD distribution - Negative binomial	92,339	2,171	114,755	4,484	118,406	3,945
7	MMD distribution - Poisson	92,787	2,178	115,288	4,495	118,954	3,955
8	MMD distribution - Non-parametric	92,775	2,170	115,350	4,484	119,028	3,945
9	OR response - random effects NMA	93,544	2,168	116,889	4,471	110,665	4,001
10	OR response - All equal to rimegepant	Rim Dominant	2,005	Rim Dominant	3,915	Rim Dominant	3,465

#	Scenario description	Erenumab		Galcanezumab		Fremanezumab	
		ICER	NMB*	ICER	NMB*	ICER	NMB*
11	Reversion rate (per cycle) – 100% (i.e., immediate full reversion to baseline)	90,830	2,148	112,932	4,450	116,533	3,916

Abbreviations: BSC, best supportive care; HCRU, healthcare resource use; ICER, incremental cost-effectiveness ratio; mAb, monoclonal antibody; MMD, monthly migraine day(s); NHWS, national health and Wellbeing Survey; NMA, network meta-analysis; NMB, net monetary benefit; OR, odds ratio; QALY, quality-adjusted life year; rim, rimegepant

*NMB at £30,000 per QALY (Rimegepant vs mAbs) a positive value indicating rimegepant is cost-effective at the WTP of £30,000.

5.2.4 Model validation and face validity check

In the CS, the company stated that extensive technical validation was undertaken by a third-party. This involved a detailed review of programming and extreme value testing. This was primarily done to ensure accuracy in calculations and programming logic. The technical validation of the model included review of implementation and typing errors, validation of the logical structure of the model, expressions, and sequences of calculations. Further, extreme value testing has been performed to investigate and ensure robustness of model behaviours for wide range of input parameter values.

The company also noted that their external experts supported following the precedent set in prior mAbs appraisals, and unless the information was redacted in these appraisals, the current model structure and assumptions are aligned with the NICE committee's preferred assumptions.

The EAG considers that the company's model validation and face validity checks of the prevention model were generally extensive and robust.

6 Additional economic analysis undertaken by the EAG

6.1 Model corrections

The External assessment Group (EAG) has identified one error in the acute model. As explained in Section 4.2.11.1.4, the company inconsistently defined the BL_severity coefficient in the quality-adjusted life hour (QALH) regression and mod_pain input in the acute model: the proportion of moderate baseline pain (vs. severe) vs the proportion of severe migraines at baseline (vs. moderate). The EAG considers the latter definition, provided at the clarification stage, to be correct.

As such, the EAG has corrected the mod_pain input in the acute model so it reflects the proportion of severe migraines ([redacted] and [redacted] in the subgroup with at least 2 triptan failures and in the modified intention-to-treat [mITT] population including study BHV3000-310, respectively) rather than the proportion of moderate migraines ([redacted] and [redacted] in the subgroup with at least 2 triptan failures and in the mITT population including study BHV3000-310, respectively). For the company's corrected base case results in the subgroup of patients with at least 2 triptan failures, see Table 79. For results in the mITT population including study BHV3000-310, see Table 80.

In both analyses, the incremental cost-effectiveness ratio (ICER) increases by around £400 when the correction is made.

Table 79. Company's corrected base case results (acute treatment) in the subgroup of patients with at least 2 triptan failures

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)
Company's base case					
BSC	£2,396	7.72	-	-	-
Rimegepant	£9,704	8.14	£7,307	0.43	£17,160
Company's corrected base case					
BSC	£2,396	7.93	-	-	-
Rimegepant	£9,704	8.34	£7,307	0.42	£17,521

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

Table 80. Company's corrected results (acute treatment) in the mITT population including study BHV3000-310

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)
Company's scenario in the mITT population including study BHV3000-310					
BSC	£2,018	8.55	-	-	-
Rimegepant	£6,368	8.78	£4,350	0.23	£19,285
Company's corrected scenario in the mITT population including study BHV3000-310					
BSC	£2,018	8.68	-	-	-
Rimegepant	£6,368	8.90	£4,350	0.22	£19,743

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; mITT, modified intention-to-treat; QALYs, quality-adjusted life years.

6.2 Exploratory and sensitivity analyses undertaken by the EAG

6.2.1 Acute migraine treatment

The company was asked to perform a number of scenarios during the clarification stage. The scenarios provided by the company include:

- Adding options to the model to enable results to be generated for a mITT population (see Section 4.2.2.1);
- Adding study BHV3000-310 to the acute pooled randomised controlled trials (RCTs) (see Section 4.2.2.1);
- Using the orally dispersible table (ODT) formulation studies only (see Section 4.2.3.1.1);
- Fitting a parametric distribution to the distribution of migraine attacks per month at baseline (see Section 4.2.6.1);
- Removing long-term reductions in monthly migraine days (MMDs) and reducing the time horizon to 2 years (see Section 4.2.7.1.4);
- Using the pain trajectories of best supportive care (BSC) all comers when patients discontinue rimegepant (see Section 4.2.4.1);
- Using the "pain free" utility value from Stafford *et al.* 2012 and Xu *et al*. 2011 to inform the baseline utility value (see Section 4.2.11.1.4);
- Using general population utilities to inform the baseline utility value (see Section 4.2.11.1.4).

However, the EAG's requests to use the acute pooled trials to inform the distribution of migraine attacks per month at baseline (see Section 4.2.6.1) and to consider including treatment-specific monitoring costs and drug wastage costs (see Section 4.2.12.1.5) were not provided by the company. The EAG still considers that these scenarios warrant further exploration.

As noted in Section 4.2.2.1, the EAG considers the full trial population to be more relevant and more robust than the subgroup of patients who previously failed 2 triptans in the trials and therefore the EAG will focus its additional analyses in this population.

6.2.2 Migraine prevention

The company was asked to perform a number of scenarios during the clarification stage. The scenarios provided by the company include:

- Using a lifetime time horizon (see Section 4.2.5.2);
- Using alternative parametric distributions to inform the MMD at baseline (see Section 4.2.6.2);
- Truncating the distribution of MMD at baseline to reflect a population with episodic migraine (EM) (see Section 4.2.6.2);
- Using the rimegepant response probability assessed as the "average over 12-weeks" (see Section 4.2.7.2).

However, the EAG's requests to use the use the network meta-analysis (NMA) results from Cycle 1 (Weeks 1 to 4) (see Section 4.2.7.2) and to consider treatment-specific long-term discontinuation rates (see Section 4.2.8.2) were not provided by the company. The EAG still considers that these scenarios warrant further exploration. Other scenarios the EAG would like to explore include using the random-effects baseline risk adjusted NMA including the phase II studies (see Section 4.2.7.2) and assuming erenumab is administered as per the dose in the BNF and marketing authorisation (every 28 days) (see Section 4.2.12.2.4).

6.3 EAG scenario analysis

6.3.1 Acute migraine treatment

Results of the EAG's scenario analyses in the mITT population including study BHV3000-310 are given in Table 81. Amending the baseline distribution of MMD had the largest impact on the results, but the ICER remained below NICE's upper willingness-to-pay (WTP) threshold of £30,000 per quality-adjusted life year (QALY) gained.

Table 81. Results of the EAG's scenario analyses (acute treatment) in the mITT population including study BHV3000-310

Results per patient	Rimegepant	BSC	Incremental value
Company's corrected base case in the mITT population including study BHV3000-310			
Total costs	£6,368	£2,018	£4,350
QALYs	8.90	8.68	0.22
ICER (£/QALY)	-	-	£19,743
Acute pooled trials to inform the distribution of migraine attacks per month at baseline (mean approach)			
Total costs	£4,695	£1,319	£3,376
QALYs	9.54	9.41	0.13
ICER (£/QALY)	-	-	£25,015
Including the cost of a specialist to prescribe rimegepant (one-off neurologist visit at £192)			

Total costs	£6,560	£2,018	£4,542
QALYs	8.90	8.68	0.22
ICER (£/QALY)	-	-	£20,615
Including drug wastage costs			
Total costs	£6,406	£2,018	£4,388
QALYs	8.90	8.68	0.22
ICER (£/QALY)	-	-	£19,918

Abbreviations: BSC, best supportive care; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; mITT, modified intention-to-treat; QALY, quality adjusted life year

6.3.2 *Migraine prevention*

Results of the EAG's scenario analyses are given in Table 82. The scenario with the largest impact on the results, in favour of the comparators, was the assumption of a class-specific long-term discontinuation rate for the injectable monoclinal antibodies (mAbs) based on a trial of erenumab. This discontinuation rate (0.8% per 28-day cycle) was [redacted] than the rate observed in the rimegepant study ([redacted] per 28-day cycle). Increasing the frequency of erenumab administrations also had a large impact on the ICER, but in favour of rimegepant.

Table 82. Results of the EAG's scenario analyses (migraine prevention)

Results per patient	Ere (4)	Gal (3)	Fre (2)	Rim (1)	Incremental value		
					(1-4)	(2-4)	(3-4)
Company base case							
Total costs	£23,134	£25,987	£25,201	£19,925	-£3,209	-£6,062	-£5,276
QALYs	9.068	9.086	9.077	9.033	-0.035	-0.053	-0.044
ICER (£/QALY)					£92,671	£115,211	£118,883
Random-effects baseline risk adjusted NMA including the phase II studies							
Total costs	£23,183	£25,957	£25,455	£19,925	-£3,258	-£6,032	-£5,530
QALYs	9.069	9.085	9.084	9.033	-0.036	-0.052	-0.051
ICER (£/QALY)					£90,396	£116,287	£109,284
Class-specific long-term discontinuation rates (mAbs 2.38% per 12 weeks, 0.80% per 28-day cycle)							
Total costs	£31,516	£36,539	£35,425	£19,925	-£11,591	-£16,614	-£15,500
QALYs	9.298	9.333	9.317	9.033	-0.265	-0.300	-0.284
ICER (£/QALY)					£43,725	£55,402	£54,586

The initial 28-day treatment acquisition costs are equal to the ongoing 28-day treatment acquisition costs							
Total costs	£23,103	£25,987	£25,165	£19,925	£3,178	£6,062	£5,240
QALYs	9.068	9.086	9.077	9.033	-0.035	-0.053	-0.044
ICER (£/QALY)					£91,777	£115,211	£118,071
Erenumab is administered as per the dose in the BNF (every 28 days)							
Total costs	£23,985	NA	NA	£19.925	-£4,060	NA	NA
QALYs	9.068	NA	NA	9.033	-0.035	NA	NA
ICER (£/QALY)					£117,242	NA	NA

Abbreviations: Ere, erenumab; Fre, fremanezumab; Gal, galcanezumab; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; Rim, rimegepant

Note: all ICERs are in the south-west quadrant (rimegepant is cheaper and less effective than the comparators)

6.4 EAG preferred assumptions

6.4.1 Acute migraine treatment

Table 83 summarises the EAG's preferred assumptions and the cumulative impact these assumptions have on the ICER.

As discussed in Section 4.2.7.1.4, the EAG is aware that clinical expert feedback to the company was supportive of including reductions in MMD by *pro re nata* (PRN) rimegepant in the model. However, in the absence of long-term comparative evidence, the EAG considers it more appropriate to remove reductions in MMD by PRN rimegepant from the base case analysis and include them in scenario analysis.

Table 84 provides the total costs and QALYs resulting from the EAG's base case and the scenario around the EAG's base case including reductions in MMD by PRN rimegepant. For probabilistic results using 1,000 iterations, see Table 85 and Figure 19 to Figure 22. The EAG considers the probabilistic sensitivity analysis (PSA) ICERs to be similar to the deterministic ICERs. However, the total costs and QALYs are notably smaller in the PSA when reductions in MMD by PRN rimegepant are included. Due to time constraints, the EAG has been unable to find an explanation for this. Furthermore, not all key parameters are varied, as discussed in Section 5.1.1.2.

Overall, if committee consider the reductions in MMD by PRN rimegepant reasonable, rimegepant could be considered cost-effective under NICE's upper WTP threshold of £30,00 per QALY.

Table 83. EAG's preferred model assumptions (acute treatment)

Preferred assumption	Section in EAG report	Cumulative ICER (£/QALY)
Company base case in the subgroup of patients with at least 2 triptan failures	5.1.1	£17,160
Corrected company base case in the subgroup of patients with at least 2 triptan failures	6.1	£17,521
Company's corrected scenario in the mITT population including study BHV3000-310 (efficacy)	4.2.2.1 and 6.1	£19,743
Baseline patient characteristics from the mITT population including study BHV3000-310*	4.2.6.1	£26,348
Patients who discontinue rimegepant follow BSC all-comer pain trajectories	4.2.4.1**Error! Reference source not found.**	£28,063
One-off cost for a specialist to prescribe rimegepant	4.2.12.1.5	£29,609
No reductions in MMD frequency	4.2.7.1.4	£31,179
2-year time horizon	4.2.5.1	£50,054

Abbreviations: BSC, best supportive care; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; mITT, modified intention-to-treat; MMD, monthly migraine day; QALY, quality adjusted life year

*Assumption requires the model to switch from the distribution-based approach to the mean-based approach

Table 84. EAG's preferred base case (acute treatment): deterministic results

Results per patient	Rimegepant	BSC	Incremental value
EAG's preferred base case (no reductions in MMD frequency and a 2-year time horizon)			
Total costs	£1,553	£151	£1,385
QALYs	1.37	1.34	0.03
ICER (£/QALY)	-	-	£50,054
EAG's scenario (reductions in MMD frequency and a 20-year time horizon)			
Total costs	£6,104	£1,810	£3,682
QALYs	12.92	12.77	0.12
ICER (£/QALY)	-	-	£29,609

Abbreviations: BSC, best supportive care; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; mITT, modified intention-to-treat; QALY, quality adjusted life year

Table 85. EAG's preferred base case (acute treatment): probabilistic results

Results per patient	Rimegepant	BSC	Incremental value
EAG's preferred base case (no reductions in MMD frequency and a 2-year time horizon)			
Total costs	£1,553	£148	£1,385

QALYs	1.35	1.32	0.03
ICER (£/QALY)	-	-	£50,139
EAG's scenario (reductions in MMD frequency and a 20-year time horizon)			
Total costs	£5,007	£1,323	£3,685
QALYs	9.58	9.45	0.12
ICER (£/QALY)	-	-	£29,717

Abbreviations: BSC, best supportive care; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; mITT, modified intention-to-treat; QALY, quality adjusted life year

Figure 19. Acute treatment: scatter plot for rimegepant vs BSC (EAG base case)

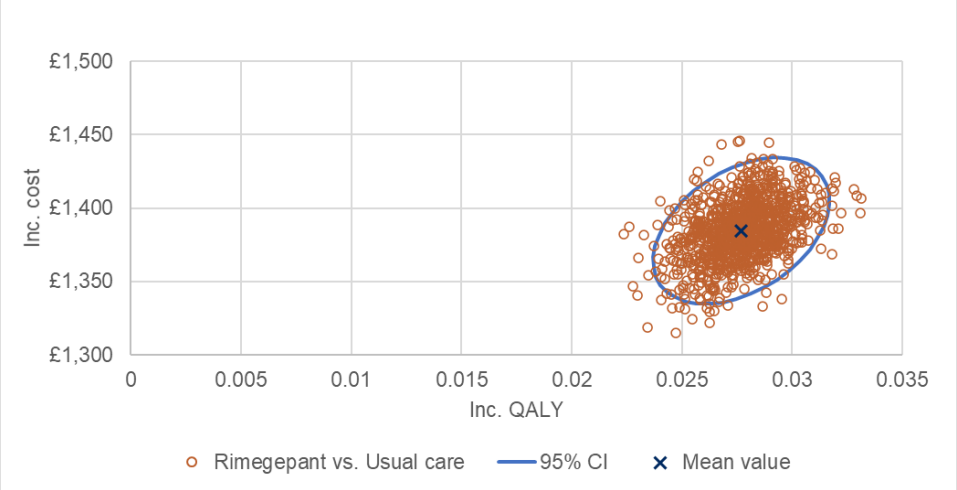


Figure 20. Acute treatment: CEAC for rimegepant vs BSC (scenario around EAG base care)

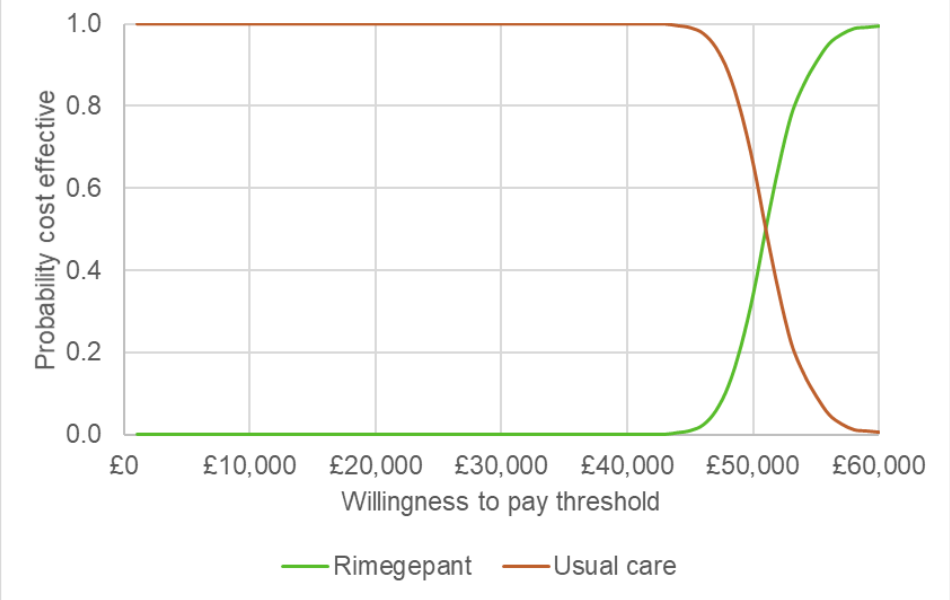


Figure 21. Acute treatment: scatter plot for rimegepant vs BSC (scenario around EAG base case)

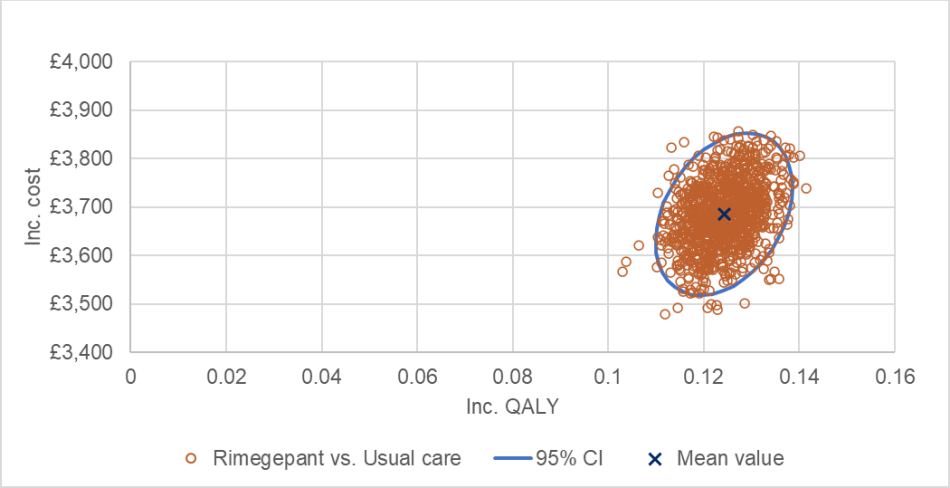
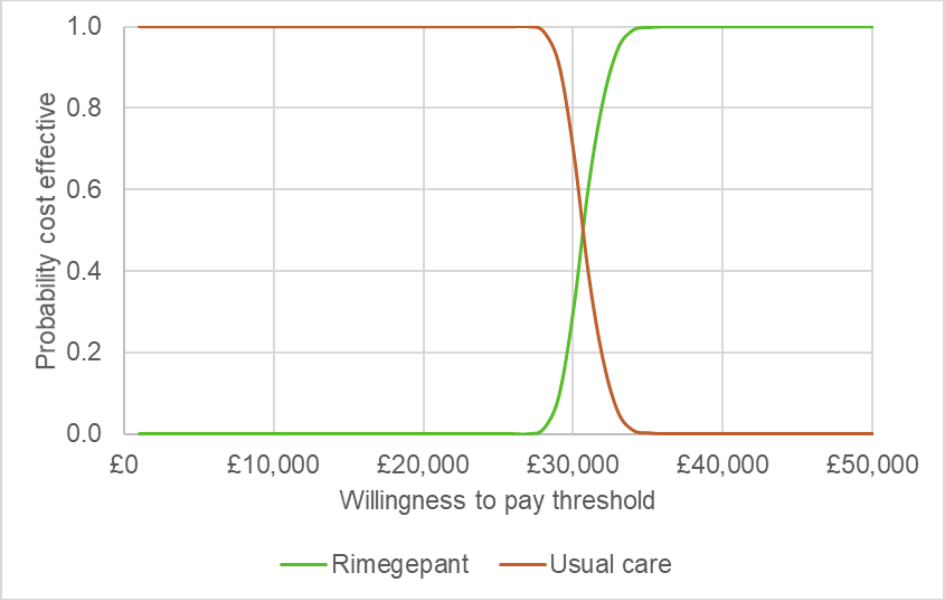


Figure 22. Acute treatment: CEAC for rimegepant vs BSC (scenario around EAG base care)



6.4.2 *Migraine prevention*

Table 86 summarises the EAG's preferred assumptions and the cumulative impact these assumptions have on the ICER. Table 87 provides the total costs and QALYs associated with the EAG's base case. Rimegepant is associated with lower costs and lower QALYs than the mAbs (i.e., a south-west quadrant ICER). Based WTP thresholds of £20,000 or £30,000 per QALY, rimegepant would be considered cost-effective compared to each mAb as the ICERs are above these WTP thresholds and the incremental net monetary benefits (NMBs) are positive. Fully incremental results are provided in Table 88. The EAG could not produce PSA ICERs for its base case as some scenarios led to errors in the PSA (i.e., #NUM! in the PSA iterations).

Table 86. Summary of EAG's preferred model assumptions and cumulative results (migraine prevention)

Preferred assumption	Section in EAG report	Cumulative ICER (£/QALY) rimegepant vs mAb			Cumulative NMB £20,000/QALY			Cumulative NMB £30,000/QALY		
		Ere	Gal	Fre	Ere	Gal	Fre	Ere	Gal	Fre
Company base case	5.2.1	£92,671	£115,211	£118,883	£2,516	£5,010	£4,388	£2,170	£4,484	£3,945
Poisson distribution for MMD at baseline	4.2.6.2	£96,311	£119,721	£123,535	£2,544	£5,052	£4,424	£2,211	£4,546	£3,997
Random-effects baseline risk adjusted NMA including the phase II studies	4.2.7.2	£93,948	£120,839	£113,566	£2,566	£5,036	£4,559	£2,219	£4,537	£4,071
Rimegepant response probability in mild-to-severe patients assessed as the "average over 12-weeks"	4.2.7.2	£84,188	£108,021	£100,489	£2,188	£4,389	£3,911	£1,847	£3,891	£3,425
Reversions to baseline MMD, once treatment is discontinued are immediate in the assessment period and post-assessment period	4.2.4.2	£82,547	£105,929	£98,540	£2,173	£4,368	£3,889	£1,826	£3,859	£3,394
The initial 28-day treatment acquisition costs are equal to the ongoing 28-day treatment acquisition costs, and erenumab is administered as per the dose in the BNF (every 28 days)	4.2.12.2.4	£102,881	£105,929	£97,812	£2,880	£4,368	£3,853	£2,533	£3,859	£3,358
Truncating the distribution of MMDs to EM	4.2.6.2	£107,748	£110,934	£102,449	£2,917	£4,421	£3,906	£2,584	£3,935	£3,432

Abbreviations: BNF, British National Formulary; EAG, External Assessment Group; Ere, erenumab; Fre, fremanezumab; Gal, galcanezumab; ICER, incremental cost-effectiveness ratio; mAb, monoclonal antibody; MMD, monthly migraine day; NMA, network meta-analysis; NMB, net monetary benefit; QALY, quality adjusted life year.

Note: all ICERs are in the south-west quadrant (rimegepant is cheaper and less effective than the comparators)

Table 87. EAG's preferred base case (migraine prevention)

Results per patient	Ere (4)	Gal (3)	Fre (2)	Rim (1)	Incremental value		
					(1-4)	(2-4)	(3-4)
Total costs	£21,781	£23,593	£23,052	£18,199	-£3,582	-£5,394	-£4,853
QALYs	9.176	9.191	9.190	9.143	-0.033	-0.049	-0.047
ICER (£/QALY)					£107,748	£110,934	£102,449

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

Note: all ICERs are in the south-west quadrant (rimegepant is cheaper and less effective than the comparators)

Table 88. EAG's preferred base case (migraine prevention) fully incremental results

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)
Rimegepant	£18,199	9.143	-	-	-
Erenumab	£21,781	9.176	£3,582	0.033	£107,748*
Fremanezumab	£23,052	9.190	£4,853	0.047	£102,449**
Galcanezumab	£23,593	9.191	£541	0.001	£432,526

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

*Extendedly dominated

**ICER for fremanezumab vs rimegepant

6.5 Conclusions of the cost effectiveness sections

6.5.1 Acute migraine treatment

The company submitted a cost-utility analysis comparing PRN rimegepant to BSC, in the acute treatment of adults with migraine (with or without aura, with EM or CM) who have had inadequate symptom relief after trials of at least 2 triptans or in whom triptans are contraindicated or not tolerated; and have inadequate pain relief with NSAIDs and paracetamol. The EAG considers the comparator and population reasonable.

Although the marketing authorisation for rimegepant is for the ODT formulation and the focus of this appraisal, two of the four RCTs (BHV3000-301 and -302) and the long-term open-label safety study used a tablet formulation (non-ODT) of rimegepant. The company notes that evidence suggests that the two formulations are bioequivalent.[56] However, the EAG's clinical experts note that formulation may have an impact on efficacy, particularly at the 2 hour assessment. During the clarification stage the company provided pooled results from trials using the ODT formulation only

and found that the ODT formulation may have contributed to a slightly higher percentage of patients receiving pain relief at 2 hours than compared to the combined tablet and ODT formulation pooled analysis, which would suggest the pooled estimate is generating a conservative ICER. However, when treatment effectiveness data from the ODT formulation trials were applied in the economic analysis, the ICER in the mITT population was £22,645, which is higher than the ICER in the mITT population including trials of both formulations (£19,285). Given that the results are at face value counterintuitive, the EAG is concerned about the robustness of the model. However, if the company can explain what is driving the change in the ICER at technical engagement, this may increase the EAG's confidence in the model and in using the pooled formulations to inform the analysis.

The model developed by the company for acute migraine treatment includes a short-term (2 hours) decision tree component, to capture the response to the first migraine attack, followed by a long-term Markov model, to capture the impact of subsequent migraine attacks. The company stated that the structure of the model is consistent with the proposed clinical care pathway for rimegepant and was informed by the ICER evidence report.[52] However, a key difference in this model compared to the ICER model, is the incorporation of potential reductions in MMD by PRN rimegepant. One of the EAG's primary concerns with the company's model is this addition, as the reductions are based on a *post-hoc* analysis of the long-term safety study which may suffer from confounding (including but not limited to a possible placebo effect). The EAG is aware that clinical expert feedback to the company was supportive of including reductions in MMD by PRN rimegepant in the model. However, in the absence of long-term comparative evidence, the EAG considers it more appropriate to remove reductions in MMD by PRN rimegepant from the base case analysis and include them in scenario analysis. If reductions in MMD by PRN rimegepant are removed from the model, the EAG also considers a shorter time horizon (2-years, as per the ICER evidence report) to be justifiable.

Another key concern with the model, is with the company's assumption that response to the first migraine attack informs the response to subsequent migraine attacks. Clinical experts to the company and EAG agree that in the treatment of acute migraine, it is generally recommended to try a particular treatment on two or three separate episodes before abandoning it. However, the EAG is unaware of any clinical data indicating how many patients would respond after taking rimegepant to treat a second or third migraine, who did not respond during their first episode and therefore considers this to be an unresolvable area of uncertainty. The EAG also considers it optimistic of the company to assume rimegepant responders will also respond to BSC when they discontinue

rimegepant. In response to the EAG's concern, the company provided a scenario assuming a mixed response, which the EAG includes in its preferred base case.

According to the company's one-way sensitivity analysis (OWSA), baseline MMD is a key model driver, with a higher baseline MMD leading to a lower ICER for rimegepant vs BSC. The baseline MMD is used as a covariate in several of the company's regression analyses including the regression to predict reductions in MMD by PRN rimegepant, baseline utility and QALHs. In the company's analysis, baseline MMDs (and other baseline patient characteristics) are taken from long-term open-label safety study (BHV3000-201), as this study included the full range of MMDs potentially observed in the UK population for the acute treatment of migraine. However, the EAG considers it more appropriate for baseline patient characteristics to come from the acute pooled RCTs, as this would ensure consistency with the sources used to inform pain relief and pain trajectories.

HRQoL was not measured in the acute RCTs, which is not unexpected given the short duration of the trials as they only cover single attacks. Thus, to estimate QALYs, the company derived a baseline utility value for patients not experiencing a migraine attack in every 48-hour cycle by mapping MSQv2 values from the BHV3000-201 trial data (PRN groups) to the EQ-5D. Health state utility values (HSUVs) by migraine pain severity (pain free, mild, moderate, severe) were obtained from Stafford *et al.* 2012,[86] which reported EQ-5D scores from UK participants with migraines. Given that the "pain free" utility in Stafford *et al.* 2012 (0.87) was relatively high compared to the interictal baseline value predicted from the study BHV3000-201 (0.687 in the company's revised base case), the company adjusted Stafford *et al.* utilities (multiplicatively) to ensure that the "pain free" utility is equivalent to the non-migraine MSQv2-mapped utility value; the utilities for other pain categories were also adjusted accordingly. The EAG was concerned that the company's approach to estimate HSUVs was unduly complex as it would not be unreasonable to assume the "pain free" utility or general population utility is equal to the non-migraine utility. Furthermore, there is the potential for migraine attacks to be double counted as the MSQv2 would capture patients experiencing migraine attacks due to the 4-week recall period.

During the clarification stage, the company provided additional justifications for their approach. The company considered double counting concerns to be muted as the overall utilities would be shifted up or down analogously for both treatment arms. The EAG is still of the opinion that this could be an issue when large reductions in MMD frequency with PRN rimegepant are included as the shift becomes unequal, potentially favoring rimegepant as rimegepant is associated with fewer MMDs

than BSC. This could be resolved by removing reductions in MMD frequency with PRN rimegepant (as per the EAG's base case) or by using EQ-5D data to inform the non-migraine utility (as per the scenarios suggested to the company at clarification). Overall, the EAG is satisfied with the company's argument that study BHV3000-201 should be used to inform baseline utility value for patients not experiencing a migraine attack in every 48-hour cycle, provided that there is no difference in MMD.

To generate QALHs over each 48-hour cycle, the time per pain category (pain free, mild, moderate, severe) was multiplied by the HSUVs and then summed over the 48-hour period. A regression analysis was then fitted to describe QALH outcomes adjusted for treatment arm, two-hour response status, baseline MMD, and baseline migraine severity.

The EAG was concerned that there were imbalances in pain severity between the treatment arms at baseline as [redacted] and [redacted] of patients in the rimegepant arms and BSC arms of the acute pooled RCTs experienced severe migraines, respectively. Even though, the company affirmed that the QALH regression adjusted for these differences, the EAG still considers the imbalances to potentially bias the patient population and efficacy outcomes in favour of rimegepant. Overall, it is unclear how much bias this imbalance introduces for the pain relief outcome, but it is thought to be lower than if the pain freedom outcome had been used to inform the economic analysis.

As for costs, the EAG has concerns that the company omitted drug wastage costs and treatment-specific monitoring costs. The company also omitted the control group from Vo *et al.* 2018 when estimating health care resource use. However, based on the EAG's scenario analysis and the company's OWSA, the EAG does not consider these omissions to have major implications for decision making.

Finally, the EAG considers the company's PSA to be somewhat incomplete as some key inputs are fixed. As such, there is potential for the true PSA ICERs to be different from the deterministic ICERs.

In the company's base case, rimegepant was associated with higher costs and higher QALYs compared to BSC) resulting in an ICER of £17,160. Following the EAG's amendments to the company's analysis the ICER is £50,054 excluding reduction in MMD frequency with PRN rimegepant and £29,609 including them. Thus, if committee consider the reductions in MMD by PRN rimegepant reasonable, rimegepant could be considered cost-effective under a WTP threshold of £30,000 per QALY.

6.5.2 *Migraine prevention*

Overall, the case made by the company to demonstrate the cost-effectiveness of rimegepant compared with relevant comparators as a preventative migraine treatment, is considered by the EAG to be generally robust. In both the company's base case analysis and EAG's preferred analysis, rimegepant is cheaper and less effective than the comparators, leading to south-west quadrant ICERs of around £100,000 per QALY. However, the EAG cautions the interpretation of the cost-effectiveness results presented in the EAG report as they are based on list prices. The cost-effectiveness results presented in the confidential appendix to the EAG report, which includes the PAS discounts for comparator treatments (rimegepant does not have a PAS discount), are more relevant for decision-making.

Although the EAG considers the model structure and modelling assumptions to be generally appropriate, and similar to other migraine prevention models submitted for NICE appraisal, there are two key unresolvable areas of uncertainty. These include the lack of treatment-specific long-term discontinuation rates (conditional on response) and the uncertainty concerning the efficacy of rimegepant vs the comparators due to a lack of direct evidence and limitations of the NMA.

7 References

1. Pfizer. Vydura (rimegepant oro-dispersible tablets [ODT]): Summary of Product Characteristics. 2022.
2. Headache Classification Committee of the International Headache S. The International Classification of Headache Disorders, 3rd edition. *Cephalalgia* 2018; **38**: 1-211.
3. Mayans L, Walling A. Acute Migraine Headache: Treatment Strategies. *American family physician* 2018; **97**: 243-51.
4. Ailani J, Burch RC, Robbins MS, Board of Directors of the American Headache S. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. *Headache* 2021; **61**: 1021-39.
5. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. *Headache: The Journal of Head and Face Pain* 2001; **41**: 646-57.
6. Gibbs SN, Shah S, Deshpande CG, Bensink ME, Broder MS, Dumas PK, et al. United States Patients' Perspective of Living With Migraine: Country-Specific Results From the Global "My Migraine Voice" Survey. *Headache: The Journal of Head and Face Pain* 2020; **60**: 1351-64.
7. Stewart WF, Shechter A, Lipton RB. Migraine heterogeneity: Disability, pain intensity, attack frequency and duration. *Neurology* 1994; **44**: S24-39.
8. Brandes JL. The Migraine Cycle: Patient Burden of Migraine During and Between Migraine Attacks. *Headache* 2008; **48**: 430-41.
9. Cutrer FM. Pathophysiology, clinical manifestations, and diagnosis of migraine in adults. 2019. Available from: https://www.uptodate.com/contents/pathophysiology-clinical-manifestations-and-diagnosis-of-migraine-in-adults. Date accessed: July 2020.
10. Arnold M. Headache classification committee of the international headache society (IHS) the international classification of headache disorders. *Cephalalgia* 2018; **38**: 1-211.
11. Demarquay G, Mawet J, Guégan-Massardier E, de Gaalon S, Donnet A, Giraud P, et al. Revised guidelines of the French headache society for the diagnosis and management of migraine in adults. Part 3: Non-pharmacological treatment. *Rev Neurol (Paris)* 2021; **177**: 753-9.
12. Goadsby PJ, Evers S. International Classification of Headache Disorders - ICHD-4 alpha. *Cephalalgia* 2020; **40**: 887-8.
13. Reuter U. GBD 2016: still no improvement in the burden of migraine. *The Lancet Neurology* 2018; **17**: 929-30.
14. National Institute for Health and Care Excellence (NICE). Botulinum toxin type A for the prevention of headaches in adults with chronic migraine: Technology appraisal guidance [TA260], 2012. Available from: https://www.nice.org.uk/guidance/ta260. Date accessed: Aug 2022.
15. National Health S. Improved NHS migraine care to save thousands of hospital stays. 2020. Available from: https://www.england.nhs.uk/2020/01/improved-nhs-migraine-care/. Date accessed: April 2022.
16. RightCare NHS. RightCare: Headache & Migraine Toolkit optimising a headache and migraine system. 2019. Available from: https://www.england.nhs.uk/rightcare/wp-content/uploads/sites/40/2020/01/rightcare-headache-and-migraine-toolkit-v1.pdf. Date accessed: June 2022.
17. National Institute for Health and Care Excellence (NICE). Headaches in over 12s: Diagnosis and management: Clinical Guideline [CG150], 2012. Available from: https://www.nice.org.uk/guidance/cg150/chapter/Key-priorities-for-implementation#tensiontype-headache-migraine-and-cluster-headache. Date accessed: May 2022.

18. Harris L, L'Italien G, O'Connell T, Hasan Z, Hutchinson S, Lucas S. A Framework for Estimating the Eligible Patient Population for New Migraine Acute Therapies in the United States. *Adv Ther* 2021; **38**: 5087-97.
19. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. A meta-analysis. *Annals of Internal Medicine* 1991; **115**: 787-96.
20. Henry D, McGettigan P. Epidemiology overview of gastrointestinal and renal toxicity of NSAIDs. *Int J Clin Pract Suppl* 2003: 43-9.
21. Hernandez-Diaz S, Rodriguez LA. Association between nonsteroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation: an overview of epidemiologic studies published in the 1990s. *Archives of Internal Medicine* 2000; **160**: 2093-9.
22. Lipton RB, Fanning KM, Serrano D, Reed ML, Cady R, Buse DC. Ineffective acute treatment of episodic migraine is associated with new-onset chronic migraine. *Neurology* 2015; **84**: 688-95.
23. Wilson M, Jimenez-Sanders R. Medication Overuse Headache. 2016. Available from: https://americanmigrainefoundation.org/resource-library/medication-overuse/. Date accessed: Aug 2020.
24. Leroux E, Buchanan A, Lombard L, Loo LS, Bridge D, Rousseau B, et al. Evaluation of Patients with Insufficient Efficacy and/or Tolerability to Triptans for the Acute Treatment of Migraine: A Systematic Literature Review. *Adv Ther* 2020; **37**: 4765-96.
25. National Institute for Health and Care Excellence (NICE). Erenumab for preventing migraine: Technology appraisal guidance [TA682], 2021. Available from: https://www.nice.org.uk/guidance/ta682/resources/erenumab-for-preventing-migraine-pdf-82609376694469. Date accessed: Aug 2022.
26. National Institute for Health and Care Excellence (NICE). Fremanezumab for preventing migraine: Technology appraisal guidance [TA764], 2022. Available from: https://www.nice.org.uk/guidance/ta764. Date accessed: Aug 2022.
27. National Institute for Health and Care Excellence (NICE). Galcanezumab for preventing migraine: Technology appraisal guidance [TA659], 2020. Available from: https://www.nice.org.uk/guidance/ta659. Date accessed: Aug 2022.
28. Lai J, Wickizer M, Olson J, Hickman C, Chou J, Patel T, et al. A Retrospective Claims Analysis of Calcitonin Gene-Related Peptides: Utilization, Adherence and Impact on Acute Migraine Therapy Among 4 Million Commercial Members (Poster G44). *Journal of Managed Care & Specialty Pharmacy* 2020; **24**: S86.
29. Lambru G, Hill B, Murphy M, Tylova I, Andreou AP. A prospective real-world analysis of erenumab in refractory chronic migraine. *The Journal of Headache and Pain* 2020; **21**: 1-10.
30. Silberstein SD, Winner PK, Chmiel JJ. Migraine Preventive Medication Reduces Resource Utilization. *Headache* 2003; **43**: 171-8.
31. Ansari H, Ziad S. Drug–Drug Interactions in Headache Medicine. *Headache: The Journal of Head and Face Pain* 2016; **56**: 1241-8.
32. Starling AJ, Dodick DW. Best practices for patients with chronic migraine: burden, diagnosis, and management in primary care. *Mayo Clin Proc* 2015; **90**: 408-14.
33. Adelman J, Freitag FG, Lainez M, Shi Y, Ascher S, Mao L, et al. Analysis of safety and tolerability data obtained from over 1,500 patients receiving topiramate for migraine prevention in controlled trials. *Pain Med* 2008; **9**: 175-85.
34. Antonaci F, Ghiotto N, Wu S, Pucci E, Costa A. Recent advances in migraine therapy. *Springerplus* 2016; **5**: 637-.
35. Tfelt-Hansen P, Pascual J, Ramadan N, Dahlöf C, D'Amico D, Diener HC, et al. Guidelines for controlled trials of drugs in migraine: third edition. A guide for investigators. *Cephalalgia* 2012; **32**: 6-38.

36. Kawata AK, Shah N, Poon JL, Shaffer S, Sapra S, Wilcox TK, et al. Understanding the migraine treatment landscape prior to the introduction of calcitonin gene-related peptide inhibitors: Results from the Assessment of TolerabiliTy and Effectiveness in Migraine Patients using Preventive Treatment (ATTAIN) study. *Headache: The Journal of Head and Face Pain* 2021; **61**: 438-54.
37. Novartis Europharm Limited. Summary of Product Characteristics: Aimovig (erenumab). 2021. Available from: https://www.medicines.org.uk/emc/product/10297/smpc. Date accessed: May 2022.
38. Eli Lilly Nederland BV. Summary of Product Characteristics: EMGALITY (galcanezumab). 2021. Available from: https://www.medicines.org.uk/emc/product/10478#gref. Date accessed: May 2022.
39. GmbH T. Summary of Product Characteristics: AJOVY (fremanezumab). 2021. Available from: https://www.medicines.org.uk/emc/product/11630/smpc. Date accessed: May 2022.
40. Aletaha D, Husni ME, Merola JF, Ranza R, Bertheussen H, Lippe R, et al. Treatment Mode Preferences in Psoriatic Arthritis: A Qualitative Multi-Country Study. *Patient preference and adherence* 2020; **14**: 949-61.
41. Hubig L, Smith T, L'Italien G, Harris L, Powell L, Johnston K, et al. Data on File: Patient preferences for calcitonin gene-related peptide (CGRP) inhibitors in the preventive treatment of migraine: A discrete choice experiment in the US and Germany. 2022.
42. Pham A, Burch RC. Patients with Migraine Headache who Switch from Erenumab to Galcanezumab Report Similar Improvement. 2020.
43. Russo A, Silvestro M, di Clemente FS, Trojsi F, Bisecco A, Bonavita S, et al. Multidimensional assessment of the effects of erenumab in chronic migraine patients with previous unsuccessful preventive treatments: a comprehensive real-world experience. *The Journal of Headache and Pain* 2020; **21**: 1-14.
44. Scheffler A, Messel O, Wurthmann S, Nsaka M, Kleinschnitz C, Glas M, et al. Erenumab in highly therapy-refractory migraine patients: First German Real-world evidence. 2020.
45. Kanaan S, Hettie G, Loder E, Burch R. Real-world effectiveness and tolerability of erenumab: A retrospective cohort study. *Cephalalgia* 2020; **40**: 1511-22.
46. Robblee J, Devick KL, Mendez N, Potter J, Slonaker J, Starling AJ. Real-World Patient Experience With Erenumab for the Preventive Treatment of Migraine. *Headache: The Journal of Head and Face Pain* 2020.
47. Thompson K, Mirzai M, Crabtree T, Zhang J, Thomas J, Kustra LA. Evaluation of persistence, switch patterns, and costs among migraine patients utilizing calcitonin gene-related peptide (cgrp) inhibitors in a u.s. medicaid population. Presented at AMCP conference.2020.
48. Hines DM, Shah S, Multani JK, Wade RL, Buse DC, Bensink M. Erenumab patient characteristics, medication adherence, and treatment patterns in the United States. *Headache: The Journal of Head and Face Pain* 2021.
49. National Institute for Health and Care Excellence (NICE). Final scope for the appraisal of rimegepant for treating or preventing migraine [ID1539], 2021. Available from: https://www.nice.org.uk/guidance/gid-ta10839/documents/final-scope. Date accessed: Aug 2022.
50. Pfizer. Data on File: Advisory Board Meeting on Rimegepant. 2022.
51. Pfizer. Data on File: CPRD Aurum Analysis. 2022.
52. Atlas S, Touchette D, Agboola F, Lee T, Chapman R, Pearson SD, et al. Acute treatments for migraine: effectiveness and value, 2020. Available from: http://icer-review.org/material/acute-migraine-evidence-report/. Date accessed: Aug 2022.
53. Touchette D, Atlas SJ, Agboola FO, Joshi M, Lee TA, Chapman RH, et al. PND15 LONG-TERM COST-EFFECTIVENESS OF LASMIDITAN, UBROGEPANT AND RIMEGEPANT FOR TREATMENT OF ACUTE MIGRAINE. *Value in Health* 2020; **23**: S261.
54. Johnston KM, L'Italien G, Harris L, Deighton A, Popoff E, Croop R, et al. Novel acute therapies in the treatment of migraine: impact of re-dosing on cost-utility outcomes. *Journal of medical economics* 2021; **24**: 512-3.

55. L'Italien G, Harris L, Mohajer A, Scripture JP, Coric V, Rosen NL. Real world evidence of reduction in point prevalence of medication overuse headache after migraine therapy with rimegepant. *Headache. Special Issue: American Headache Society 64th Annual Scientific Meeting*. 2022. p. American Headache Society 64th Annual Scientific Meeting; 9-12 June 2022; Denver (CO), USA.
56. Croop R, Ivans A, Stock D, Hould J, Morris BA, Stringfellow J, et al. A phase 1 study to evaluate the bioequivalence of oral tablet and orally dissolving tablet formulations of rimegepant in healthy adult subjects under fasting conditions (Abstract PF116LB). *Headache: The Journal of Head and Face Pain* 2018; **58**: 1303-4.
57. Reuter U, Goadsby PJ, Lanteri-Minet M, Wen S, Hours-Zesiger P, Ferrari MD, et al. Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study. *The Lancet* 2018; **392**: 2280-7.
58. Ferrari MD, Diener HC, Ning X, Galic M, Cohen JM, Yang R, et al. Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial. *The Lancet* 2019; **394**: 1030-40.
59. Mulleners WM, Kim BK, Lainez MJA, Lanteri-Minet M, Pozo-Rosich P, Wang S, et al. Safety and efficacy of galcanezumab in patients for whom previous migraine preventive medication from two to four categories had failed (CONQUER): a multicentre, randomised, double-blind, placebo-controlled, phase 3b trial. *The Lancet Neurology* 2020; **19(10)**: 814-25.
60. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS medicine* 2009; **6**: e1000097.
61. Croop R, Goadsby PJ, Stock DA, Conway CM, Forshaw M, Stock EG, et al. Efficacy, safety, and tolerability of rimegepant orally disintegrating tablet for the acute treatment of migraine: a randomised, phase 3, double-blind, placebo-controlled trial. *The Lancet* 2019; **394**: 737-45.
62. Biohaven Pharmaceuticals I. Data on File: Clinical study report BHV3000-301: A phase 3, double-blind, randomized, placebo-controlled, safety and efficacy trial of BHV-3000 (rimegepant) for the acute treatment of migraine. 2019.
63. Lipton RB, Croop R, Stock EG, Stock DA, Morris BA, Frost M, et al. Rimegepant, an oral calcitonin gene–related peptide receptor antagonist, for migraine. *New England Journal of Medicine* 2019; **381**: 142-9.
64. Marcus R, Goadsby PJ, Dodick D, Stock D, Manos G, Fischer TZ. BMS-927711 for the acute treatment of migraine: a double-blind, randomized, placebo controlled, dose-ranging trial. *Cephalalgia* 2014; **34**: 114-25.
65. Biohaven Pharmaceuticals I. Data on File: Clinical study report BHV3000-201: A multicenter, open-label long-term safety study of BHV-3000 in the acute treatment of migraine. 2020.
66. Biohaven Pharmaceuticals I. Data on file: Clinical study report BHV3000-310: A Phase 3: Double-Blind, Randomized, Placebo Controlled, Safety and Efficacy Trial of BHV-3000 (rimegepant) 75 mg for the Acute Treatment of Migraine. 2020.
67. National Institute for Health and Care Excellence (NICE). NG81 Appendix A: Literature search strategies. Available from: https://www.nice.org.uk/guidance/ng81/documents/search-strategies. Date accessed: May 2022.
68. Biohaven P. Data on File: Clinical study report BHV3000-305-(Final-Week-12-CSR). A Phase 2/3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Rimegepant in Migraine Prevention. 2020.
69. Dodick DW, Goadsby PJ, Spierings EL, Scherer JC, Sweeney SP, Grayzel DS. Safety and efficacy of LY2951742, a monoclonal antibody to calcitonin gene-related peptide, for the prevention of

migraine: a phase 2, randomised, double-blind, placebo-controlled study. *The Lancet Neurology* 2014; **13**: 885-92.
70. Scottish Intercollegiate Guidelines Network (SIGN). Search Filters. Available from: https://www.sign.ac.uk/what-we-do/methodology/search-filters/. Date accessed: May 2022.
71. Goadsby PJ, Dodick DW, Ailani J, Trugman JM, Finnegan M, Lu K, et al. Safety, tolerability, and efficacy of orally administered atogepant for the prevention of episodic migraine in adults: a double-blind, randomised phase 2b/3 trial. *Lancet neurol* 2020; **19**: 727-37.
72. Croop R, Lipton RB, Kudrow D, Stock DA, Kamen L, Conway CM, et al. Oral rimegepant for preventive treatment of migraine: a phase 2/3, randomised, double-blind, placebo-controlled trial. *The Lancet* 2021; **397**: 51-60.
73. Goadsby PJ, Reuter U, Hallström Y, Broessner G, Bonner JH, Zhang F, et al. A Controlled Trial of Erenumab for Episodic Migraine. *New England journal of medicine* 2017; **377**: 2123-32.
74. Wang SJ, Roxas AA, Saravia B, Kim BK, Chowdhury D, Riachi N, et al. Randomised, controlled trial of erenumab for the prevention of episodic migraine in patients from Asia, the Middle East, and Latin America: the EMPOwER study. *Cephalalgia* 2021.
75. Sakai F, Takeshima T, Tatsuoka Y, Hirata K, Lenz R, Wang Y, et al. A Randomized Phase 2 Study of Erenumab for the Prevention of Episodic Migraine in Japanese Adults. *Headache* 2019; **59**: 1731-42.
76. Stauffer VL, Dodick DW, Zhang Q, Carter JN, Ailani J, Conley RR. Evaluation of Galcanezumab for the Prevention of Episodic Migraine: The EVOLVE-1 Randomized Clinical Trial. *JAMA Neurol* 2018; **75**: 1080-8.
77. Detke HC, Millen BA, Zhang Q, Samaan K, Ailani J, Dodick DW, et al. Rapid Onset of Effect of Galcanezumab for the Prevention of Episodic Migraine: Analysis of the EVOLVE Studies. *Headache* 2020; **60**: 348-59.
78. Skljarevski V, Matharu M, Millen BA, Ossipov MH, Kim BK, Yang JY. Efficacy and safety of galcanezumab for the prevention of episodic migraine: results of the EVOLVE-2 Phase 3 randomized controlled clinical trial. *Cephalalgia* 2018; **38**: 1442-54.
79. Sakai F, Ozeki A, Skljarevski V. Efficacy and safety of galcanezumab for prevention of migraine headache in Japanese patients with episodic migraine: a phase 2 randomized controlled clinical trial. *Cephalalgia reports* 2020; **3**.
80. Skljarevski V, Oakes TM, Zhang Q, Ferguson MB, Martinez J, Camporeale A, et al. Effect of Different Doses of Galcanezumab vs Placebo for Episodic Migraine Prevention: A Randomized Clinical Trial. *JAMA Neurol* 2018; **75**: 187-93.
81. Dodick DW, Silberstein SD, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Effect of Fremanezumab Compared With Placebo for Prevention of Episodic Migraine: a Randomized Clinical Trial. *Jama* 2018; **319**: 1999-2008.
82. Sakai F, Suzuki N, Kim BK, Tatsuoka Y, Imai N, Ning X, et al. Efficacy and safety of fremanezumab for episodic migraine prevention: multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in Japanese and Korean patients. *Headache* 2021; **61**: 1102-11.
83. Bigal ME, Dodick DW, Rapoport AM, Silberstein SD, Ma Y, Yang R, et al. Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of high-frequency episodic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. *Lancet neurol* 2015; **14**: 1081-90.
84. Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU TECHNICAL SUPPORT DOCUMENT 2: A GENERALISED LINEAR MODELLING FRAMEWORK FOR PAIRWISE AND NETWORK META-ANALYSIS OF RANDOMISED CONTROLLED TRIALS: REPORT BY THE DECISION SUPPORT UNIT, 2016. Available from: https://www.sheffield.ac.uk/sites/default/files/2022-02/TSD2-General-meta-analysis-corrected-2Sep2016v2.pdf. Date accessed: Aug 2022.

85. Dias S, Sutton AJ, Welton NJ, Ades AE. NICE DSU TECHNICAL SUPPORT DOCUMENT 3: HETEROGENEITY: SUBGROUPS, META-REGRESSION, BIAS AND BIAS-ADJUSTMENT REPORT BY THE DECISION SUPPORT UNIT, 2012. Available from: https://www.sheffield.ac.uk/sites/default/files/2022-02//TSD3-Heterogeneity.final-report.08.05.12.pdf. Date accessed: Aug 2022.
86. Stafford MR, Hareendran A, Ng-Mak DS, Insinga RP, Xu R, Stull DE. EQ-5D™-derived utility values for different levels of migraine severity from a UK sample of migraineurs. *Health and Quality of Life Outcomes* 2012; **10**: 65.
87. Xu R, Insinga RP, Golden W, Hu XH. EuroQol (EQ-5D) health utility scores for patients with migraine. *Quality of life research* 2011; **20**: 601-8.
88. Harris L, L'Italien G, Croop R, Coric V, Robbins J, Woolley J, et al. POSC202 Estimated Migraine Patient Population in England Progressing Beyond First-Line Acute Management. *Value in Health* 2021; **25**.
89. Irimia P, Garrido-Cumbrera M, Santos-Lasaosa S, Aguirre-Vazquez M, Correa-Fernández J, Colomina I, et al. Impact of monthly headache days on anxiety, depression and disability in migraine patients: results from the Spanish Atlas. *Sci Rep* 2021; **11**: 8286.
90. Southwell J, Afridi SK. The burden of migraine on acute and emergency services in a London teaching hospital. *Cephalalgia* 2021; **41**: 905-12.
91. Mahon R, Lang A, Vo P, Huels J, Cooney P, Danyliv A, et al. Cost-effectiveness of erenumab for the preventive treatment of migraine in patients with prior treatment failures in Sweden. *PharmacoEconomics* 2021; **39**: 357-72.
92. Batty AJ, Hansen RN, Bloudek LM, Varon SF, Hayward EJ, Pennington BW, et al. The cost effectiveness of onabotulinumtoxinA for the prophylaxis of headache in adults with chronic migraine in the UK. *Journal of medical economics* 2013; **16**: 877-87.
93. Gillard PJ, Devine B, Varon SF, Liu L, Sullivan SD. Mapping from disease-specific measures to health-state utility values in individuals with migraine. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2012; **15**: 485-94.
94. Vo P, Fang J, Bilitou A, et al. Patients' perspective on the burden of migraine in Europe: a cross-sectional analysis of survey data in France, Germany, Italy, Spain, and the United Kingdom. *The Journal of Headache and Pain* 2018; **19**: 82.
95. NHS Improvement. National Schedule of NHS costs - Year 2019-2020. Available from: https://www.england.nhs.uk/national-cost-collection/. Date accessed: Aug 2022.
96. Jones KC, Burns A. Unit Costs of Health and Social Care, 2021. Available from: https://kar.kent.ac.uk/92342/. Date accessed: Aug 2022.
97. Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press, 2022. Available from: https://bnf.nice.org.uk/. Date accessed: July 2022.
98. Bash. NATIONAL HEADACHE MANAGEMENT SYSTEM FOR ADULTS 2019, 2019. Available from: https://www.bash.org.uk/downloads/guidelines2019/01_BASHNationalHeadache_Management_SystemforAdults_2019_guideline_versi.pdf. Date accessed: Aug 2022.
99. Diener HC, Holle-Lee D, Nagel S, et al. Treatment of migraine attacks and prevention of migraine: Guidelines by the German Migraine and Headache Society and the German Society of Neurology. *Clinical & Translational Neuroscience* 2019: 1-40.
100. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013 - Process and methods [PMG9], 2013. Available from: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781. Date accessed: Aug 2022.
101. Bonafede M, Cai Q, Cappell K, Kim G, Sapra SJ, Shah N, et al. Factors associated with direct health care costs among patients with Migraine. *Journal of Managed Care and Specialty Pharmacy* 2017; **23**: 1169-76.

102. Hu XH, Markson LE, Lipton RB, Stewart WF, Berger ML. Burden of Migraine in the United States: Disability and Economic Costs. *Archives of Internal Medicine* 1999; **159**: 813-8.
103. L'Italien G, Popoff E, Johnston K, McGrath D, Conway CM, Powell L, et al. Rimegepant 75 mg for acute treatment of migraine is associated with significant reduction in monthly migraine days: Results from a long-term, open-label study. *Cephalalgia Reports* 2022; **5**: 25158163221075596.
104. Johnston KM, L'Italien G, Popoff E, Powell L, Croop R, Thiry A, et al. Mapping Migraine-Specific Quality of Life to Health State Utilities in Patients Receiving Rimegepant. *Adv Ther* 2021; **38**: 5209-20.
105. Johnston K, Harris L, Powell L, Popoff E, Coric V, L'Italien G, et al. Monthly migraine days, tablet utilization, and quality of life associated with Rimegepant – post hoc results from an open label safety study (BHV3000–201). *The Journal of Headache and Pain* 2022; **23**: 10.
106. Ashina M, Dodick D, Goadsby PJ, Reuter U, Silberstein S, Zhang F, et al. Erenumab (AMG 334) in episodic migraine: Interim analysis of an ongoing open-label study. *Neurology* 2017; **89**: 1237-43.
107. Schürks M, Rist PM, Shapiro RE, et al. Migraine and Mortality: A Systematic Review and Meta-Analysis. *Cephalalgia* 2011; **31**: 1301-14.
108. Office for National Statistics (ONS). National life tables, United Kingdom 2018-2020, 2021. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2018to2020. Date accessed.
109. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2010; **13**: 509-18.
110. Office for National Statistics (ONS). Employee earnings in the UK: 2021. 2021. Available from: https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/earningsandworkinghours/bulletins/annualsurveyofhoursandearnings/2021. Date accessed: March 2022.
111. Office for National Statistics (ONS). Labour market overview, UK: March 2022. 2022. Available from: https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/employmentandemployeetypes/bulletins/uklabourmarket/march2022. Date accessed: March 2022.
112. Doane MJ, Gupta S, Fang J, et al. The Humanistic and Economic Burden of Migraine in Europe: A Cross-Sectional Survey in Five Countries. *Neurol Ther* 2020: 1-15.
113. Department of Health and Social Care. eMIT national database, 2021. Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit. Date accessed: Aug 2022.

8 Appendices

8.1 Acute treatment – additional analyses

A comparison of results for pain relief at 2 h across all analyses requested at clarification, and the company's preferred analysis in the original company submission (CS), for acute migraine treatment is provided in Table 89 below. The External Assessment Group (EAG) notes that the [redacted] using the modified intention to treat (mITT) population preferred by the EAG and the subgroup data for at least two triptan failures favoured by the company; all variations within [redacted] are similar. Concerns about the robustness of the subgroup with at least two triptan failures (as described in Section 2.3.1.1) and the absence of any strong rationale to exclude study -310 or only focus studies using the orally dispersible (ODT) formulation (lack of clinical rationale for study -310 and [redacted]) means the EAG's preference is for response rates to be based on the largest sample size.

Table 89. Proportion with pain relief at 2 h – comparison between analyses requested at clarification and company's preferred analysis

	Four included RCTs (-301, -302, -303 and -310), mITT population – EAG's preferred analysis			Three included RCTs (-301, -302 and -303), mITT population			Two included RCTs (-303 and -310, focused on OD formulation)		
Outcome	Rimegepant n/N (%)	Placebo n/N (%)	Risk difference (95% CI; p-value)	Rimegepant n/N (%)	Placebo n/N (%)	Risk difference (95% CI; p-value)	Rimegepant n/N (%)	Placebo n/N (%)	Risk difference (95% CI; p-value)
Pain relief at 2 h	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; EAG, External Assessment Group; mITT, modified intention to treat; ODT, orally dispersible tablet; RCTs, randomised controlled trials.

Data for the EAG's preferred analysis are from the response to clarification questions A4, A5 and A12, data for the company's preferred analysis are from Table 20 of the CS, data in the mITT population for three inclu the pooled results only including the two studies using the ODT formulation are from the response to clarification question A11b.

8.2 Prevention – Baseline characteristics for studies included in the NMA for episodic migraine prevention

Baseline characteristics for each of the studies included in the EAG's preferred network meta-analysis (NMA) are provided in Table 90 below (adapted from Table 32 in response to clarification question A18).

Table 90. Baseline patient characteristics for studies included in the migraine prevention NMA (all 14 studies included in the EAG's preferred analysis, adapted from Table 32 in the response to clarification question A18)

Trial	Study arm	Patients treated, n	Mean (SD) age, years	Sex, % female	Race, % white	Migraine with aura, %	EM, %	Mean (SD) migraine duration, years	Mean (SD) MMDs at baseline	Use of other preventive treatment	
										Prior, %	Current, %
Erenumab 140 mg monthly											
STRIVE (NCT02456740)[73]	ERE 140	319	40.4 (11.1)	85.3	NR	NR	100.0	NR	8.3 (2.5)	38.9	2.5
	PBO	319	41.3 (11.2)	85.9	NR	NR		NR	8.2 (2.5)	41.1	3.1
EMPOwER (NCT03333109)[74]	ERE 140	224	37.1 (9.6)	82.1	15.6	73.7	100.0	11.2 (9.7)	8.3 (3.1)	53.1	NR
	PBO	338	38.0 (10.1)	83.1	17.8	67.2		12.6 (10.2)	8.4 (2.8)	53.0	NR
LIBERTY (NCT03096834)[57]	ERE 140	121	44.6 (10.5)	80.0	93.0	35.0	100.0	NR	9.2 (2.6)	100.0	0.0
	PBO	125	44.2 (10.6)	82.0	92.0	36.0		NR	9.3 (2.7)	100.0	0.0
Sakai *et al.* 2019 (NCT02630459; phase II study)[75]	ERE 140	137	Median 45 (range, 23 to 64)	81.8	NR	27.0	100.0	NR	8.1 (2.4)	56.2	10.9

	PBO	136	Median 45 (range, 21 to 61)	86.8	NR	24.3		NR	7.7 (2.3)	55.9	9.6
Fremanezumab 225 mg (monthly) and 675 mg (quarterly)											
HALO EM (NCT02629861)[81]	FRE 225	290	42.9 (12.7)	84.1	NR	NR	100.0	20.7 (12.9)	8.9 (2.6)	NR	21.4
	FRE 675	291	41.1 (11.4)	86.3	NR	NR		20.0 (12.1)	9.3 (2.7)	NR	19.9
	PBO	294	41.3 (12.0)	84.0	NR	NR		19.9 (11.9)	9.1 (2.7)	NR	21.1
Sakai *et al.* 2021 (NCT03303092)[82]	FRE 225	121	44.4 (9.5)	83.5	NR	NR	100.0	22.0 (12.9)	8.6 (2.5)	NR	19.8
	FRE 675	119	41.9 (10.1)	84.9	NR	NR		18.3 (11.4)	8.7 (2.5)	NR	19.3
	PBO	117	44.2 (10.7)	85.5	NR	NR		19.4 (13.3)	9.0 (2.8)	NR	18.8
FOCUS (NCT03308968)[58]	FRE 225[a]	283	45.9 (11.1)	84.0	93.0	NR	40.0	24.0 (13.7)	14.1 (5.6)	100.0	0.0
	FRE 675[a]	276	45.8 (11.0)	83.0	95.0	NR		24.3 (12.8)	14.1 (5.6)	100.0	0.0
	PBO[a]	279	46.8 (11.1)	84.0	94.0	NR		24.3 (13.6)	14.3 (6.1)	100.0	0.0
Bigal *et al.* 2015 (NCT02025556; phase II study)[83]	FRE 225	96	40.8 (12.4)	91.0	77.0	NR	100.0	18.9 (12.9)	11.5 (1.9)	33.0[b]	34.0
	PBO	104	42.0 (11.6)	88.0	82.0	NR		21.1 (14.1)	11.5 (2.24)	27.0[b]	27.0
Galcanezumab 120 mg monthly											

EVOLVE-1 (NCT02614183)[76]	GAL 120	213	40.9 (11.9)	85.0	79.3	NR	100.0	12.1 (13.0)	9.2 (3.1)	62.4	NR
	PBO	443	41.3 (11.4)	83.6	82.2	NR		19.9 (12.3)	9.1 (3.0)	59.4	NR
EVOLVE-2 (NCT02614196)[78]	GAL 120	231	40.9 (11.2)	85.3	71.9	NR	100.0	19.9 (11.7)	9.1 (2.9)	68.0	NR
	PBO	461	42.3 (11.3)	85.3	70.5	NR		21.2 (12.8)	9.2 (3.0)	64.6	NR
CONQUER (NCT03559257)[59]	GAL 120[c]	137	45.9 (11.2)	82.0	86.0	47.0	100.0	21.7 (12.7)	9.5 (3.0)	100.0	0.0
	PBO[c]	132	46.3 (11.8)	89.0	87.0	42.0		22.9 (13.1)	9.2 (2.7)	100.0	0.0
CGAN (NCT02959177; phase II)[79]	GAL 120	115	43.2 (10.0)	82.6	NR	NR	100.0	21.1 (11.8)	8.6 (2.8)	59.1	0.0
	PBO	230	44.2 (10.0)	85.2	NR	NR		21.2 (11.6)	8.6 (3.0)	60.9	0.0
CGAB (NCT02163993; phase II)[80]	GAL 120[d]	273	40.6 (11.9)	84.6	NR	NR	100.0	NR	6.7 (2.6)	NR	NR
	PBO	137	39.5 (12.1)	79.6	NR	NR		NR	6.6 (2.7)	NR	NR
Rimegepant 75 mg EOD											
BHV3000-305 (NCT03732638)[72]	RIM 75[a]	370	41.3 (13.0)	81.0	80.0	41.0	77.0	Median 18 (IQR, 14 to 28)	10.3 (3.2)	[redacted]	[redacted]
	PBO[a]	371	41.1 (31.1)	84.0	83.0	39.0		Median 18 (IQR, 13-28)	10.1 (3.1)	[redacted]	[redacted]

Abbreviations: CM, chronic migraine; CSR, clinical study report; EAG, External Assessment Group; EM, episodic migraine; EOD, every other day; FRE, fremanezumab; GAL, galcanezumab; IQR, interquartile range; NMA, network meta-analysis; NR, not reported; PBO, placebo; RIM, rimegepant; SD, standard deviation.

Note that baseline characteristics are given for the treated populations in studies, which differs to the numbers analysed for each study. Studies indicated as phase II were not included in the company's preferred analysis but were included in the EAG's preferred analysis.

[a] Baseline characteristics provided for the whole trial population, including EM and CM patients
[b] Reported as the proportion that discontinued prior preventives due to lack of efficacy
[c] Note that the conquer study included EM and CM patients but data, including baseline characteristics in this table, were provided specifically for the EM subgroup and used in the analysis (stratified for EM vs CM at randomisation)
[d] Baseline characteristics not provided specifically for GAL 120 mg dose (estimates are for all patients receiving GAL in the trial)
[e] From BHV3000-305 CSR

8.3 Prevention – additional NMA analyses

Results from two of the other NMA models that may be of interest are presented in Table 91 and Table 92 below. These were selected for presentation here as they represent alternatives to the EAG's and company's preferred models presented in Table 30 and Table 31 in Section 3.2.4.4. The EAG's preferred use of random effects adjusted for baseline risk (with inclusion of phase II studies) is varied by presenting results below for the fixed effects adjusted model (for ≥50% reduction in monthly migraine days [MMDs] over 12 weeks outcome) or random effects model unadjusted for baseline risk (for change from baseline in MMDs at weeks 9-12 outcome) with phase II studies included. The company's preferred use of the fixed effects adjusted for baseline risk (for ≥50% reduction in MMDs over 12 weeks outcome) or random effects model unadjusted for baseline risk (for change from baseline in MMDs at weeks 9-12 outcome) with exclusion of phase II studies is varied by presenting results below for the random effects adjusted model with phase II studies excluded. The EAG notes that these are neither the EAG's nor the company's preferred analyses, but they are presented for information.

8.3.1 ≥50% reduction in MMDs over 12 weeks

Table 91. ≥50% reduction in MMDs from baseline over 12 weeks – median ORs for rimegepant and mAbs vs placebo and mAbs vs rimegepant (alternative analyses)

Intervention	Fixed effects adjusted for baseline risk (phase II studies included) – fixed effects adjusted alternative to the EAG's preferred NMA Median OR (95% CrI)	Random effects adjusted for baseline risk (phase II studies excluded) – random effects adjusted alternative to the company's preferred NMA Median OR (95% CrI)
Compared to placebo		
Erenumab 140 mg	[redacted]	[redacted]
Galcanezumab 120 mg	[redacted]	[redacted]
Fremanezumab 225 mg	[redacted]	[redacted]
Fremanezumab 675 mg	[redacted]	[redacted]
Rimegepant 75 mg	[redacted]	[redacted]
Compared to rimegepant		
Erenumab 140 mg	[redacted]	[redacted]
Galcanezumab 120 mg	[redacted]	[redacted]
Fremanezumab 225 mg	[redacted]	[redacted]
Fremanezumab 675 mg	[redacted]	[redacted]

Abbreviations: CrI, credible interval; EAG, External Assessment Group; mAbs, monoclonal antibodies; MMDs, monthly migraine days; NMA, network meta-analysis; OR, odds ratio.

Bold text indicates values that are significant at a 5% level.

Figures for the fixed effect adjusted alternative of the EAG's preferred NMA are from the company's response to clarification question A18 and figures for the random effects adjusted alternative of the company's preferred NMA are from Addendum 3 of the clarification questions.

8.3.2 Change in MMDs from baseline at 12 weeks

Table 92. Change from baseline in MMDs at 12 weeks (weeks 9-12) – median mean differences for rimegepant and mAbs vs placebo and mAbs vs rimegepant (alternative analyses)

Intervention	Random effects unadjusted for baseline risk (phase 2IIstudies included) – random effects unadjusted alternative to the EAG's preferred NMA Median mean difference (95% CrI)	Random effects adjusted for baseline risk (phase II studies excluded) – random effects adjusted alternative to the company's preferred NMA Median mean difference (95% CrI)
Compared to placebo		
Erenumab 140 mg	[redacted]	[redacted]
Galcanezumab 120 mg	[redacted]	[redacted]
Fremanezumab 225 mg	[redacted]	[redacted]
Fremanezumab 675 mg	[redacted]	[redacted]
Rimegepant 75 mg	[redacted]	[redacted]
Compared to rimegepant		
Erenumab 140 mg	[redacted]	[redacted]
Galcanezumab 120 mg	[redacted]	[redacted]
Fremanezumab 225 mg	[redacted]	[redacted]
Fremanezumab 675 mg	[redacted]	[redacted]

Abbreviations: CrI, credible interval; CS, company submission; EAG, External Assessment Group; mAbs, monoclonal antibodies; MMDs, monthly migraine days; NMA, network meta-analysis.

Bold text indicates values that are significant at a 5% level.

Figures for the random effects unadjusted alternative to the EAG's preferred NMA are from the company's response to clarification question A18 and figures for the random effects adjusted alternative to the company's preferred NMA are from Table 41 of the CS.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Rimegepant for treating or preventing migraine [ID1539]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Thursday 8 September** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Comparative efficacy between mAbs and rimegepant in the prevention model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
ID1539 rimegepant ERG report 30082022CM [ACIC] page 21 *"the mAbs are better at reducing MMDs than rimegepant…"* Pfizer believes the above statement may be misinterpreted.	Pfizer proposes to replace the statement with the following text: *"in the change from baseline in MMD, there are no significant differences for any of the mAbs compared to rimegepant, however the mAbs show higher proportion of patients achieving ≥ 50% MMD reduction, with statistical significance for galcanezumab 120 mg and fremanezumab 225 mg."*	The original statement may imply that the mAbs are statistically significance at reducing MMDs (in both outcomes: change from baseline MMD and proportion of patients with >50% MMD reduction). The proposed amendment is aligned with EAG conclusion on page 106 and 109 of the report.	Thank you for highlighting this, the text has been amended in the EAG report.

Issue 2 Long-term discontinuation rates in the acute model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
ID1539 rimegepant ERG report 30082022CM [ACIC] page 159 The title (see below) of Table 57 is incorrect. Please note, this was an error made on the company's part in the response to the clarification questions. *"Table 57. Reasons for discontinuation in study BHV3000-201 used to inform the long-term discontinuation rate in the acute model (subgroup with at least 2 triptan failures)"*	Pfizer proposes to replace the title in Table 57 with the following: *"Table 57. Reasons for discontinuation in study BHV3000-201 used to inform the long-term discontinuation rate in the acute model"*	The original title was incorrect.	Thank you for highlighting this, the title and supporting text has been amended in the EAG report.

- This is not the subgroup with at least 2 triptan failures it is taken from those who were in the BHV3000-301, 302, and 303 who enrolled into the BHV300-201 study. - Please note, [redacted] reflects those who discontinue with at least 2 triptan failures.			

Issue 3 Long-term discontinuation rate in the preventive model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
ID1539 rimegepant ERG report 30082022CM [ACIC] page 160 ***Please note this is an explanation and not a factual check**** *"In light of this, the EAG is unclear why the company used an annual rate of [redacted] and not [redacted]."* The company decided on the annual rate of [redacted] as it was derived from patient level data facilitating the running of the Kaplan-Meier curve rather than a proportionate value.	The company acknowledge either method is acceptable and are happy for the EAG to decide their preferred discontinuation rate.	In the CS, the point estimate from the Kaplan-Meier curve was used at Year 1 ([redacted]) as opposed to the raw proportion ([redacted]), EAG's preferred approach.	Thank you for highlighting this, the text has been amended in the EAG report.

Issue 4 Inclusion of a specialist cost to prescribe rimegepant

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
ID1539 rimegepant ERG report	The initial specialist visit cost included	In the STA for Erenumab [ID1188] in the	This is not a factual inaccuracy and

30082022CM [ACIC] pages 172, 199 The EAG considers it important to include the cost of the initial visit with a specialist in its preferred base case. Pfizer considers the additional cost of a specialist initial visit (£192) in the rimegepant arm only to be unwarranted and inconsistent with previous mAb STAs.	for rimegepant should be removed from the models. If the EAGs believes the initial visit cost should be considered in the model, it should be applied to both treatment arm, rimegepant and BSC, in which case the cost will cancel out.	committee papers page 154, only the one-off cost for training of the patient on how to use injection (£40.04) was included. In the STA for Fremanezumab [ID1368] in the committee papers page 153, one hour training session with band 5 hospital-based nurse, (£37.00) was included. In the STA Galcanezumab [ID1372] in the committee papers, one hour of working time for a band 5 hospital nurse, (£39.68) was included as an initiation cost.	therefore no changes to the report are required. The cost of a specialist visit has not been added to BSC as BSC would not be initiated in secondary care.

Issue 5 Minor Factual Error (typo)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
ID1539 rimegepant ERG report 30082022CM [ACIC] page 25 A typo was identified in the text below: *"During the clarification stage company was requested to provide a scenario using the acute pooled RCTs to inform the distribution of MMD at baseline. The company did not provide the requested scenario as they did think it was an appropriate distribution to consider. The EAG would urge the company to*	The text should be updated to included text in red below. "*During the clarification stage company was requested to provide a scenario using the acute pooled RCTs to inform the distribution of MMD at baseline. The company did not provide the requested scenario as they did not think it was an appropriate distribution to consider. The EAG would urge the company to reconsider this."*	The text should be updated so it is factually correct.	Thank you for highlighting this, the text has been amended in the EAG report.

reconsider this."			

Issue 6 Minor Factual Error (typo)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
ID1539 rimegepant ERG report 30082022CM [ACIC] page 121 A typo was identified in the text below: *"Whether study BHV3000-301 is included or excluded."*	The text should be updated with the text in red below. "*Whether study BHV3000-310 is included or excluded"*	The text should be updated to the correct study as the EAG is referring to the Asian study, BHV3000- 310.	Thank you for highlighting this, the text has been amended in the EAG report

Issue 7 Minor discrepancies between the acute model and the report

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
ID1539 rimegepant ERG report 30082022CM [ACIC] pages 30-31 and page 121 Minor errors have been identified in Table 15 and Table 37. Pfizer has identified discrepancies between the report and the model when the EAG's scenarios analysis are run, with differences being less than £50/QALY.	No amendment required. Please note, given the negligible impact of these discrepancies, Pfizer does not believe these need to be addressed as a matter of priority.	N/A	Thank you for highlight this. However, the EAG is unable to confirm the differences flagged by the company in the FAC. If the differences are less than £50/QALY, the EAG agrees that the impact of the discrepancies is negligible.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Rimegepant for treating or preventing migraine [ID1539]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' 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

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.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response 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.

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.

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.

About you

Table 1 About you

Your name	**Pfizer Ltd**
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	**Pfizer Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Acute Migraine		
Exclusion of chronic migraine (CM) patients from acute randomised controlled trials (RCTs) and extrapolating evidence from episodic migraine (EM) patients	Yes (references)	**Observed comparative data of EM versus CM is not available, however, no difference is expected by the EAG and clinical experts** • The inclusion criteria of <8 migraine attacks per month was chosen in line with previous acute migraine trials.[1,2] • Pfizer agrees with the EAG report that there is nothing that can be done within the trials to assess whether results for the CM group would differ to the EM group covered in the trials. As noted, additional evidence beyond the trials requested by the EAG assessing the difference between the efficacy of acute treatment in EM and CM is not available. • However, Pfizer agrees with the EAG's clinical experts on how they do not expect there to be differences in the efficacy of acute treatment between EM and CM patients. **Increased risk of MOH in CM patients suggested by EAG clinical experts is contrary to clinical trial and real-world evidence**

		• While certain analgesics and medicines such as triptans are associated with an increase in the risk of MOH. In rimegepant clinical trials, only one case (0.1%) of MOH, (reported verbatim term of rebound headaches, considered possibly related to study drug was reported in study 201). • In addition, a recently published real-world analysis demonstrates that treatment with rimegepant ODT is associated with clinically significant reduction in the burden of MOH.[3] • Therefore, we do not expect more frequent medication in this subpopulation, and which would have led to a higher ICER in this subgroup. **Acute usage in CM is aligned with the SmPC** Please note, the SmPC does not preclude the use of rimegepant in the acute treatment of migraine among CM patients.
Cost-effectiveness results based on the orally dispersible tablet (ODT) formulation trials	Yes (references)	Pfizer reconfirm the population in BHV3000 -301, -302, and -303 studies are more reflective of the UK population given cultural differences in pain reporting, whereby the Asian population in study BHV3000-310 are demonstrating a higher threshold for pain reporting, shown in our exploration to understand what was driving the ICER and in the literature. **Cultural differences in reporting pain is the key driver of the ICER which explains what may appear as counterintuitive results** • As requested by the EAG please see an explanation of what is driving the change in the ICER, which explains what may appear as counterintuitive results: ○ The responder coefficient is smaller in the ODT-only regression than any of the others. The mITT (incl. 310) population (which was included in Table 83 of the EAG report scenario) responder coefficient is lower

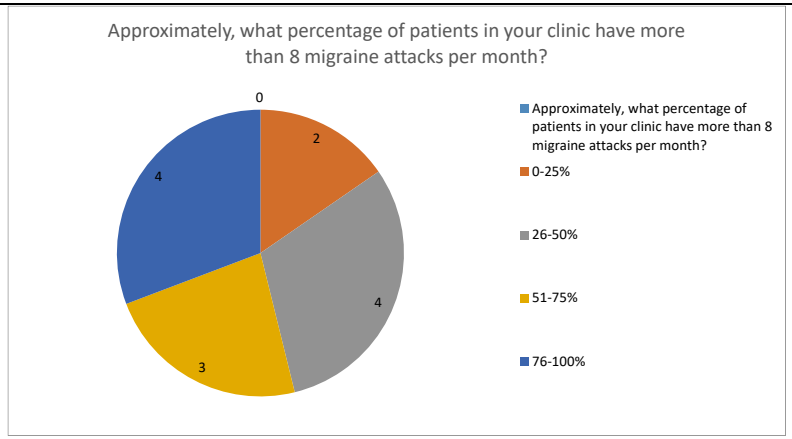
		than the original mITT (excl 310) scenario, since mITT (incl. 310) includes the non-ODT trials the impact of 310 is diluted. ▪ Overall, the response rate is similar across the ODT and tablet formulation trials as demonstrated in the model. ▪ At baseline, more patients in the 301-303 trials experience severe migraine pain compared to the 310 trial. • 30.9%, 35.0%, and 29.7% of patients in the 301, 302 and 303 studies experience severe pain at baseline, whereas in 310, the Asian study, it was 18.0% of patients. ▪ Consequently, responding means more to a subject in the 301-303 studies compared to the 310 study. ▪ Based on utilities, moving from Severe [-0.200] to Moderate [0.530], is a much larger gain than moving from Moderate [0.530] to Mild [0.660]). **BHV3000-301, -302, and –303 studies are more reflective of the UK population** Given the cultural differences in reporting pain severity in the literature and is shown above in our exploration to understand what was driving the ICER, the 301-303 data is more reflective of the UK population. • Yi et al., 2014 noted Asian people had a higher pain threshold compared to Caucasian Europeans possibly because of the differences in skull shape between these races.[4] • Houghton et al., 1992 stated Asians had a higher threshold for pain compared to Europeans.[5] **ODT versus non-ODT bioequivalence**

		As noted in the original submission the ODT formulation is bioequivalent to the oral tablet formulation. Further, data supporting the bioequivalence of the two formulations is below:
		• The results of bioequivalence studies in healthy subjects demonstrated that rimegepant ODT administered sublingually or on the tongue is bioequivalent to rimegepant oral tablet.[6,7]
		• Statistical comparisons of the ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} of rimegepant ODT administered sublingually versus rimegepant tablet showed that all 90% CIs of geometric mean ratios were within the predefined range (80%-125%) for bioequivalence.
		• In addition, the rate of absorption was faster with rimegepant ODT administered sublingually compared with rimegepant oral tablet, with an earlier median time to maximum concentration (T_{max}) of 1.5 versus 2 hours, respectively.[8]
		• Regulatory approvals of Vydura (rimegepant) by the EMA and MHRA, referring the trials in (1) and (2) above
		(note in the SmPC Study 1 (303) refers to Vydura whereas study 2 and 3 (301, 302) and study 4 (305) refer to rimegepant 75mg).
		• The EPAR summarises the bioequivalence data, and concludes at the end of the following sections:
		  ○ *Bioequivalence between ODT sublingual (SL) and Tablets, Study BHV3000-110:* results indicated bioequivalence of the rimegepant formulations
		  ○ *Bioequivalence between ODT on top of the tongue and tablets, Study BHV3000-113:* demonstrated bioequivalence under fasting conditions in healthy subjects for each parameter.
		• Our 90% CIs of geometric mean ratios for AUC were also within the more stringent 90.00-111.11% intervals required for bioequivalence of narrow therapeutic index drugs.[9]
		
		Additional quality check identified no issues

		In addition to explaining the counterintuitive results, Pfizer also undertook an additional quality check of the model, whereby: • Patient-level data from Study BHV3000-301, -302, -303, and -310 were utilised (303 and 310 in the ODT only scenario). Pain intensity level (none, mild, moderate, severe) was characterised over the 48-hour migraine period, and an area-under-the curve (AUC) approach was used to apply health state utilities by pain category and estimate the cumulative quality-adjusted time spent by treatment arm. Regression analyses were conducted to adjust the AUC values for patient covariates related to demographics and clinical disease characteristics of patients in the trials, with resultant QALHs out of a maximum 48 per migraine event, based on pain trajectories and regression analysis. • The approaches described were validated independently for the original set of submitted regression models, by two analysts using both R and STATA. Subsequent models including BHV3000-310 were run in an analogous fashion. • Relating to what we see in the combined ODT scenario specifically, the subjects used in these analyses were more severe in the BHV3000-303 study compared to the BHV3000-310 study. In BHV3000-303, 29.7% of subjects had severe pain at baseline (the rest had moderate pain); whereas in BHV3000-310, 18.0% of subjects had severe pain at baseline (the rest had moderate pain). Therefore, on average, being a responder means more to a subject in BHV3000-303 compared to BHV3000-310 (since moving from Severe [-0.200] to Moderate [0.530], is a much larger gain than moving from Moderate [0.530] to Mild [0.660]). • In addition to the quality checks mentioned above, the raw data preparation was reviewed again. • No inconsistencies were identified during this process.

Using response to the first migraine attack to inform response to subsequent migraine attacks	No	We agree with the EAG and accept there is currently no long-term data to inform how response to a single attack may predict response on future migraine episodes.
Baseline distribution of monthly migraine days (MMDs)	Yes (clinical expert input)	**Pfizer received consensus from clinical experts that the BHV3000-201 MMD distribution is most reflective of real-world practice in the UK.** • Pfizer sent an online survey to 15 clinicians which included one specialist headache nurse, two General Practitioners with a special interest in headache, one General practitioner, two neurologists with a special interest in headache working in district general hospitals, three neurologists working in a tertiary headache clinics, two academic neurologists with a special interest in headache, two pain specialists, one pain specialist with a special interest in headache, an American neurologist with a special interest in headache and extensive experience with managing patients with rimegepant as well as with the clinical trials. • 14 responses were received. One clinician recused himself due to a conflict of interest. One response was spoilt and excluded, and one response could not be identified as the clinician did not provide their name in a mandatory field of the questionnaire but was included in the analysis. • Of the 13 analysed responses, 9 agreed for Pfizer to provide their names and work details, which can be provided to the EAG/NICE on request. Responses relevant to this question are detailed below with responses: • "In your experience, and based on what you see in clinical practice can patients experience more than 8 moderate to severe migraine attacks a month?" o 100% of respondents responded "yes". • Would you still consider that these patients would need acute treatment(s) for their migraine attacks along with other (e.g., preventative) migraine treatments? • 100% responded "Yes" • Free text clarification comments to this question included:

		○ As a GP I see a wide variety of patients, a proportion of which have migraine and a subset of which have very frequent migraine ○ The ideal is that prevention is used to get the days needed to be treated acutely to 4 days a month as the primary end point. ○ In tertiary care seeing patients with 8 or more migraine days a month is not uncommon; they are highly disabled by the disorder ○ A majority of patients in tertiary care have chronic migraine with frequent severe migraine days ○ Most patients referred to specialist service have either debilitating high freq episodic migraine or chronic migraine, both of which can have more than 8 migraines per month, the latter having additional migraine/ headache days to a min of 15 per month. ○ I do 2 headache sessions a week in secondary care and a large percentage of my clinic are patients with chronic migraine, I have some unpublished data. ○ Most (80%) patients with migraine presenting to tertiary or quaternary practices including ours have chronic migraine ○ My practice is a mixture of unselected secondary headache referrals from GP, and tertiary referrals for specialist treatment from colleagues. About one-third of my patients have chronic migraine, and perhaps the same number have high frequency episodic migraine. • Approximately, what percentage of patients in your clinic have more than 8 migraine attacks per month?



- The other studies (301-303 and 310) are restricted to patients experiencing <8 migraine attacks per month.
- Therefore, the 201-study, which includes patients experiencing 2-14 migraine attacks per month, is the most reflective of real-world practice in the UK and the most appropriate source to inform the baseline distribution of MMDs. This is aligned with 1-1 discussions with 3 neurologists who have a special interest in headache who confirm this view.

Clinical experts suggest there is no relationship between migraine frequency and severity

During the Technical Engagement Meeting the EAG queried if there was a relationship between migraine severity and MMD as when they spoke to their clinical experts, they noted there might be a relationship between the severity of the migraine and frequency of the migraine especially if a patient experiences 9 or more migraines a month. Therefore, the EAG thought there might be a disconnect

		between using the acute pooled trial for the pain relief at 2 hours and the pain trajectories for the long-term study for the baseline distribution. • Pfizer's spoke to clinical experts who confirmed there is no relationship between MMD and migraine severity and noted, patients can present with low frequency, high severity migraines and vice versa; high frequency, low severity migraines.
Assuming rimegepant p*ro re nata* (PRN) can result in reductions in MMDs	Yes (clinical expert input and references)	**Rimegepant PRN reducing MMDs was observed in clinical studies, is biologically plausible and is supported by clinical experts** • Pfizer disagrees with the EAG, that rimegepant PRN reductions in MMDs is highly uncertain. • MMD reduction among high frequency rimegepant PRN users has been observed data in the 201 study and described by three peer reviewed publications.[10-12] • Given rimegepant has a dual indication, it is biologically plausible patients will benefit from the prevention properties of acute rimegepant PRN, albeit at a lesser extent than if taking every other day. o The concept was also presented and unanimously accepted by all the UK clinicians consulted during the NICE advisory boards held in May 2022. It is also seen as significant advantage of rimegepant for these patients by the clinical experts. **A 2-year time horizon is not appropriate** • Pfizer is concerned that a 2-year time horizon disadvantages the asset vs acute alternatives which do not have long-term data to support additional benefit beyond acute attacks (in this case, a preventative effect, for which rimegepant is also indicated). • In consultation with three neurologists with an interest in headache, the following views were shared with Pfizer:

		○ The common scenario in migraine is onset during teens then decrease in frequency around 40-50 years of age ○ Migraine is easier to keep under control vs to get under control - therefore clinically it is ideal to reduce frequency over time where possible. ○ There is no justified reason that the effect will stop or wane in the data, and there is no evidence the benefit disappears over time. ○ There is a trend seen, as well as a tendency to decrease MMDs over time, and there is good evidence to support prevention both physiologically and from the RCTs. ○ Even if this effect is modest, it is clinically relevant, and it continues: it is unreasonable not to include this over a 20-year time horizon. ○ One of the three experts agreed the 20-year timeline was reasonable, and in fact stated there is an argument for a longer timeframe (Neurologist with a special interest in headache from a London Border County). Another Neurologist with a special interest in headache from the north of England felt an indeterminate time horizon was more appropriate. A third neurologist with a special interest in headache from London felt 5 years would be a minimum acceptable time horizon, and that a longer time horizon was not unreasonable. • Importantly, Pfizer believes the 2-year time horizon suggested by the EAG compared to the model time horizon (20 years) is inadequate in capturing patient's experience with migraine and the benefits of patients taking acute treatment in terms of decreasing MMD. ○ The time horizon should be long enough to capture all the associated health outcomes and costs. In general, a lifetime horizon is a preferred assumption by NICE. ▪ While Pfizer acknowledges that a shorter time horizon may be appropriate under specific circumstances such as for acute conditions (e.g., respiratory infection), migraine does not fall into

		this category, as it is a chronic disease that requires ongoing disease management, hence the short time horizon of two years adopted by ERG is not warranted. ▪ Furthermore, clinical experts noted patients begin to experience migraine during puberty which can continue until they are in their forties. Additionally, another KOL noted although patients are taking rimegepant PRN, they will still benefit from its preventative properties as demonstrated by the long-term data. ○ Furthermore, sensitivity analyses with a lifetime horizon requested by the ERG during the CQs suggested there is no clinical rationale to adopt a shorter time horizon. • It should be noted that intermediate time horizons of 5 and 10 years were also provided in the submission.
Migraine prevention		
Discrepancy between the population described in the marketing authorisation1 and the decision problem described by the company (at least four migraine attacks per month vs at least four MMDs)	No	The company believes that the decision problem should read as 'at least four migraine attacks per month' as this most closely aligns to the inclusion criteria for the relevant pivotal studies and with the rimegepant SmPC.
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)	No	The company agrees with the EAG that the issue is unresolvable as data were not collected to allow any assessment of how prior treatment failures may affect rimegepant efficacy in the BHV3000-305 trial (i.e., comparing groups with one, two or no prior treatment class failures). However, the observation that the refractory trials included in the NMA (LIBERTY, FOCUS and CONQUER) tend to have numerically larger odds ratios than the non-refractory trials for the same intervention, which may suggest that the BHV3000-305 trial provides a conservative estimate of Rimegepant in a more refractory population.

Uncertainty concerning the efficacy of rimegepant vs mAbs due to a lack of direct evidence and limitations of the network meta-analysis (NMA)	No	The company agrees with EAG regarding the NMA, i.e., given the absence of direct evidence from an RCT comparing rimegepant and mAbs, the random effects NMAs with adjustment for baseline risk provides the most appropriate estimate of the efficacy for rimegepant versus mAbs for use in the cost-effectiveness analyses given readjusted analysis shows we are equivalent.
Gradual vs immediate reversion to baseline MMD during the assessment period and after the assessment period	Yes (model)	The suggested change has been implemented using tunnel states to allow a gradual reversion to baseline for all patients who discontinue treatment having been 12-week responders. • Applying tunnel states to graduate the reversion to baseline in 12-week responders reduces the ICERs (as the EAG anticipated) due to the retention of some element of treatment effect post-discontinuation – i.e., it is assumed that patients discontinue despite maintaining treatment benefit and only subsequently begin to lose this.
Response probability for rimegepant	Yes (clinical expert input)	Pfizer does not agree with the alternative approach the EAG has suggested for the following reasons: • The NMA in the original submission was conducted using the over-12 weeks data in order to broaden the evidence base given that at 12 weeks data was not available in several Studies (not making this assumption would have removed 5 studies from the network and made a comparison to galcanezumab not feasible). o When both outcomes were available, Pfizer compared the relative effects under both definitions to highlight consistency in the relative effects under both approaches (Document B Figure 13 page 122). • The at 12-week response probability is the appropriate quantity to which these relative effects should be applied. o Adopting an over 12-week measure would have the perverse effect of treating some 12-week responders as non-responders, leading to an underestimation for patients for whom rimegepant and mAbs are effective. • In an online questionnaire sent to Pfizer advisers described in response to issue 4 above, 85% of respondents chose (out of two options) “Outcomes

		at 12 weeks" (vs average outcome over 12 weeks) to the question "How do you assess clinical outcome(s) in response to treatment after a 3-month period?" ○ A general primary care GP, and pain specialist (both considering themselves not to have a special interest in headache) responded "average outcome over 12 weeks". ○ Free text clarification comments to this question included: ▪ I would look to see a downward trend over the period ▪ Both actually, HIT-6 (thus last 4 weeks) and also mostly headache days. ▪ To evaluate a preventive effect one need a three-month review. For acute benefit patient could be reviewed in one month through a telephone consultation ▪ Since effects build, I prefer to look at the recent period rather than the whole period ▪ improvements often increase over time. we want to see the cumulative benefit once maximal improvement has incurred ▪ Monthly number of headache/ migraine days are assessed over 3 months taking into account the minumum alongside subjective improvement ratings as a percentage ▪ in fact look at diary evidence for the 3 months but concentrate on the 2 weeks before clinic as patients usually seen at 12-14 weeks ▪ The benefit to any preventive effect increases over time. I am much more interested in capturing the impact at 9-12 weeks after treatment than averaging over 12 weeks and including the first 4 weeks while dose titration occurs or onset of effect may be delayed. The cumulative benefit of a drug even continues of months 4-6 (and even longer) as well, such that even weeks 9-12 may not capture the ultimate long-term benefit of a particular medication.

		▪ In a chronic condition, it is preferable to have a treatment with a profile of benefit over a sustained period of time, rather than an early effect which doesn't endure. In addition, where the responder rate increases over time, it is more meaningful to compare outcomes at three months with baseline, rather than an average over the full treatment time. ▪ Average outcome is meaningless as some patients take longer than others to respond but will achieve the same eventual response at 3 months and beyond. It is where you get to that is important, not how long it takes to get there! ○ In consultation with three neurologists with an interest in headache, all three agreed that the outcome at 12 weeks was the appropriate outcome measure. ○ In summary, based on clinical experts with a special interest in migraine, they noted they would only consider at 12-weeks as an appropriate outcome as this is when patients are assessed in clinical practice. • The option to employ the "over 12-week" response probability is available in the model as a scenario analysis, but it should not be applied to the base case analysis for the reasons above.
Applying the NMA results from Cycle 1 vs Cycle 3	Yes (model)	• Pfizer agrees early benefits may accrue in some patients prior to 12 weeks. ○ However, this could be reflected in the overall 4- and 8-week MMD distributions for all patients (as all patients remain on treatment through this period). ○ The company accepts that specifically addressing the reduction in MMD at these time points is reasonable. • When MMD reductions for responders earlier than 12 weeks were included in the analyses it resulted in a reduction in the ICERs. ▪

Comparator treatment acquisition costs	Yes (model)	Pfizer accepts the alternative approaches suggested by the EAG for the comparator treatment acquisition costs and therefore Pfizer have implemented the following: o 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). o Matching the regimen for erenumab to the regimen reported in the BNF and marketing authorisation.

References

1. Lasmiditan Compared to Placebo in the Acute Treatment of Migraine: - Full Text View - ClinicalTrials.gov
2. A Study of Lasmiditan (LY573144) Over Four Migraine Attacks - Full Text View - ClinicalTrials.gov
3. L'Italien G, Harris L, Mohajer A, Scripture J, Coric V, Rosen N, editors. Real world evidence of reduction in point prevalence of medication overuse headache after migraine therapy with rimegepant. American Headache Society 64th Annual Scientific Meeting; 2022; Denver (CO), USA
4. Yi, X., Fisher, K. M., Lai, M., Mansoor, K., Bicker, R., & Baker, S. N. (2014). Differences between Han Chinese and Caucasians in transcranial magnetic stimulation parameters. Experimental brain research, 232(2), 545-553

5. Houghton, I. T., Aun, C. S. T., Gin, T., & Lau, J. T. F. (1992). Inter-ethnic differences in postoperative pethidine requirements. Anaesthesia and intensive care, 20(1), 52-55.
6. Lipton RB, Croop R, Stock EG, et al. Rimegepant, an oral calcitonin gene-related peptide receptor antagonist, for migraine. N Engl J Med. 2019;381(2):142-149.
7. Lipton RB, Conway CM, Stock EG, et al. Efficacy, Safety, and Tolerability of Rimegepant 75 mg, an Oral CGRP Receptor Antagonist, for the Acute Treatment of Migraine: Results from a Phase 3, Double-Blind, Randomized, Placebo-Controlled Trial, Study 301. 60th Annual Scientific Meeting of the American Headache Society; June 29, 2018; San Francisco, CA. [Poster].
8. Croop R, Ivans A, Stock D, et al. A Phase 1 Study to Evaluate the Bioequivalence of Oral Tablet and Orally Disintegrating Tablet Formulations of Rimegepant, a Small Molecule CGRP Receptor Antagonist. 17th Biennial Migraine Trust International Symposium; September 6-9, 2018; London, UK. [Poster].
9. Guideline on the Investigation of Bioequivalence (europa.eu)
10. Johnston, K. M., L'Italien, G., Popoff, E., Powell, L., Croop, R., Thiry, A., ... & Lipton, R. B. (2021). Mapping migraine-specific quality of life to health state utilities in patients receiving rimegepant. Advances in Therapy, 38(10), 5209-5220.
11. Johnston, K., Harris, L., Powell, L., Popoff, E., Coric, V., L'Italien, G., & Schreiber, C. P. (2022). Monthly migraine days, tablet utilization, and quality of life associated with Rimegepant–post hoc results from an open label safety study (BHV3000–201). The journal of headache and pain, 23(1), 1-8.
12. L'Italien G, Popoff E, Johnston K, McGrath D, Conway CM, Powell L, et al. Rimegepant 75 mg for acute treatment of migraine is associated with significant reduction in monthly migraine days: Results from a long-term, open-label study. Cephalalgia Reports. 2022;5:25158163221075596.

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Acute migraine			
Additional issue 1: It is more plausible for rimegepant responders at 2 hours who discontinue treatment in the long-term to follow the trajectories of BSC all-comers rather than BSC responders	4.2.4.1	No	Although there is no data to support this statement, we agree that it is plausible for rimegepant responders at 2 hours who discontinue treatment in the long-term to follow the trajectories of BSC all-comers.
Additional issue 2 The BL_severity coefficient in the QALH regression appears to be applied to the wrong proportion of migraine attacks in the economic analysis	4.2.11.1.4	Yes	Thank you, the BL_severity coefficient in the QALH regression has now been applied to the correct proportion of migraine attacks in the economic analysis, with minimal impact on results.
Additional issue 3: There is an unexplainable discrepancy in the long-term discontinuation rates reported in the CS and provided in response to clarification	4.2.8.1		Please note, this issue was also addressed in the FAC. The title of Table 57 in the TE is incorrect. Please note, this was an error made on the company's part in the response to the clarification questions. *"Table 57. Reasons for discontinuation in study BHV3000-201 used to inform the long-term*

			discontinuation rate in the acute model (subgroup with at least 2 triptan failures)" • This is not the subgroup with at least 2 triptan failures it is taken from those who were in the BHV3000-301, 302, and 303 who enrolled into the BHV300-201 study. • Please note, 9.7% reflects those who discontinue with at least 2 triptan failures. Pfizer proposes to replace the title in Table 57 with the following: *"Table 57. Reasons for discontinuation in study BHV3000-201 used to inform the long-term discontinuation rate in the acute model"*
Additional issue 4: The company should include drug wastage costs	4.2.12.1.5	No	Drug wastage is included in the first cycle, based on the assumption that patients who do not respond to rimegepant would discontinue after the first dose but would incur the cost of a full pack. After this, all patients continuing with rimegepant are those who initially responded. While discontinuation is incorporated throughout the time horizon, it is assumed that patient who respond to rimegepant would finish their current pack prior to discontinuing.

			Given only a proportion of patients experience a migraine each cycle, there would be substantial complexity in estimating exactly how many pills are expected to remain in a pack at time of discontinuation and as such, it is not feasible to incorporate wastage.
Additional issue 5: The control group in Vo et al. 2018 should be used to estimate HCRU and the company should update the MMDs used to calculate the weighted average of the frequency groups to reflect the selected population	4.2.12.1.5	No	Consistent with prior NICE TAs, HCRU is defined as absolute as opposed to migraine-attributable, based on that reported for migraine patients in Vo et al. It is noted that the alignment with MMDs of the patient population and the categories reported by Vo et al. are approximate and require assumption for use within the model. Given that HCRU costs are not a significant model driver, the additional complexity of updating these values based on MMD was not felt to be justified.
Additional issue 6: The company should provide a scenario using HSUVs from Xu et al. 2011	5.1.3		Based on consultation with clinical experts, the HSUVs from Xu et al. were found to lack face validity and therefore were not included in the model; the value reported for the pain-free state exceeds population normative values and is substantially higher than interictal utilities estimated for patients with migraine (e.g., in 201 or 305). As noted at the clarification stage, in section B3.4.3., we consider that Xu et al lacks face validity for modelling the UK population, the utility of 0.4 associated with 'severe pain' is implausibly high, given the EQ-5D score by setting the pain dimension to the highest level, and assuming perfect health on all dimensions would result in a hypothetical maximal utility value of 0.264

			(< 0.4). This conclusion was supported in discussion with UK clinical experts.
Migraine prevention			
Additional issue 7: The distribution of baseline MMD should reflect the marketing authorisation (EM)	4.2.6.2	No	BHV3000-305 baseline MMD distribution includes adults with 4-18 migraine attacks per month reflecting SmPC where it is defined as preventive treatment of episodic migraine in adults who have at least 4 migraine attacks per month.
Additional 8: There is an unexplainable discrepancy in the long-term discontinuation rates reported in the CS and provided in response to clarification	4.2.8.2	No	Please note, this issue was also addressed in the FAC. The discrepancy is due to different approaches being used to estimate the long-term discontinuation rates. • In the CS, the point estimate from the Kaplan-Meier curve was used at Year 1 (23.0%) as opposed to the raw proportion (21.6%), EAG's preferred approach.
Additional 9: The company should provide the baseline EQ-5D from the rimegepant and placebo arms of study BHV3000-305	4.2.11.2.1	No	The baseline EQ-5D from the rimegepant and placebo arms of the study BHV3000-305 are as follows: Treatment N Mean EQ-5D SD EQ-5D Placebo* 346 0.5976 0.1447

			Rimegepant 348 0.6136 0.1432 Note: *1 placebo patient was missing data at baseline.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Acute Model			
Additional issue 2 - The BL_severity coefficient in the QALH regression appears to be applied to the wrong proportion of migraine attacks in the economic analysis	The BL_severity coefficient in the QALH regression was applied to the wrong proportion of migraine attacks in the economic analysis	Thank you, the BL_severity coefficient in the QALH regression has now been applied to the correct proportion of migraine attacks in the economic analysis, with minimal impact on results.	ICER resulting from the change described (on its own): £19,158 Change from the company's original base-case ICER: £18,257 Δ=£901
PSA: Company's base case following technical engagement (or revised base case)	QALYs: 0.43	Costs: £7,397	Revised base-case ICER: £17,359
Deterministic: Company's base case following technical	QALYs: 0.42	Costs: £7,307	Revised base-case ICER: £17,521

<table>
<tr><td>engagement (or revised base case)</td><td></td><td></td><td></td></tr>
<tr><td colspan="4">Prevention model</td></tr>
<tr><td>Key issue 9 – Gradual vs immediate reversion to baseline MMD during the assessment period and after the assessment period</td><td>Pfizer assumed a reversion to baseline MMD during the assessment period to take 12 months and an immediate reversion to baseline MMD after the assessment period.</td><td>Applied a scenario where reversion to baseline during and after the assessment took 12 months.</td><td>ICER resulting from the change described (on its own):
<table><tr><th colspan="3">ICER versus baseline (£/QALY) rimegepant vs mAb</th></tr><tr><th>Ere</th><th>Gal</th><th>Fre</th></tr><tr><td>£84,826</td><td>£109,167</td><td>£102,583</td></tr></table>Change from the company’s original base-case ICER:
<table><tr><th colspan="3">ICER (£/QALY) change from baseline base case ICER, rimegepant vs mAb</th></tr><tr><th>Ere</th><th>Gal</th><th>Fre</th></tr><tr><td>£92,671</td><td>£115,211</td><td>£118,883</td></tr></table></td></tr>
<tr><td>Key issue 11 – Applying the NMA results from cycle 1 vs Cycle 3</td><td>NMA results were implemented in the economic analyses from cycle 3.</td><td>Results from the NMA were implemented in the economic analyses from cycle 1 rather than cycle 3.</td><td>ICER resulting from the change described (on its own):
<table><tr><th colspan="3">ICER versus baseline (£/QALY) rimegepant vs mAb</th></tr><tr><th>Ere</th><th>Gal</th><th>Fre</th></tr><tr><td>£88,399</td><td>£113,736</td><td>£106,883</td></tr></table>Change from the company’s original base-case ICER:
<table><tr><th colspan="3">ICER (£/QALY) change from baseline base case ICER, rimegepant vs mAb</th></tr><tr><th>Ere</th><th>Gal</th><th>Fre</th></tr><tr><td>£92,671</td><td>£115,211</td><td>£118,883</td></tr></table></td></tr>
</table>

<table>
<tr>
<td>Key issue 12 – Comparator treatment acquisition costs</td>
<td>Different acquisition costs in the initial 28-day cycle and subsequent 28-day cycles were applied. For rimegepant, the acquisition cost in the initial 28-day cycle is the same as subsequent 28-day cycles.

The monthly regimen assumed for erenumab (offered every 30.4 days) does not match the regimen included in the BNF and marketing authorisation (offered every 28 days).</td>
<td>Pfizer equated the initial 28-day treatment acquisition cost to the ongoing 28-day treatment acquisition cost for all treatments (except for the loading dose for galcanezumab).

Additionally, Pfizer matched the regimen for erenumab to the regimen reported in the BNF and marketing authorisation.</td>
<td>ICER resulting from the change described (on its own):
<table>
<tr><th colspan="3">ICER versus baseline (£/QALY) rimegepant vs mAb</th></tr>
<tr><th>Ere</th><th>Gal</th><th>Fre</th></tr>
<tr><td>£114,127</td><td>£116,287</td><td>£108,572</td></tr>
</table>
Change from the company's original base-case ICER:
<table>
<tr><th colspan="3">ICER versus baseline (£/QALY) rimegepant vs mAb</th></tr>
<tr><th>Ere</th><th>Gal</th><th>Fre</th></tr>
<tr><td>£92,671</td><td>£115,211</td><td>£118,883</td></tr>
</table>
</td>
</tr>
<tr>
<td>Company's base case following technical engagement (or revised base case)</td>
<td>Incremental QALYs:
<table>
<tr><th colspan="2">Incremental QALYs, rimegepant vs mAb</th></tr>
<tr><td>Ere</td><td>0.039</td></tr>
<tr><td>Gal</td><td>0.056</td></tr>
<tr><td>Fre</td><td>0.055</td></tr>
</table>
</td>
<td>Incremental costs:
<table>
<tr><th colspan="2">Incremental costs, rimegepant vs mAb</th></tr>
<tr><td>Ere</td><td>£4,105</td></tr>
<tr><td>Gal</td><td>£6,020</td></tr>
<tr><td>Fre</td><td>£5,482</td></tr>
</table>
</td>
<td>Revised base-case ICER:
<table>
<tr><th colspan="2">Incremental ICER, rimegepant vs mAb</th></tr>
<tr><td>Ere</td><td>Dominated</td></tr>
<tr><td>Gal</td><td>£390,791</td></tr>
<tr><td>Fre</td><td>£99,802</td></tr>
</table>
</td>
</tr>
</table>

Sensitivity analyses around revised base case
N/A

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	David Kernick
2. Name of organisation	NHS
3. Job title or position	GP with special interest in headache
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.	nil
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)	Reduce bio psych social burden of illness

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)	Not possible to state succinctly – see above aim
10. In your view, is there an unmet need for patients in migraine?	Significant
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?	Well defined pathways. Technology could be an important addition.
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 what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) •	Clinical setting is a key question. No reason clinically why cannot be used in primary care, indeed should be.
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?	If it is more generally available than MABs – yes significantly so.

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
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)	Easy to use although use for acute and chronic will give rise to confusion in prescribers and patients
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Probably useful to check liver function at onset and 3 and 6 months?
17. Do you consider that the use of the technology will 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	Oral formulation and lower side effect profile with confer benefit
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?	Yes

• 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?	Yes Yes – a need for an alternative oral formulation than currently available
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?	minimal
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?	Not exactly – see below Important outcomes measured
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No but interesting there is no data for chronic migraine. Could there have been studies undertaken that were not published?
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
23. How do data on real-world experience compare with the trial data?	?
24. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any	no

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 • 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.*	

Clinical expert statement

Would you expect similar 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?*	Not necessarily. Structural differences can be demonstrated and co-morbidity is much higher No No
Cost-effectiveness results based on the orally dispersible tablet (ODT) formulation trials	
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.*	General recommendation is three attacks. I am also concerned there is no consideration of the addition of a prokinetic (essential) and other formulations of a Triptan (nasal, injection). The Triptan may not work as it is not getting absorbed.

Would you agree in the 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?*	no
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,*	No view here

pain trajectories and baseline MMDs. *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?*	This is given in the literature but can't put my hand on it
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 is reasonable to assume MMD's reduced but this mixed approach really murkies the water.

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)	
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 population. The ERG disagreed.	
Is the rimegepant trial generalisable to the group with at least three prior preventative drug treatment failures?	This is always tricky as invariably, particularly in the UK people are not treated with a high enough dose for a long enough period.
Would you expect people with higher numbers of prior treatment failures to indicate refractory migraines?	A reasonable first approximation
In your opinion, are refractory migraines more difficult to treat with new drug classes?	No. But this may be in part due to the fact that preventers have not been used appropriately.
Uncertainty concerning the efficacy of rimegepant vs mAbs due to a lack of direct evidence and limitations of the network meta-analysis (NMA)	
Gradual vs immediate reversion to baseline MMD during the assessment period and after the assessment period	
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)?*	Not sure without knowing the assumptions which I cannot clearly find
Are there any important issues that have been missed in ERG report?	No

Part 3: Key messages

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

Some major clinical concerns – only 2 Triptan failure, other Triptan formulations not considered, addition of prokinetic.
I would want to know why chronic migraine was excluded
Use of acute and chronic makes it very confusing for the prescriber. If you are taking it preventatively do you use a Triptan for relief or will you be tempted to have an extra Rimagepant? What do you do on the days when you have taken a preventer and need relief?
Could be a very useful addition but key is to have it available to primary care if the burden of migraine is to be addressed. There is already push back from secondary care for the MABs and having this oral drug specialist care only would put major pressure on neurology services. There is no reason why this should not be a primary care drug apart from affordability considertions.
Click or tap here to enter text.

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

Patient expert statement and technical engagement response form

Rimegepant for treating or preventing migraine [ID1539]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The evidence review group (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 you about living with migraine or caring for a patient with migraine. 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).

A patient 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.

Patient expert statement

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

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

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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.

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.

Your response should not be longer than 15 pages.

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.

Patient expert statement

NICE National Institute for Health and Care Excellence

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.

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.

Part 1: Living with this condition or caring for a patient with migraine

Table 1 About you, migraine, current treatments and equality

1. Your name	Andy Bloor
2. Are you (please tick all that apply)	☒ A patient with migraine? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with migraine? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Migraine Trust
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☒ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with migraine? **If you are a carer (for someone with migraine) please share your experience of caring for them**	I have suffered with migraines for around 25 years, the last 10 of them being chronic (on average 3-5 a week). I have been through a range of prophylactic approaches and have for a number of years found a combination of Lamotrigine and Botox effective. Since working with the Migraine Trust as a patient representative, I have heard the accounts of other migraineurs and been able to contrast them with my own experience.
7a. What do you think of the current treatments and care available for migraine on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	a: Botox was a 'game changer' and is efficacious for a number of patients at the chronic end of the condition. There are a number of off-license drugs that can help, but I am not convinced that knowledge around them is widespread. The difficulty with migraine is that it is a very individual condition in terms of triggers and presentation. As a result a 'one size fits all' account is difficult. My most significant difficulty is not the pain but the aura and it is a shame that so much of the treatment is situated around pain. For me the difficulties I experience with sensory distortion (around gross motor control and depth perception) coupled with the psychological impact of feeling emotionally vulnerable means that I often feel the medication available does not fit my symptomology. b: I think the experiences of the wider population will be impacted by the manifestation; if the pain is your main difficulty, then this (as with a medication such as triptans) could have significant impact. If however it is aura like mine then this may not have the same impact.
8. If there are disadvantages for patients of current NHS treatments for migraine (for example, how rimegepant is given or taken, side effects of treatment, and any others) please describe these	None that I am aware of other than clinics to administer being few and far between.

9a. If there are advantages of rimegepant over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does rimegepant help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	This is difficult for me to comment on as the question seems to assume I am on rimegepant, which I am not. The ability to administer clearly at home would be an advantage, as would continued treatment in the community via GPs. I would not advocate that this is initially prescribed in the community though: migraines are very complex and beyond beta-blockers, I remain personally unconvinced that GPs will have the expertise to prescribe this as a front-line medication. An initial diagnosis from a neurologist is necessary, simply because Migraine can be symptomatically similar to other neurological difficulties, including some that are life threatening. One of the first things that happened on my journey to diagnosis was I was given an MRI to rule out other issues, and I was glad of this.
10. If there are disadvantages of rimegepant over current treatments on the NHS please describe these. For example, are there any risks with rimegepant? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Not that I am aware of.
11. Are there any groups of patients who might benefit more from rimegepant or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I think the targeting of non-chronic patients is problematic as detailed below in Part 2.
12. Are there any potential equality issues that should be taken into account when considering migraine and rimegepant? Please explain if you think any groups of people with this condition are particularly disadvantaged	None that I am aware of.

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 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.	
13. Are there any other issues that you would like the committee to consider?	None.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the ERG report are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the ERG report, please let us know in the space provided at the end of this section.

For information: the patient 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, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from ERG report

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.*	The difficulty is that an individual patient can, depending on their current level of migraines, fluctuate between moderate to chronic. How this would be managed I am not sure. It may be better to consider the root difficulties (pain, aura etc.) rather than how episodic it is. In short, someone could start the trial eligible with this criteria and then become 'ineligible' in the middle of it due to an escalation of attacks. I am not sure how these results would then be interpreted.

Patient expert statement

Would you expect similar 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	
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.*	As stated above, this may be problematic as a patient may transition in frequency. In relation to the number of times a medication should be used, I would suggest potentially even longer. For example, I have Botox for migraines. As I get closer to the date I am due for a treatment, my migraines become exceptionally problematic and an acute medication would have a different effect before that date as opposed to slightly afterwards. I would suggest a medication should be used for a period of time rather than number of attacks – for example 3-6 months.

Would you agree in the 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,*	I agree with the ERGs analysis here.

pain trajectories and baseline MMDs. *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?*	

Migraine prevention	
Discrepancy between the population described in the marketing authorisation1 and the decision problem described by the company (at least four migraine attacks per month vs at least four MMDs)	As stated above, the upper figure is of more concern.
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*	

conservative estimate of treatment effect for a refractory 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? a*	
Uncertainty concerning the efficacy of rimegepant vs mAbs due to a lack of direct evidence and limitations of the network meta-analysis (NMA)	
Gradual vs immediate reversion to baseline MMD during the assessment period and after the assessment period	
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)?*	
Are there any important issues that have been missed in ERG report?	Not that I am aware.

Part 3: Key messages

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

- The distinction between chronic and episodic is not as clear cut as is made out and a patient can fluctuate between the two.
- The trial may be better placed to consider symptomatic presentation rather than number of episodes.
- The drug should be applied in tertiary care at least and only used in primary for ongoing repeat medication.
- Click or tap here to enter text.
- Click or tap here to enter text.

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 NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Rimegepant for treating or preventing migraine [ID1539]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The evidence review group (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 you about living with migraine or caring for a patient with migraine. 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).

A patient 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.

Patient expert statement

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

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

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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.

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.

Your response should not be longer than 15 pages.

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.

Patient expert statement

NICE National Institute for Health and Care Excellence

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.

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.

Part 1: Living with this condition or caring for a patient with migraine

Table 1 About you, migraine, current treatments and equality

1. Your name	Deborah Sloan
2. Are you (please tick all that apply)	☒ A patient with migraine? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with migraine? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	The Migraine Trust
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with migraine? **If you are a carer (for someone with migraine) please share your experience of caring for them**	I have lived with migraine most of my life. As I child I would experience the neurological symptoms only (aura, Alice in Wonderland Syndrome). The head pain started when I was 17. They gradually changed from episodic (related to menstrual cycle) to chronic from ages 30 to present (58). Over the course of my migraine condition I have tried most available treatments – the list is extensive: anti-depressants, Propranalol, anti-epilepsy drugs, all types of pain killers, Triptans (all brands/types), neuropathic drugs, most holistic treatments, Cefaly, Tens machine, magnetic treatment. Every treatment has been ineffective or (especially in the case of Triptans) caused severe and unbearable rebound headaches. Untreated, my attacks last for 3 days – most of that time in severe/unbearable pain. On occasion the pain has been so bad, I have thumped my head with my fists or hit my head against the wall. I have been hospitalised several times, having collapsed through dehydration and probably the strain of such intense pain. Twice, my migraine attack has been so bad I lost the ability to speak and I was rushed to hospital with a suspected brain haemorrhage. My migraines have affected my life and that of my family and friends profoundly. I had to give up my counselling career – something I worked incredibly hard to achieve and I was very proud to have established a busy practice that was helping people who needed emotional support. I have missed countless social and family occasions and live constantly with the fear of 'letting someone down'.

	I have spent a fortune on possible treatments and consultations with both main stream and alternative practitioners. Finally, in 2019 I became suicidal. I couldn't see a time when I wouldn't live with the migraine version of the Sword of Damocles hanging over me. In 2020 I read about Rimegepant and went out to New York for a consultation and to buy the medication. I have now returned to work and I'm the happiest I have been in decades.
7a. What do you think of the current treatments and care available for migraine on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	**7a. As described above, none of the current treatments are suitable for me. They are either ineffective or produce dreadful rebound headaches.** **There seems to be a huge 'hole' in the knowledge base of medical practioners regarding migraines. In addition there seems to be no protocol when it comes to treating someone who has been experiencing a prolonged attack.** **I have been treated with varying degrees of expertise and compassion. Often I've been dismissed as over-reacting. I've been misdiagnosed and given medication that is totally unsuitable.** **7b. My story seems to match that of many of the people I've met with chronic migraine.**
8. If there are disadvantages for patients of current NHS treatments for migraine (for example, how rimegepant is given or taken, side effects of treatment, and any others) please describe these	Current treatments - most current treatments are known to have side-effects and produce adverse reactions or worsening of headaches/migraines. For instance, Triptans cause dreadful rebound headaches. Any type of pain killer taken for too long can give MOH syndrome. Unfortunately, many people who have migraine are hyper-sensitive to normal medications such as NSAIDS. This is often not know about when we seek urgent medical attention. Anti-epilepsy drugs cause cognitive problems. I had paradoxical reactions to many drugs including anti-depressants – which made me feel depressed.

	I've been taking Rimegepant since 2021 and I get no side effects and do not experience MOH syndrome or rebound headaches.
9a. If there are advantages of rimegepant over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does rimegepant help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	**9a. As above, Rimegepant does not cause any cognitive issues, MOH or rebound headaches. The only side-effect is mild tiredness for a few hours.** **Without Rimegepant I would not be able to have returned to work, would not be able to care for my nieces when needed and would have missed many family and social events. Above all, having Rimegepant has meant that my husband no longer has to care for me for 3 days, cancelling work or social engagements. In addition, the emotional strain on him has been removed. Rimegepant has also given me back my mental health – I was on the verge of a mental breakdown before receiving it.** **9b. Recovering my mental health. Without that I would have nothing and the pressure on my husband, wider family and friends would be excessive.**
10. If there are disadvantages of rimegepant over current treatments on the NHS please describe these. For example, are there any risks with rimegepant? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I haven't heard of any potential side-effects that concern me. Of course, as with any medication one worries in case there is a side effect not discovered or yet experienced. But for the moment I have no concerns.
11. Are there any groups of patients who might benefit more from rimegepant or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	The only disadvantage I can think of is if someone has dexterity problems, getting the dissolvable tablet out of the casing might be tricky. I don't' see it having any greater or lesser problems than any other drug for someone with cognitive impairment. In a way it's easier – one tablet on the tongue and no need for water. Being a dissolvable tablet means that anyone with a sensitive stomach will still be able to absorb the drug.
12. Are there any potential equality issues that should be taken into account when considering migraine and rimegepant? Please explain if you think any groups of	I can't think of any potential issues – apart from pregnancy, which is an issue with many drugs.

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 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.	
13. Are there any other issues that you would like the committee to consider?	Rimegepant is one of the first anti-CGRP class of drugs developed for acute as well as preventative use. For me, being able to use it acutely feels more comfortable than permanently suppressing CGRP peptides.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the ERG report are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the ERG report, please let us know in the space provided at the end of this section.

For information: the patient 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, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from ERG report

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.*	I don't have the medical knowledge to be able to answer this question.

Patient expert statement

Would you expect similar 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	
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.*	In my own experience, Rimegepant is the only medication that has worked first time and subsequently. I couldn't extrapolate from my own experience to others'.

Would you agree in the 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?*	I would agree that trying the drug for two or three episodes seems a fair way of assessing its efficacy in an individual. No
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,*	Not qualified to answer this question.

pain trajectories and baseline MMDs. *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?*	Not qualified to answer this question.

Patient expert statement

Migraine prevention	
Discrepancy between the population described in the marketing authorisation1 and the decision problem described by the company (at least four migraine attacks per month vs at least four MMDs)	
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*	

conservative estimate of treatment effect for a refractory 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? a*	
Uncertainty concerning the efficacy of rimegepant vs mAbs due to a lack of direct evidence and limitations of the network meta-analysis (NMA)	
Gradual vs immediate reversion to baseline MMD during the assessment period and after the assessment period	
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)?*	
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:

- Prior to taking Rimegepant my migraines were intractable, chronic, life-limiting.
- Rimegepant has enabled me to return to work and to make social, family plans without fear of missing them.
- Many current treatments provided by the NHS are not suitable for many people living with chronic migraine.
- Without appropriate protocols, treatments and knowledge base for migraine conditions, an effective, acute treatment is invaluable in enabling people living with migraine to avoid having to visit A&E or call out emergency doctors.
- Rimegepant has given me back my life and allowed me to contribute to society and the economy.

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 NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Rimegepant for treating or preventing migraine [ID1539]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' 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

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.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response 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.

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.

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.

About you

Table 1 About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Association of British Neurologists advisory group on headache and pain
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**none**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Acute Migraine		
Exclusion of chronic migraine (CM) patients from acute randomised controlled trials (RCTs) and extrapolating evidence from episodic migraine (EM) patients	No	Chronic migraine is generally considered more refractory to acute and preventive treatment than episodic migraine and within that cohort many patients may also have medication overuse headache, therefore extrapolating evidence for treatment from episodic to chronic headache may overestimate the therapeutic benefit
Cost-effectiveness results based on the orally dispersible tablet (ODT) formulation trials	No	Cost effectiveness results should be based on the formulation use in the trials: ODT may be more expensive but may also have greater efficacy
Using response to the first migraine attack to inform response to subsequent migraine attacks	No	Response to treatment may vary considerably between attacks, placebo effect may vary considerably
Baseline distribution of monthly migraine days (MMDs)	No	Distribution of MMDs is a key factor in data analysis: as stated above, those with Chronic Migraine may respond differently to those with episodic migraine
Assuming rimegepant p*ro re nata* (PRN) can result in reductions in MMDs	No	This assumption is not based on robust long term data and is uncertain

Migraine prevention		
Discrepancy between the population described in the marketing authorisation1 and the decision problem described by the company (at least four migraine attacks per month vs at least four MMDs)	No	Recommend that the number of migraine *days* per month, rather than number of migraine *attacks* per month, is used in the analysis as this reflects the burden of migraine for the patient better and keeps the guidance in line with other NICE appraisals for migraine treatments (e.g. mABs and botulinum toxin)
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)	No	Patients who have at least 3 prior treatment failure may represent a more difficult cohort to treat but extrapolating from the comparator mAb trials in refractory population is unlikely to provide accurate data (not least the variation in placebo response with variation in method of administration). The magnitude of this effect is uncertain but is likely to increase, rather than decrease, ICER
Uncertainty concerning the efficacy of rimegepant vs mAbs due to a lack of direct evidence and limitations of the network meta-analysis (NMA)	No	Agreed that there is considerable uncertainty about comparison of efficacy measures between rimegepant and mABs – direct comparisons between trials cannot be made due to variability in study design and variation in placebo response
Gradual vs immediate reversion to baseline MMD during the assessment period and after the assessment period	No	Time period of reversion to baseline after discontinuation of treatment is uncertain, but gradual (up to 12 months) is more plausible than immediate reversion to baseline after discontinuing treatment
Response probability for rimegepant	No	Agree that response probability based on the “average over 12-weeks” in patients with mild-to-severe migraine attacks should be used, rather than response at 12 weeks. 12 week average response is in keeping with analysis of mAb treatment. However, many other preventive treatments for migraine (e.g. betablockers, topiramate) may take 6-8 weeks to show response
Applying the NMA results from Cycle 1 vs Cycle 3	No	Although rimegepant effectiveness may be seen within the first few weeks of treatment, there may be some incremental improvement tin response between

		Cycle 1- 3, over 12 weeks, and so applying results from cycle 1 to cycle 3 may not be accurate
Comparator treatment acquisition costs	Yes/No	Agreed that costing of erenumab should be based on 28 day treatment cycle. There is no justification for different costing of mAbs in different cycles

NICE National Institute for Health and Care Excellence

Technical engagement response form

Rimegepant for treating or preventing migraine [ID1539]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' 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

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.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response 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.

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.

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

About you

Table 1 About you

Your name	[redacted]
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
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Acute Migraine		
Exclusion of chronic migraine (CM) patients from acute randomised controlled trials (RCTs) and extrapolating evidence from episodic migraine (EM) patients	No	The trial included patients between 4-18 days of headache per month. Hence some patients with chronic migraine were in the study (those with 15-18 days per month). However including all patients with Chronic Migraine will have those with 19-30 days per month which were not part of the study. Hence evidence from episodic migraines were used. Chronic Migraine is generally considered refractory to acute treatment than episodic variety. Around 60-80% patients with chronic migraine have medication overuse issue and are not a good substrate to evaluate efficacy in acute randomised trials.
Cost-effectiveness results based on the orally dispersible tablet (ODT) formulation trials	No	If the trials were conducted on the orally dispersible formulation than it is reasonable to perform cost-effectiveness on the same formulations.
Using response to the first migraine attack to inform response to subsequent migraine attacks	No	Response to treatment varies from one attack to another. In practice a lack of response to treatment in three attacks means the treatment is ineffective. However, a good response to first treatment means subsequent attacks will respond to treatment, although this is based on physician's clinical experience rather than evidence based.

Baseline distribution of monthly migraine days (MMDs)	No	Monthly Migraine Days is the key parameter in any data analysis for both acute and preventive treatments.
Assuming rimegepant p*ro re nata* (PRN) can result in reductions in MMDs	No	The data has shown that use of Rimegepant every other day reduced the total number of mean monthly migraine days. It is, therefore, reasonable to assume that if one uses frequent Rimegepant for acute treatment it will have some preventive effect and will reduce the monthly migraine days, although this is not based on a robust long term data.
Migraine prevention		
Discrepancy between the population described in the marketing authorisation1 and the decision problem described by the company (at least four migraine attacks per month vs at least four MMDs)	No	Migraine attacks may go on for longer than a day and hence reduction in the number of migraine attacks should not be used. A reduction in monthly migraine days is along the lines taken by NICE in other appraisals for CGRP MAB and Botox.
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)	No	Rimegepant trials excluded patients with failure of two or more preventive treatments and hence the results from this trial cannot be applied to those with failure of three prior treatments.
Uncertainty concerning the efficacy of rimegepant vs mAbs due to a lack of direct evidence and limitations of the network meta-analysis (NMA)	No	There is no direct trial between Rimegepant and CGRP mAbs hence the efficacy of the two cannot be compared due to variability in study design and variation in placebo response.
Gradual vs immediate reversion to baseline MMD during the assessment period and after the assessment period	No	A gradual reduction in MMD is more plausible than immediate reduction

Response probability for rimegepant	No	The response to Rimegepant over a period of 12 weeks should be used rather than assessment at 12 weeks
Applying the NMA results from Cycle 1 vs Cycle 3	No	Rimegepant may work immediately although there may be incremental response with time and hence applying results from cycle 1 to cycle 3 may not be accurate.
Comparator treatment acquisition costs	No	Agreed that costing of erenumab or any mAbs should be based on 28 day treatment cycle.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Rimegepant for treating or preventing migraine [ID1539]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' 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

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.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response 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.

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.

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.

About you

Table 1 About you

Your name	
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**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Acute Migraine		
Exclusion of chronic migraine (CM) patients from acute randomised controlled trials (RCTs) and extrapolating evidence from episodic migraine (EM) patients	Yes/**No**	Please provide your response to this key issue, including any new evidence, data or analyses. ***We feel it is possible to extrapolate evidence to the chronic migraine population, particularly in those who experience migraine on >=4 days per month.*** ***People with Chronic Migraine will typically experience a greater negative impact but those with Episodic Migraine, also experience attacks that have similar features, severity and impact.*** ***Some comments from our CGRP mAbs 2022 patient experience survey (with EM and CM), demonstrate the impact of migraine attacks and the benefit of an effective treatment:*** " it has reduced the number of days dramatically that I need to go to bed, and reduced the uncertainty of having to cancel social events with the result that my mood is much better."

		"Head feels clearer. More able to tackle major jobs." "Fewer severe headaches". "Migraines are less intense so I may recover from the pain phase with a few hours rather than a few days".
Cost-effectiveness results based on the orally dispersible tablet (ODT) formulation trials	Yes/**No**	Please provide your response to this key issue, including any new evidence, data or analyses ***We do not have cost information for the treatment. However, we are keen for people with migraine to have a treatment that allows them to return to normal function and activities including work, education and social activities and this should be considered in cost calculations***.
Using response to the first migraine attack to inform response to subsequent migraine attacks	Yes/**No**	Please provide your response to this key issue, including any new evidence, data or analyses ***People with migraine want a treatment that is reliable and effective and will have greater confidence in a treatment that demonstrates effectiveness for more than 1 attack.***
Baseline distribution of monthly migraine days (MMDs)	Yes/**No**	Please provide your response to this key issue, including any new evidence, data or analyses **MMD*s are a preferred measure to assess the impact of migraine on patients' lives and function and is a useful measure of treatment impact.***

Assuming rimegepant p*ro re nata* (PRN) can result in reductions in MMDs	Yes/**No**	Please provide your response to this key issue, including any new evidence, data or analyses ***While we do not have evidence of use of this medicine in the UK from people who contact us, we feel that if the treatment can be safely used PRN, potential greater benefit may be derived, as the likelihood of side effects from using different types of treatments, is minimised.***
Migraine prevention		
Discrepancy between the population described in the marketing authorisation1 and the decision problem described by the company (at least four migraine attacks per month vs at least four MMDs)	Yes/**No**	Please provide your response to this key issue, including any new evidence, data or analyses ***In practice, due to the variation in migraine attack duration, MMDs offer a more meaningful measure of the migraine impact.***
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)	Yes/**No**	Please provide your response to this key issue, including any new evidence, data or analyses ***We do not have evidence to comment on the generalisability of the trial.***
Uncertainty concerning the efficacy of rimegepant vs mAbs due to a lack of direct evidence and limitations of the network meta-analysis (NMA)	Yes/**No**	Please provide your response to this key issue, including any new evidence, data or analyses ***We do not have new evidence to add.***
Gradual vs immediate reversion to baseline MMD during the assessment period and after the assessment period	Yes/**No**	Please provide your response to this key issue, including any new evidence, data or analyses ***We do not have new evidence to comment.***

Response probability for rimegepant	Yes/**No**	Please provide your response to this key issue, including any new evidence, data or analyses ***Patients/public who contact us, have not yet used this treatment and we therefore cannot speculate about the response probability.***
Applying the NMA results from Cycle 1 vs Cycle 3	Yes/**No**	Please provide your response to this key issue, including any new evidence, data or analyses
Comparator treatment acquisition costs	Yes/**No**	Please provide your response to this key issue, including any new evidence, data or analyses

NICE National Institute for Health and Care Excellence

Technical engagement response form

Rimegepant for treating or preventing migraine [ID1539]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' 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

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.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response 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.

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.

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.

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Novartis Pharmaceuticals UK Limited
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Since April 2005, Novartis has exclusively licensed glycopyrronium bromide and certain intellectual property relating to its use and formulation from Vectura and its co-development partner, Sosei Heptares. The following inhaled medications are comprised of, or contain, glycopyrronium bromide: • Seebri® Breezhaler® (glycopyrronium bromide), used as a maintenance treatment for Chronic Obstructive Pulmonary Disease (COPD) • Ultibro® Breezhaler® (indacaterol/glycopyrronium bromide), used as a maintenance treatment for COPD • Enerzair® Breezhaler® (indacaterol/glycopyrronium bromide/mometasone furoate), used as a maintenance treatment for asthma uncontrolled with long-acting beta-agonist (LABA)/inhaled corticosteroid (ICS). Phillip Morris International (a tobacco company) has acquired Vectura Group Limited (formerly Vectura Group plc).

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Acute Migraine		
Exclusion of chronic migraine (CM) patients from acute randomised controlled trials (RCTs) and extrapolating evidence from episodic migraine (EM) patients	No	No comment
Cost-effectiveness results based on the orally dispersible tablet (ODT) formulation trials	No	No comment
Using response to the first migraine attack to inform response to subsequent migraine attacks	No	No comment
Baseline distribution of monthly migraine days (MMDs)	No	No comment
Assuming rimegepant p*ro re nata* (PRN) can result in reductions in MMDs	No	No comment

Migraine prevention		
Discrepancy between the population described in the marketing authorisation1 and the decision problem described by the company (at least four migraine attacks per month vs at least four MMDs)	No	Novartis agrees with the External Assessment Group (EAG) that a migraine attack can last for >24 hours and that "at least four migraine *attacks* per month" and "at least four migraine *days* per month" describe populations that are overlapping but not the same. More specifically, the population with "at least four migraine *days* per month" specified by the company in their decision problem may be broader than the population defined by "at least four migraine *attacks* per month" specified in the marketing authorisation for rimegepant. Novartis agrees with the EAG request for clarification on this point. If the NICE recommendation wording were based on "at least four migraine *days* per month" this would constitute a recommendation for use of rimegepant outside of the licensed population.
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)	No	As noted by the EAG in their report, and acknowledged by the company in their submission, the rimegepant BHV3000-305 trial did not provide data for the subgroup of patients for whom three or more prior preventive drug treatments have failed, as the trial excluded patients with non-response to more than two classes of preventive medicines. Therefore, the submitting company have not presented clinical trial data to support the positioning they are pursuing. In contrast, the NICE recommendations for all three of the monoclonal antibodies (erenumab, fremanezumab, galcanezumab) as preventive migraine treatment in patients for whom at least three preventive drug treatments have failed were based on an assessment of clinical and cost effectiveness in this subgroup of patients. The clinical trial subgroup analyses provided as part of the appraisals of the three monoclonal antibodies were not without limitations with regards to their post-hoc nature and/or limited sample size. Nevertheless, the decisions of the NICE Committee in all three appraisals were informed by clinical trial subgroup data that corresponded to the specific population of interest for the decision problem. In contrast, whilst the rimegepant manufacturer is seeking the same positioning as the monoclonal antibodies with regards to the

		requirement for three prior preventive treatment failures, the rimegepant clinical trials do not provide data in this population.
Uncertainty concerning the efficacy of rimegepant vs mAbs due to a lack of direct evidence and limitations of the network meta-analysis (NMA)	No	Novartis agrees that the lack of direct evidence and the limitations of the network meta-analysis (NMA) create uncertainty in the relative effectiveness comparison of rimegepant and the monoclonal antibodies. We also agree with the EAG's preference for the random effects model. Although baseline risk has been adjusted for by the submitting company, and efforts have been made to remove differences in outcome measures across trials, important sources of heterogeneity between the studies included in the NMA remain (not least the important differences in prior treatment history of the recruited populations) and therefore a random effects NMA is more appropriate. Finally, it should be noted that the erenumab, fremanezumab and galcanezumab appraisals all presented NMAs based on data for the subgroup of patients with ≥3 prior treatment failures, i.e. for the population that aligned to that of the decision problem. In contrast, because of the lack of data for rimegepant in this population, the submitting company has conducted an NMA based on only the full trial populations of included studies. There is therefore an inconsistency with other migraine appraisals in terms of the indirect evidence of comparative efficacy that is available to the NICE Committee to inform their decision-making, due to the lack of rimegepant data in the relevant subgroup.
Gradual vs immediate reversion to baseline MMD during the assessment period and after the assessment period	No	Novartis shares the EAG concerns regarding the inconsistent approach applied in the submitting company's model for the timeframe over which monthly migraine days (MMDs) revert to baseline for patients who are non-responders at the end of the assessment period compared to those who initially respond but then discontinue active treatment. As outlined in Table 41 of the EAG report provided for this Technical Engagement, in previous migraine prevention appraisals the Committee-preferred approaches at final Appraisal Committee Meeting have maintained consistency in the handling of

		these two groups, either both reverting to baseline MMDs immediately or both returning to baseline MMDs gradually over the course of 12 months. We consider that for consistency with prior appraisals, the rimegepant appraisal should treat the two groups of patients in the same manner with regards to the timeframe over which MMDs revert to baseline.
Response probability for rimegepant	No	Novartis agrees with the EAG that the absolute probability of response to which the odds ratios from the NMA are applied in the cost-effectiveness model should be the absolute response probability that aligns to the definition used for the NMA (i.e. the average response probability over 12 weeks). The odds ratios derived from the NMA represent the relative treatment effect of rimegepant versus other comparators as an average over 12 weeks, and therefore it is logically appropriate to apply this relative effect to a baseline absolute probability that represents the same.
Applying the NMA results from Cycle 1 vs Cycle 3	No	No comment
Comparator treatment acquisition costs	No	As noted by the EAG, the submitting company have erroneously modelled erenumab as being administered monthly, rather than every 4 weeks as specified in the summary of product characteristics (SmPC) for erenumab. In the submitting company's model this leads to a modelled ongoing treatment cost for erenumab of £355.50 per 4-week (28-day) model cycle, calculated by multiplying the pack price for erenumab (£386.50) by '28/(365.25/12)'. As the correct erenumab dosing frequency is consistent with the 4-week cycle length of the submitting company's model, there is no need to adjust the per cycle "ongoing" cost of erenumab to reflect a monthly dosing frequency; the ongoing per-cycle (4-weekly) cost of erenumab should simply reflect the cost of one erenumab 140 mg dose, which is £386.50 at list price. Furthermore, we note that the submitting company's model refers to an erenumab dose of 70 mg. However, the NICE-recommended dose of erenumab is the 140 mg dose and not the 70 mg dose, and therefore **all references to erenumab as a comparator should relate to the 140 mg**

		dose. Given the mislabelling in the submitting company's model, we politely request that the EAG check that in their analyses incorporating the comparator patient access schemes (PAS) they are applying the PAS that is in place for **erenumab 140 mg**.

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue		
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue		

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)

Sensitivity analyses around revised base case

NICE National Institute for Health and Care Excellence

Technical engagement response form

Rimegepant for treating or preventing migraine [ID1539]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' 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

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.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response 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.

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.

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.

About you

Table 1 About you

Your name	[redacted]
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

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Acute Migraine		
Exclusion of chronic migraine (CM) patients from acute randomised controlled trials (RCTs) and extrapolating evidence from episodic migraine (EM) patients	No	Teva believes that the exclusion of patients with CM from the RCTs investigating the acute use of rimegepant leads to a high level of uncertainty about the efficacy of this treatment within this patient population. Based on what was presented within this appraisal, there is no reliable evidence currently available to demonstrate the size of any treatment effect for rimegepant within the CM patient population. This is further demonstrated by the fact that studies show that there are substantial differences in burden between EM and CM. People with chronic migraine experience greater headache-related disability, headache impact, reduced health-related quality of life, greater healthcare costs and higher rates of comorbid medical and psychiatric conditions (Burch RC *et al*. *Neurol Clin* 2019; 37: 631-649; Hjalte F *et al*. *J Headache Pain* 2019; 20: 65). Given these stark differences between the EM and CM populations, the size of the treatment effect for rimegepant in CM patients can be seen to be associated with high levels of uncertainty. The EAG's suggestion for a comparison of the efficacy of acute treatments in CM and EM would provide some indirect evidence relevant to this issue. However, this indirect evidence would still leave the size of any effect for rimegepant in CM patients highly

		uncertain due to this evidence being from different acute treatments with distinct mechanisms of action to that of rimegepant. Further limitations in the RCT data include the generalisability of the efficacy results to the proposed UK patient population (after two triptan failures). The majority of patients within the trials had not failed two triptans (only 8.5% of rimegepant patients and 10.1% of placebo patients had failed >2 triptans). Indeed, the more specific patient population group (>2 triptan failure patients) leads to a limited group size that increases the uncertainty of any analyses based on this *post hoc* group. A further limitation that potentially impacts the generalisability of these data is the fact that evidence is available only from RCTs conducted in the USA. The differences in migraine management and healthcare systems mean that the lack of any data on European patients adds further uncertainty into the applicability of these results, and brings into question relevance of the studied patient population to the UK migraine patient population under consideration. Finally, as already noted, the acute RCTs for rimegepant were conducted using only patients with EM; however, the characteristics of these patients and how representative they are of the full range of patients with EM is unclear. Considering the pooled trial data, these patients are stated to have a mean of [redacted] migraine attacks *per* month (p255 of TE papers), combining this with the breakdown of length of migraine attack (p355 of TE papers) gives an estimate of around [redacted] migraine days *per* month. However, only limited details of the spread within these data are presented (no median or range data are presented), and so it is not possible to judge the range of patients included. Teva notes that the HALO EM population had a [redacted] baseline mean MMDs, which raises a question as to how well the rimegepant clinical trials captured patients [redacted]. This raises further questions as to the generalisability of these data to a more general migraine population as would be expected in UK practice. Overall, Teva believes that additional information and evidence are required to address these key areas of uncertainty and their impacts in the acute cost-effectiveness analysis. There is the potential that additional evidence which may help address some of these issues will be available from planned clinical trials (*e.g.* NCT05509400 in Q3 2024).

Cost-effectiveness results based on the orally dispersible tablet (ODT) formulation trials	No	Teva believes that the cost-effectiveness results should be based on the most appropriate and relevant data for UK clinical practice, and in line with the licence for the product. The ODT formulation is the only licensed formulation in the UK. From the information available in the Technical Engagement documents, it would appear that the counterintuitive changes to the ICER noted by the EAG are related to the pain trajectories and BSC responses. Given the information available within the consultation documents, Teva cannot comment in more detail on this, but the analyses conducted would appear to indicate the importance of the pain trajectories and BSC response in the economic modelling. Teva therefore feels that the source of these inputs (and their validity and generalisability) should be carefully considered within this appraisal.
Using response to the first migraine attack to inform response to subsequent migraine attacks	No	This assumption leads to a high degree of uncertainty in the economic modelling as there are currently no data to confirm the response to rimegepant beyond a single dose for acute treatment. Whilst assumptions around the long-term effectiveness are always a challenge during NICE appraisals for new technologies, this is particularly questionable in this case as the results of a single administration of treatment are being used to drive efficacy results over a 20-year horizon. It is clear that this assumption must be associated with a very high degree of uncertainty. Furthermore, it is clearly recognised that clinical observation of migraine patients demonstrates the variability of how this disease manifests not only across different patients, but more importantly within the same individual. What this suggests is that there is heterogeneity across attacks within the same patient (Nappi G *et al*. *Conf Cephalal et Neurol* 2017; 27: 91-97). Given this, using data from treatment of a single attack raises high uncertainty when informing response to subsequent attacks. In analysing this issue, the EAG has considered the case where patients do not respond to an initial dose but do respond to a second or third dose. Teva notes that the inverse is also possible, with a patient showing an initial response (either to one dose or to multiple doses) which then dissipates. Although this effect may be accounted for, to some extent, by the long-term discontinuation rate applied within the modelling (if it is assumed that these patients discontinue treatment), it is not certain that this would fully account for the potential of this effect. This is especially true as this

		treatment is positioned as a last-line treatment, meaning that patients may be less likely to discontinue (even if efficacy is reduced) as they would have no further treatment options available to them. This would lead to patients remaining on treatment with reduced efficacy to that assumed within the modelling. The uncertainty in this area could, therefore, cause a significant impact on the ICER (in either direction).
Baseline distribution of monthly migraine days (MMDs)	No	Teva believes that this is a challenging issue with no ideal solution. The normal practice within economic modelling would be to use the clinical trial characteristics to ensure consistency between the data sources (as mentioned by the EAG). However, this leads to a significant divergence from the UK patient population proposed by the company (which is primarily caused by Issue 1 above, the exclusion of patients with CM from the RCTs). Conversely, using baseline utilities is more in line with the proposed UK patient population, but leads to questions about the consistency in data sources and their applicability to the modelled patient population. This would be especially true for the treatment response and pain trajectories, which were collected in a different patient population within the RCT (no patients with CM were included). These questions are particularly relevant when there is a lack of data for rimegepant on the response to acute treatment for patients with CM. The EAG's preferred approach is to use 'acute pooled' data to ensure consistency between the data sources and thus maximise the reliability of this economic analysis. Teva agrees that this appears to be the most reasonable assumption to make in this area. However, this set of assumptions would limit the applicability of this economic modelling to patients with CM, and lead to a very high degree of uncertainty in the cost-effectiveness for this patient population.
Assuming rimegepant *pro re nata* (PRN) can result in reductions in MMDs	No	Teva believes that the assumption of an overall reduction in MMDs with PRN dosing of rimegepant cannot be justified given the currently available evidence. The evidence presented is based on exploratory efficacy analyses of data from an open-label, uncontrolled trial. In addition, only minimal data and details are provided on these data within the company submission (CS), making any meaningful review of these data challenging. Overall, Teva does not feel that the data presented are compelling enough for this effect to be included within the economic modelling.

		Furthermore, Teva has some concerns with the analyses conducted to demonstrate these effects and their applicability to higher MMD/migraine attack health states. As mentioned by the company within their submissions, rimegepant has no restrictions on MMDs or migraine attacks within its licensed indication. However, the data presented to justify this effect come from Study BHV3000-201. In this study, there were two PRN dosing groups, a group with 2-8 migraine attacks *per* month and a group with 9-14 migraine attacks *per* month (the third group in this trial utilised a combined EOD + PRN dosing schedule). Therefore, the groups included in this analysis do not cover the full range of migraine patients in clinical practice and excludes the most severely affected patients. The analysis presented relies on a regression analysis, which is utilised to extend the results from the studied group across all patients. This adds further uncertainty to this analysis in the most severely affected patient group, where the evidence is based only upon an extrapolation of an effect seen in an open-label, uncontrolled study of less severely affected patients. This again feeds back to Issue 1 and highlights how the exclusion of patients with CM from RCTs, and severely affected patients from Study BHV3000-201, applies limitations to many analyses conducted across this appraisal.
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)	No	Teva notes that the guide for Technology Appraisals limits appraisals to be within the Marketing Authorisation of a product ("unless the Department of Health and Social Care specifically indicates otherwise"). Therefore, as the licensed indication of rimegepant is for use in "preventive treatment of episodic migraine in adults who have at least 4 migraine attacks *per* month", this is where the appraisal must be conducted. Teva agrees with the EAG's assessment that migraine days and migraine attacks are not interchangeable concepts. Migraine attacks can last longer than 24 hours, and up to 72 hours (https://www.nhs.uk/conditions/migraine/symptoms/; ICHD-3 – *Cephalagia* 2018; 38: 1-211); whereas a migraine day is any day where migraine symptoms are present. Therefore, there is a difference in disease burden and disability associated with a migraine attack and a migraine day, with a migraine attack having a substantially greater impact on a patient. In addition, Teva notes that the RCT used to inform the preventive side of this appraisal (Study BHV3000-305) included patients with 4 to 18

		migraine attacks of moderate to severe intensity *per* month and not patients with four or more migraine days *per* month. Given all of these facts, Teva believes the decision problem can only include a population of at least four migraine attacks *per* month. Teva also notes that the difference between migraine days and migraine attacks must be clearly observed throughout this appraisal.
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)	No	Teva believes that there are serious questions as to the generalisability of the RCT results to the population of interest. The primary concern is that the trial excluded patients within this group (through exclusion of patients with >2 previous preventive failures). This means there is no direct evidence available for rimegepant in the key population of interest, which contrasts with previous appraisals of migraine preventive therapies, where additional trials have been conducted to investigate efficacy in this patient population (*e.g.* FOCUS, LIBERTY and CONQUER). It is clearly recognised that migraine patients who have failed multiple previous preventive therapies tend to have higher burden of headache- and migraine-related disability, are more likely to experience disease worsening, compared with those that have not failed multiple previous therapies; this is potentially as a consequence of longer periods of exposure to pain (Lipton RB *et al*. *Neurology* 2015; 84: 688-695; Bigal ME *et al*. *Headache* 2008; 48: 1157-1168). Therefore, there are high levels of uncertainty as to whether the effects of rimegepant treatment from the RCT for rimegepant can be generalised to the at least 3 failure population due to clear clinical differences between these populations. Moving beyond this issue, there are also a number of additional factors that limit the generalisability of the RCT to the population of interest, which are: the inclusion of CM patients (*versus* a target population of EM only), the use of a tablet formulation (rather than the licensed ODT formulation) and the fact that the RCT was carried out in the USA with no European patients (differences in migraine management and healthcare systems). Altogether, these limitations of the available data raise serious questions as to its generalisability. Crucially, the company has not been able to submit any direct data to demonstrate efficacy within the population proposed for this appraisal. Furthermore, as noted by the EAG and clinical experts, patients with multiple prior treatment failures are considered to be a difficult-to-treat population (page 58 EAG report). The multiple failure

		population group has noticeable differences in patient characteristics (as can be seen within Table 32, p106 of the CS). The three trials focussed on the difficult-to-treat patient group (FOCUS, LIBERTY and CONQUER) can be seen to have older average patients who have had migraine for a longer time. This demonstrates that there is a distinction in this patient group and underlines the necessity for RCT data within the difficult-to-treat patient group (as has been gathered for fremanezumab, erenumab and galcanezumab, and Teva notes is planned for rimegepant in trial NCT05518123 [due for completion in Q3 2024]). Without such available data, it is very challenging to have any confidence in the generalisability of RCT evidence available for rimegepant in this distinct patient group.
Uncertainty concerning the efficacy of rimegepant vs mAbs due to a lack of direct evidence and limitations of the network meta-analysis (NMA)	Yes	Teva acknowledges that many of the issues associated with the NMA stem from a lack of direct comparative evidence and the heterogeneity between studies (influenced by placebo type, placebo response, endpoint definitions, patient populations [including disease state EM/CM, and number of previous failures]). Combined, these factors mean that the results have a very high degree of uncertainty. Teva notes that whilst many of these factors are beyond the control of the company, the data included for rimegepant increases the uncertainty in the analysis as no data in patients with prior treatment failure are included, and some CM patients are included. The fact that the RCT for rimegepant excluded the most relevant patient population also limits the NMA and its applicability to this appraisal, as mentioned in the Key Issue response above. The differences between placebos in the RCTs adds a high degree of heterogeneity into the NMA. Furthermore, the differences in placebo type and administration route raise questions about the validity of the comparison through placebo (which is in fact many different placebos) that is undertaken in this NMA. At best, this issue can be seen to lead to a high degree of uncertainty within the NMA results. Whilst the company has standardised the endpoint definitions used to some extent (in terms of timepoint of the analysis), important differences still remain. The definition of what constitutes a migraine day has not been consistent across clinical trials and important differences can be seen in this definition. For example, Study BHV3000-305 (rimegepant) uses a definition that requires a migraine to last ≥30 minutes; whereas FOCUS (fremanezumab) used a definition that required migraine lasting ≥4

consecutive hours (where the latter is aligned with the ICHD-3 criteria for migraine attacks – *Cephalagia* 2018; 38: 1-211). Teva believes this is an important issue that has not been fully considered thus far. These differences in what constitutes a migraine day impact all outcomes from this NMA as both are based on measurements of migraine days. The heterogeneity in definition makes comparison between trials more challenging and leads to further uncertainty in this analysis.

The EAG also makes a comment regarding concerns about the inclusion of CM patients in the FOCUS data, and that the availability of FOCUS data in EM patients would help strengthen the NMA by limiting it to the most relevant patients. Teva notes that some of the relevant ≥50% response data were included within the NICE appraisal of fremanezumab (marked as confidential) and are able to reproduce these data below to assist with this appraisal. Teva has also sourced the required data for change from Baseline in MMDs and these data are also included below.

FOCUS trial – EM patients	**Placebo (n=111)**	**Fremanezumab quarterly (n=107)**	**Fremanezumab monthly (n=110)**
Proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of fremanezumab			
Number achieving endpoint (%)	[redacted]	[redacted]	[redacted]
Odds ratio *vs* placebo (95% CI)		[redacted]	[redacted]
P-value *vs* placebo		[redacted]	[redacted]
Change from Baseline in mean monthly migraine days in Month 3 (Weeks 9–12) after the 1st dose of fremanezumab ('At 12 weeks')			
LSM change (95% CI)	[redacted]	[redacted]	[redacted]

Difference *vs* placebo (95% CI)		[redacted]
P-value *vs* placebo		[redacted]

For completeness, baseline characteristics in this group are also provided below.

FOCUS trial – EM patients Baseline characteristic	**Placebo (n=111)**	**Fremanezumab quarterly (n=107)**	**Fremanezumab monthly (n=110)**
Age, years			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Sex, n (%)			
Male	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]
Time since initial migraine diagnosis, years			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Number of migraine days during run-in period			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]

When considering the NMA results, these numerically favour the mAbs and in a number of cases reach statistical significance. This suggests that the mAbs are more efficacious treatments than rimegepant, but the uncertainty in the NMA means that the

		magnitude of any difference in treatment effect is highly uncertain. Overall, the limitations and uncertainties that the use of this NMA carries forward into the economic analysis must be borne in mind. Furthermore, it must be noted when considering the economic analysis that this is based on a difference in **response rate only**, with any difference in MMD reduction not included. As the NMA shows that it is likely that the mAbs are also superior in terms of MMD reductions compared to rimegepant, the fact that this effect was not included within the economic analyses must be considered. This additional benefit for the mAbs has the potential to substantially shift the balance of cost-effectiveness towards the mAbs, as it would lead to reduced overall MMDs for mAbs, leading to greater QALYs and lower health-related costs for these treatments compared with rimegepant.
Gradual *vs* immediate reversion to baseline MMD during the assessment period and after the assessment period	No	Teva agrees with the EAG that this is an important issue and notes that this represents a substantial deviation from the approach taken in previous appraisals (most particularly the assumptions applied within TA764). Teva firstly would like to clarify the committee's preferred assumptions as applied in TA764, as these are recorded incorrectly within Table 41 of the EAG report (p136). The assumptions for BSC are correctly recorded, but those for active treatment are incorrect. 'Non-responders to active treatment at 12-weeks' and 'responders to active treatment who discontinue treatment' both immediately reverted to baseline MMDs. In the original CS for TA631 (p160 of committee papers: https://www.nice.org.uk/guidance/ta764/documents/committee-papers), the assumptions on MMDs after treatment cessation are summarised as a return to baseline MMDs (after negative stopping at 12 weeks for non-responders) and a return to best supportive care (BSC) MMDs (after *per* cycle discontinuation for responders). Both of these changes were modelled as occurring immediately. Section 3.16 of the TAG states "The EAG explained that assuming migraine frequency would revert to that of best supportive care after discontinuation from all causes was overly optimistic. .... To account for this, the EAG did a scenario analysis. In this, people reverted to baseline migraine days after fremanezumab discontinuation (from all causes), and the treatment effect for people whose migraine responded to best supportive care diminished to baseline over 1 year. The committee agreed that this scenario was more in line with how the clinical experts expected treatment effectiveness could change

		after stopping treatment. The committee concluded that the company's post-discontinuation assumptions were overly optimistic. It agreed that it would consider the EAG's scenario in which people revert to baseline MMDs after stopping fremanezumab, botulinum toxin type A or best supportive care." This altered the assumptions for an immediate reversion to baseline for responders who discontinue active treatment. Separately to this, the EAG applied a waning to the placebo effect so that this dissipated over one year to ensure that a balance was maintained between arms in the model (as, previously, Teva had modelled the placebo effect to be maintained throughout the time horizon as a conservative assumption in the absence of evidence to the contrary). When the post-discontinuation assumptions were altered to lead to an immediate return to baseline for all patients after discontinuing active treatment, an alteration to the behaviour of the placebo effect in the model was necessary to prevent a long-term enduring benefit in the BSC arm related to the placebo response (*i.e.* without the waning of the placebo effect, fremanezumab responders who discontinued would return to baseline MMDs, whilst BSC responders would maintain the placebo efficacy [MMDs lower than baseline] throughout the time horizon). The waning over 12 months was, therefore, only ever applied to the BSC responders following the 12-week assessment time point (to address this issue and ensure that baseline MMDs was the long-term endpoint for all patients in both arms of the model). Teva is therefore clear that, in TA764, there was no assumption of a response to BSC after discontinuation of active treatment. The only appraisal where a waning back to baseline following the discontinuation of active treatment was applied was that for galcanezumab. This effect in the galcanezumab appraisal was based on washout data from the galcanezumab RCTs showing a gradual return of MMDs after treatment cessation. No such data have been presented to show an equivalent effect in rimegepant, and therefore Teva believes that such an effect should not be included for rimegepant. Therefore, the only appropriate assumption that can be made, which is in line with previous appraisals, is that there is an immediate reversion to baseline after the cessation of active treatment (for whatever cause). Furthermore, consideration of the clinical situation for these patients highlights that the assumption of a placebo effect after active treatment cessation is flawed. Within the

		appraisals of migraine preventive medications, BSC has been defined as acute migraine treatment only. Acute migraine treatment is continued in patients receiving preventive treatment and so those discontinuing will stop preventive treatment only and remain on the same acute treatment. Therefore, there would be no expectation of any additional placebo response in these patients based on a treatment they are already receiving.
Response probability for rimegepant	No	Teva agrees with the EAG that there is a need for consistency between inputs with regard to the outcome definition for response. Therefore, the at least 50% response "average over 12-weeks" including mild-to-severe MMDs would appear to be the most appropriate data for the response of rimegepant. As noted by the EAG, this issue is particularly important when the response rates for the other treatments included within this economic modelling are based on this response rate for rimegepant. In addition, Teva notes that, in clinical practice, MMDs rather than migraine attacks are the most commonly utilised measure. Also, all MMDs are likely to be assessed in clinical practice, rather than only a focus on moderate to severe migraine. Teva also notes some inconsistency in the reporting around this issue between MMDs and migraine attacks. It appears that the CS is consistent in referring to this endpoint as at least 50% reduction in MMDs (see Table 8, p55 CS). However, within the EAG report the wording of migraine attacks is used in relation to this issue. Teva would like to ensure that there is consistency and accuracy in the use of these two distinct terms and notes that the data for other treatments are collected using a definition of at least 50% reduction in MMDs.
Applying the NMA results from Cycle 1 *vs* Cycle 3	No	Teva believes that the most appropriate approach to this issue depends on the detail of the model structure and how responders and non-responders are modelled. Teva agrees with the EAG that there should be consistency in the application of analyses to ensure the economic modelling is as robust as possible. Teva also notes that in clinical practice the assessment of efficacy will occur at 12 weeks and will be based on the response during the initial treatment period. However, this does not impact how the efficacy of treatment should be modelled during this initial 12-week period, which should occur in the most fair and balanced way possible.

		Teva does not find the explanation of this issue entirely clear, as the EAG refers to this regarding the application of the NMA results (Teva assumes this means response rate) at time points earlier than 12 weeks, but then also mentions the application of MMD distributions. Teva is therefore unsure whether the issue refers solely to the application of NMA data or whether this issue also covers the modelling of efficacy during this 12-week assessment period. For clarity and to aid committee discussions, Teva wishes to outline the committee's preferred approach in this area within the appraisal of fremanezumab. Firstly, it must be noted that the fremanezumab model separately modelled responders and non-responders at all time points. MMD distributions were applied separately to these responder and non-responder groups (separate distributions were also applied to active treatment *versus* BSC). These MMD distributions were then adjusted based on mean MMDs taken from RCT data for responders. For non-responders, the committee preferred a scenario where no efficacy for fremanezumab non-responders was assumed (as noted by Teva in page 66 of the committee papers: https://www.nice.org.uk/guidance/ta764/documents/committee-papers-2). Therefore, within the modelling for fremanezumab, non-responder patients were assumed to remain at baseline MMDs throughout the model time horizon (it had already been assumed that these patients reverted to baseline MMDs after discontinuation at 12 weeks).
Comparator treatment acquisition costs	No	Teva agrees with the EAG assessment in this area and notes that the costs of treatment acquisition should be in line with the product licences and consistent to the model cycle length. Teva notes that the prices used by the EAG in their additional analysis to correct for the first cycle cost issue are never stated within the EAG report (only acquisition costs as applied by the company are noted in the EAG report, Table 67, p176). Teva believes that an incorrect consideration over how to apply the loading dose costs for galcanezumab may have caused this issue. As the EAG's corrected approach is never fully detailed, Teva would like to add its interpretation of how the loading dose should be considered and the relevant acquisition costs. As stated by the EAG, the *per* cycle treatment cost should be equal across all cycles and representative of the cycle length and treatment dosing frequency (*i.e.* for fremanezumab and galcanezumab this will be £414.00 *per* cycle as stated in EAG report, Table 67, p176).

		This cost should be applied to all cycles (including Cycle 1) to cover the basic dosing requirements (225mg monthly for fremanezumab and 120mg monthly for galcanezumab). When considering the loading dose for galcanezumab, what is required is the additional administration of one 120mg dose at treatment initiation (Cycle 1). This cost should be for a full dose (£450.00) rather than the *pro rata* cycle cost (£414.00) as this is a one-off administration and the full cost of this initial loading dose is needed to be captured (however the cost for the ongoing dose in captured within the *per* cycle cost). This would make the Cycle 1 cost for galcanezumab £864.00 rather than £828.00, if the *per* cycle cost was simply doubled. The detail on how this cost was adjusted is not stated within the EAG report and so Teva is not sure how this has been applied. Teva also notes that Patient Access Schemes (PAS) are in operation for fremanezumab, erenumab, and galcanezumab, and that those prices were used to judge the cost-effectiveness of these other treatments by NICE. This is mentioned briefly in the EAG report where it is noted that analyses conducted using these PAS prices are contained within a confidential appendix. Teva would like to note that any changes in the application of the treatment acquisition costs will need to be applied in the same manner to these confidential analyses.

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Class specific discontinuations	4.2.8.2	No	**Teva Key Issue** Teva notes that this issue was raised by the EAG, but seemingly was not applied to the updated modelling. Teva believes that this is an important issue in this appraisal, especially given its potential impact on ICER values. Teva believes that, as the EAG states, there is no reason to expect the same discontinuation rate across such different treatments (mAbs *versus* rimegepant). Rimegepant and the mAbs 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 mAbs. Teva feels that the EAG's suggestion of an imposition of a class effect between mAbs predicated on the long-term discontinuation rate for erenumab would be the fairest assumption that could be applied.

Additional issue 2: Impact and interplay of acute and preventive indications	N/A	No	**Teva Key Issue** As mentioned by the company, this is the first treatment with a dual indication for preventive and acute treatment of migraine. Teva feels that how this treatment would likely be used within the NHS is an important consideration for this appraisal, especially considering the potential overlap between these indications. For example, within the company submission it is mentioned that, during the long-term study (BHV3000-302), patients using rimegepant preventively (EOD dosing) were able to take additional doses as an acute treatment (PRN dosing) on a day when they were not due to take rimegepant under their EOD schedule. However, no efficacy data have been presented in this appraisal for this combined dosing. Teva believes that how any interplay between indications works in clinical practice is a relevant question for this appraisal. Teva has heard from clinical experts that current migraine treatment is based on a clear division between acute and preventive treatments. How rimegepant fits into and alters this treatment paradigm is therefore worthy of consideration. Teva also notes that rimegepant appears likely to remain the only treatment with both an acute and preventive indication in migraine for the foreseeable future, as other gepants in development appear to be currently focussed on either an acute or a preventive indication. Whilst individual economic analyses make sense for the consideration of each of these two indications, this does not address any potential interplay between indications for a patient using rimegepant for both acute and preventive therapy concurrently. This combined use has been investigated in the long-term study (BHV3000-302) with no relevant efficacy data presented (*i.e.* does use in one indication influence the efficacy in the other indication). Therefore, there is a lack of data and a high degree of uncertainty in this area. An additional related consideration is the potential for misuse of rimegepant related to these dual, overlapping indications. This risk would appear to be particularly high in patients receiving rimegepant for one indication whilst being ineligible for its use in the other indication (*e.g.* a patient using rimegepant

			acutely, but who is using an oral preventive [*i.e.* has not failed on three preventive medications]; or a patient taking rimegepant preventively who is using triptans as an acute treatment). Teva feels that these issues should be considered by the committee.
Additional issue 3: Time horizon in economic models	4.2.5	No	For the preventive modelling, Teva believes that the model time horizon should match that of previous appraisals and be a lifetime horizon. Teva also notes that a discrepancy persists between appraisals as to what is appropriate for a lifetime horizon. Teva would like to clarify the horizon used in TA764 was a lifetime horizon (which was extended to be 58 years by the ERG). In the ACD for TA631 it was stated that "The committee concluded that it preferred a lifetime time horizon of at least 30 years to ensure that all relevant costs and benefits associated with fremanezumab were captured". For the acute modelling, Teva feels that the precedence of previously published analysis provides strong evidence for consideration of a two-year horizon. This is particularly relevant for the acute indication where the costs and benefits are immediate and related to each individual administration of treatment (there are no long-term effects). Also, given the weakness in the RCT data, which is based on response to a single attack only, it would seem prudent to limit the time horizon to reduce long-term uncertainties. In addition, the relatively small changes in ICER when lengthening the time horizon suggests that most benefits are within two years and are captured under this shorter duration horizon.

Additional issue 4: Limitations of safety data	3.1.3.6 & 3.2.3.5	No	Teva believes that a relevant issue is the limited safety data in patients receiving more than 14/15 doses of rimegepant *per* month. The safety data presented includes EOD dosing (14 tablets *per* 28 days) and PRN dosing of up to 14 migraine attacks *per* month (14 tablets *per* 28 days). The only exception to this is Group 3 of Study BHV3000-201, which included a patient group using a combined (EOD and PRN dosing). It is stated in the CS that a mean dose of rimegepant was [redacted] (SD: [redacted]) tablets *per* 28 days in this patient group (page 127 of TE papers). This implies that only a limited number of patients with higher usage of rimegepant were included in this study (or that there was a very high rate of non-compliance). This is further reinforced by the FDA having applied a label warning in the USA that there are no safety data on rimegepant for >18 tabs *per* month. Teva believes that the limitations in the safety data are an important consideration for this appraisal. This has implications for both acute dosing (for CM patients experiencing more than 14 attacks *per* month) and for the preventive indication (EOD combined with acute PRN use). Teva has one further query on the safety data presented. This surrounds the rate of AEs in Group 3 of study BHV3000-201 (Table 22, p75 EAG report). Group 3 is the group with the highest exposure to rimegepant (combined EOD and PRN dosing), yet the rate of AEs and treatment-related AEs are lower in this group than in either Group 1 or Group 2 (using PRN dosing on up to 14 migraine attacks *per* month). Teva finds that this results does not follow the expected dose-response relationship as the group with the highest drug exposure has the lowest rate of AEs. No explanation is given for this within the EAG report or TE papers. Teva wishes to raise this apparently counterintuitive result to ensure that this has been fully considered within this appraisal.

Additional issue 4: Trajectories of rimegepant responders after discontinuation in acute model	4.2.4.1 & 1.4 & 1.5.1	No	This point refers to the issue identified by the EAG and included as the first 'other Key Issue' in Table 14 (p30 EAG report). This issue is referred to in this table as "It is more plausible for rimegepant responders at 2 hours who discontinue treatment in the long-term to follow the trajectories of BSC all-comers rather than BSC responders" Teva refers to the response to 'Gradual *vs* immediate reversion to baseline MMD' above as many of the points around maintenance of efficacy after discontinuation also apply here. Firstly, it must be noted that no clinical evidence was presented to support this potential effect (that patients discontinuing rimegepant would respond to BSC for 12 months). Secondly, the nature of BSC in this situation must be considered. The company has positioned rimegepant as the last-line acute treatment and therefore BSC would be expected in clinical practice to consist of either no acute treatment or a suboptimal treatment (that is likely to already have been trialled), as outlined in Table 1 of the CS (p22 of TE papers). Therefore, the expectation of any placebo effect in these patients would appear to be unlikely, or small and transient at best. Teva feels that this is an important issue identified by the EAG and that there should be a consistency in application of post-discontinuation treatment efficacy, with previous preventive migraine appraisals modelling an immediate return to baseline MMDs in these patients. Furthermore, Teva also finds that the application of this effect effectively counteracts the application of the placebo effect in the BSC arm and thus potentially overstates the effectiveness of rimegepant. Firstly, it must be noted that this impacts responder patients only, as non-responders (BSC and rimegepant) all follow the pain trajectories of BSC non-responders. As BSC response (placebo response) is applied to rimegepant responders who discontinue treatment (which Teva assumes to account for most of this group over the 20-year horizon modelled), this means that this effect is applied equally to responders in both arms of the economic model. Therefore, any benefit in the BSC model arm from the placebo effect is negated by this modelling assumption. In addition, as the response rate is higher for rimegepant, this means that this effect is applied to a greater extent to patients in the rimegepant

			arm, meaning that this arm benefits from a greater placebo effect than is seen in the BSC arm. Teva finds that this is a highly optimistic and unjustifiable assumption. The proposed solution included in the EAG report for this (p131) was to model rimegepant responders to follow the pain trajectories of BSC allcomers after discontinuation. However, Teva finds that this still appears to be an overly optimistic scenario as it still allows the application of a placebo effect to patients discontinuing last-line rimegepant treatment where there would be no realistic expectation for a placebo effect to occur. Teva believes that the application of BSC non-responder pain trajectories is the only logical option in this area to ensure that an erroneous placebo benefit is not included within the modelling of rimegepant.
Additional issue 4: Treatment effect on utilities in prevention of migraine	4.2.11.2	No	The inclusion of differential utilities for on- and off-treatment health states was not accepted by the committee during the initial appraisals of migraine preventive treatments. This effect was first accepted and applied in the appraisal of galcanezumab (TA659), when the company presented detailed evidence of this effect. The evidence presented for this effect in rimegepant appears minimal and lacking in detail. From the information included in the CS, Teva cannot ascertain whether equivalent analyses have been robustly conducted to demonstrate this effect for this treatment. Teva wishes to ensure that equivalent evidence is presented for rimegepant to that presented for other treatments to justify this effect.
Additional issue 5: BSC arm in preventive economic model	2.3.2.3 & 5.2.4		Whilst Teva agrees that the inclusion of a BSC arm would not provide results that are likely to be relevant to decision making, the inclusion of a modelled BSC arm would have allowed for a more effective assessment of external validity of this economic model against the modelling conducted in previous appraisals. Such a comparison of BSC arms between models would have provided significant reassurance around the external validity of this model.

Additional issue 6: Typographical errors	4.2.12.2.1, 4.2.3.2.2	No	Teva has noticed a couple of typographical errors within the document: • Table 31 of the CS (p103/4) states the NCT number of the Sakai 2021 study to be NCT03303105. Teva believes that this should be NCT03303092 (the NCT number of the double-blind portion of this trial rather than the NCT number for the long-term extension), and notes that this is stated correctly in Table 36 of the CS (p113). • Table 79 of the CS (p206 of TE papers) incorrectly states the initial costs for fremanezumab and galcanezumab (it appears these have been reversed). However, this is correct within Table 67 of the EAG report (p176). Teva would like to be sure that no loading dose has been included for fremanezumab, as this is not required under its licence. • On p127 & 128 of the EAG report, there is an error for fremanezumab dosing, where it is stated that there is a dosing schedule of 775mg every three months. This is not a licensed dose of fremanezumab, and the dose that was being referred to here is 675mg every three months. • Teva has some minor concerns around the use and implementation of HCRU data. Firstly, Teva would like to note (as is stated in the CS for TA631) that the resource use data used in the appraisals of fremanezumab is taken from TA682 and adjusted to match the 4-week cycle length in the fremanezumab model (*versus* the 12-week cycle used for TA631). In Table 81 of the CS (p210 of TE papers), there is an error in the acute medication use for 28 MMD, which was derived from TA631. This is stated to be 16.33, but should correctly be 13.633. Teva believes that this will have been superseded by the updated figures applied by the EAG (Table 68 of EAG report, p177). However, Teva notes that these figures are presented as taken from TA682 and so relate to a 12-week cycle. It is not clear from the EAG report if these have been appropriately converted to match the 4-week cycle of the rimegepant model.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the ERG report	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

Rimegepant for treating or preventing migraine [ID1539]

Technical engagement response

November 2022

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's (EAG's) critique of the company's response to technical engagement (TE) for the appraisal of rimegepant for treating or preventing migraine [ID1539]. Each of the issues outlined in the TE report are discussed in detail in Section 2. For a summary of the EAG's judgement on each issue, see Table 1. The company's updated base case analyses are outlined in Section 3 and the EAG's analyses are reported in Section 4.

Table 1. Issues for TE and current status regarding issue resolution

Key Issue		Status according to the EAG	Company approach	EAG approach
Acute migraine treatment				
1	Exclusion of CM patients from acute RCTs and extrapolating evidence from EM patients	Unresolved (considered unresolvable due to data limitations)	Further comment provided	Acknowledges the company's comments but considers that uncertainty remains
2	Cost-effectiveness results based on the ODT formulation trials	Partly resolved	Pooled analysis excluding study BHV3000-310	Pooled analysis including study BHV3000-310
3	Using response to the first migraine attack to inform response to subsequent migraine attacks	Unresolved (considered unresolvable due to data limitations)	Agrees with the uncertainty expressed by the EAG	Accepts the company's assumption but considers that uncertainty remains
4	Baseline distribution of MMDs	Partly resolved	Observed data from study BHV3000-201	Parametric distribution from study BHV3000-201
5	Assuming rimegepant PRN can result in reductions in MMDs	Unresolved (different opinions)	Included in the base case	Included in scenario analysis
+	Subgroup with at least 2 triptan failures vs mITT	Unresolved (different opinions)	Subgroup with at least 2 triptan failures	mITT
+	Trajectories of rimegepant responders after discontinuation	Unresolved (different opinions)	BSC responders	BSC all-comers
Migraine prevention				
6	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)	Resolved	Wording in line with marketing authorisation	

7	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)	Unresolved (considered unresolvable due to data limitations)	Further comment provided	Acknowledges the company's comments but considers that uncertainty remains
8	Uncertainty concerning the efficacy of rimegepant vs mAbs due to a lack of direct evidence and limitations of the NMA	Unresolved (considered unresolvable due to data limitations)	Further comment provided	Acknowledges the company's comments but considers that uncertainty remains
9	Gradual vs immediate reversion to baseline MMD during the assessment period and after the assessment period	Resolved	Gradual reversions during both assessment periods	
10	Response probability for rimegepant	Unresolved (different opinions)	At 12-weeks and moderate-to-severe MMDs	As per the NMA: average over 12 weeks and mild-to-severe MMDs
11	Applying the NMA results from Cycle 1 vs Cycle 3	Partly resolved	NMA results applied from Cycle 1 using option 1	NMA results applied from Cycle 1 using option 2
12	Comparator treatment acquisition costs	Resolved	Initial cycles equal to subsequent cycles (with the exception of the loading dose for galcanezumab) and erenumab regimen as per the BNF	
+	Incorporation of baseline EQ-5D data in the regression	Partly resolved	Excluded	Included

Abbreviations: BSC, best supportive care; BNF, British National Formulary; CM, chronic migraine; EAG, Evidence Review Group; EM, episodic migraine; mAbs, monoclonal antibodies; mITT, modified intention-to-treat; MMDs, monthly migraine days; NMA, network meta-analysis; ODT, orally dispersible tablet; PRN, *pro re nata* (as needed); RCTs, randomised controlled trials. TE, technical engagement.

2 Issues for technical engagement

2.1 Acute migraine treatment

2.1.1 Key Issue 1: Exclusion of CM patients from acute RCTs and extrapolating evidence from EM patients

In the EAG report, the exclusion of chronic migraine (CM) patients from the acute randomised controlled trials (RCTs) was highlighted by the EAG as an area of uncertainty in terms of whether evidence from these trials, which focused on episodic migraine (EM) patients, could also be applied to the CM population. While the EAG's clinical experts do not expect there to be a large difference in the efficacy of treatments for acute attacks in these two populations, they note that it is possible

given that medication overuse headache (MOH) is often a bigger problem in CM compared to EM, which could make the CM group more difficult to treat in terms of acute attacks and result in a higher incremental cost-effectiveness ratio (ICER) for this subgroup. They note that a lack of evidence comparing acute treatment efficacy between EM and CM patients means there is uncertainty as to whether a difference would be seen between the two groups.

In the company's TE response, they note the following:

- the Summary of Product Characteristics (SmPC) does not preclude the use of rimegepant in the acute treatment of migraine among CM patients;
- the inclusion criterion of <8 migraine attacks per month (<15 headache days per month) in the acute RCTs was chosen in line with previous acute migraine trials;[1, 2]
- evidence comparing acute treatment efficacy between EM and CM patients is not available within the rimegepant RCTs or from trials of other acute treatments;
- they agree with the EAG's clinical experts that they do not anticipate differences between the two groups;
- for rimegepant, they do not agree with concerns about MOH in the CM population possibly leading to a higher ICER for this subgroup, as they highlight [redacted] MOH [redacted] in the long-term evidence for rimegepant (BHV3000-201) and a real-world analysis suggesting that the rimegepant orally dispersible tablet (ODT) is associated with a reduction in MOH burden.[3]

The EAG acknowledges the company's comments but notes that uncertainty remains as there is an absence of evidence comparing the efficacy of acute treatments in EM and CM, even for treatments other than rimegepant. Although there was [redacted] MOH [redacted] in the long-term evidence for rimegepant (study BHV3000-201) and the company highlights that rimegepant ODT may reduce MOH burden,[3] the EAG notes that this does not rule out the possibility that treatment efficacy of rimegepant would not differ between EM and CM patients; the presence of MOH at baseline due to the use of other acute treatments, which may be more likely in a CM population and make this a more complex group to treat, could impact on the subsequent efficacy of rimegepant if it were to be used. It is also unclear how robust the monitoring for MOH was in study BHV3000-201. The EAG considers that there is a lack of evidence available to address the uncertainty about acute treatment efficacy in EM vs CM patients.

Most stakeholders (four of five) that commented on this key issue shared the EAG's concerns but one considered that evidence could be extrapolated from EM to CM, as indicated in Table 2. In response to the stakeholder comment in the second row of this table, the EAG notes that the RCTs for acute rimegepant use (BHV3000-301, -302, -303 and -310) limited inclusion to those with <15 headache days per month and that it is the rimegepant prevention trial (BHV3000-305) that allows inclusion of some CM patients (4 to 18 migraine attacks of moderate-to-severe intensity, at least 6 migraine days and up to 18 headache days per month).

The EAG also acknowledges further comments from Teva about the generalisability of the trial (small proportion in the trials with ≥2 triptan failures, all RCTs being based solely in the USA [or Asia as for BHV3000-310] and how well the RCTs reflect EM patients). The modified intention to treat (mITT) population was favoured by the EAG over the triptan failure subgroup due to various limitations of the subgroup (Section 2.3.1.1 of the EAG report). Although they acknowledge that more robust evidence within this subgroup would be preferable and increase confidence, it is not something that is currently available. Similarly, the EAG acknowledge that there are no trials including UK patients. Although Teva highlights that the rimegepant trials may not be reflective of the EM population, the EAG's clinical experts reviewed baseline characteristics of included trials and considered them to be a reasonable representation of UK practice.

Table 2. Stakeholder responses to Key Issue 1: Exclusion of CM patients from acute RCTs and extrapolating evidence from EM patients

Stakeholder	Comment
Association of British Neurologists advisory group on headache and pain	Chronic migraine is generally considered more refractory to acute and preventive treatment than episodic migraine and within that cohort many patients may also have medication overuse headache, therefore extrapolating evidence for treatment from episodic to chronic headache may overestimate the therapeutic benefit.
British Association for the Study of Headache	The trial included patients between 4-18 days of headache per month. Hence some patients with chronic migraine were in the study (those with 15-18 days per month). However including all patients with Chronic Migraine will have those with 19-30 days per month which were not part of the study. Hence evidence from episodic migraines were used. Chronic Migraine is generally considered refractory to acute treatment than episodic variety. Around 60-80% patients with chronic migraine have medication overuse issue and are not a good substrate to evaluate efficacy in acute randomised trials.
Clinical expert	*When asked whether they would expect similar efficacy of an acute treatment between people with EM and CM in clinical practice:* not necessarily. Structural differences can be demonstrated and co-morbidity is much higher. *When asked whether it is appropriate to extrapolate evidence from the included acute RCTs to the CM population and whether they are aware of any evidence comparing the effectiveness of acute migraine treatments in EM and CM:* no.

Patient expert	I don't have the medical knowledge to be able to answer this question.
Migraine Trust	We feel it is possible to extrapolate evidence to the chronic migraine population, particularly in those who experience migraine on ≥4 days per month. People with Chronic Migraine will typically experience a greater negative impact but those with Episodic Migraine, also experience attacks that have similar features, severity and impact. […]
Novartis	No comment.
Teva	Teva believes that the exclusion of patients with CM from the RCTs investigating the acute use of rimegepant leads to a high level of uncertainty about the efficacy of this treatment within this patient population. Based on what was presented within this appraisal, there is no reliable evidence currently available to demonstrate the size of any treatment effect for rimegepant within the CM patient population. This is further demonstrated by the fact that studies show that there are substantial differences in burden between EM and CM. People with chronic migraine experience greater headache-related disability, headache impact, reduced health-related quality of life, greater healthcare costs and higher rates of comorbid medical and psychiatric conditions. Given these stark differences between the EM and CM populations, the size of the treatment effect for rimegepant in CM patients can be seen to be associated with high levels of uncertainty. The EAG's suggestion for a comparison of the efficacy of acute treatments in CM and EM would provide some indirect evidence relevant to this issue. However, this indirect evidence would still leave the size of any effect for rimegepant in CM patients highly uncertain due to this evidence being from different acute treatments with distinct mechanisms of action to that of rimegepant. Further limitations in the RCT data include the generalisability of the efficacy results to the proposed UK patient population (after two triptan failures). The majority of patients within the trials had not failed two triptans (only 8.5% of rimegepant patients and 10.1% of placebo patients had failed >2 triptans). […] A further limitation that potentially impacts the generalisability of these data is the fact that evidence is available only from RCTs conducted in the USA. The differences in migraine management and healthcare systems mean that the lack of any data on European patients adds further uncertainty into the applicability of these results, and brings into question relevance of the studied patient population to the UK migraine patient population under consideration. […] the characteristics of these patients and how representative they are of the full range of patients with EM is unclear. Considering the pooled trial data, these patients are stated to have a mean of 4.6 migraine attacks per month (p255 of TE papers), combining this with the breakdown of length of migraine attack (p355 of TE papers) gives an estimate of around 7 migraine days per month. However, only limited details of the spread within these data are presented (no median or range data are presented), and so it is not possible to judge the range of patients included. Teva notes that the HALO EM population had a higher baseline mean MMDs, which raises a question as to how well the rimegepant clinical trials captured patients at the more severe end of the EM spectrum. This raises further questions as to the generalisability of these data to a more general migraine population as would be expected in UK practice.

Abbreviations: CM, chronic migraine; EAG, External Assessment Group; EM, episodic migraine; MMDs, monthly migraine days; RCTs, randomised controlled trials; TE, technical engagement.

2.1.2 *Key Issue 2: Cost-effectiveness results based on the ODT formulation trials*

During the clarification stage, the company provided pooled results from the RCTs using ODT formulation only (trials BHV3000-303 and 310) and found that the ODT formulation may have contributed to a slightly higher percentage of patients receiving pain relief at 2 hours compared to the pooled tablet and ODT formulation analysis. This would suggest the pooled estimate is generating a conservative ICER. However, when treatment effectiveness data from the ODT formulation trials were applied in the economic analysis, the ICER was higher than the ICER in including trials of both formulations, which is counterintuitive. The company was asked to explain what was driving the change in the ICER during TE.

In response to TE, the company explained that the BHV3000-310 trial was conducted in China and Korea and there are cultural differences in reporting pain, which is why the ODT formulation analysis leads to a counterintuitive ICER. The company explained how responding means more to patients in the -301, -302 and -303 trials than patients in the -310 trial, as shown by the smaller responder coefficient in the ODT-only quality-adjusted life hour (QALH) regression [redacted] Additionally, more patients in the -301, -302 and -303 trials (30.9%, 35.0%, and 29.7%, respectively) experienced severe pain at baseline compared to the 310 trial (18%) and there is a larger gain in utility moving from severe pain to moderate pain (-0.20 to 0.53) than moderate pain to no pain (0.53 to 0.66). The EAG considers the company's explanations for the counterintuitive ICER to be reasonable. The company also undertook extensive additional model checks to ensure the model was working correctly and provided further data supporting the bioequivalence of the two formulations. For these reasons, the EAG is satisfied that the pooled formulation results can be used to inform the economic analysis and that the model does not appear to contain any errors.

The company also provided two additional studies to demonstrate how there are cultural differences in reporting pain severity (Asians have a higher threshold for pain compared to Europeans) and why the BHV3000-310 trial should not be included in the base case analysis. The EAG reviewed these studies. Yi *et al.* 2014 included 16 patients, aged 21 to 28 years, in each racial group (Han Chinese and Caucasians).[1] Houghton *et al.* 1992 was a preliminary study of 24 hours' postoperative analgesia undertaken in eight European and fourteen Asian adult patients over 30 years ago.[2] The EAG considers these studies to be of limited relevance and quality to draw any meaningful conclusions. The EAG also notes that BHV3000-301, -302 and -303 studies were all in

USA populations, which following the same argument could equally vary in terms of reporting of pain severity compared to a UK population.

As noted in the EAG report, inclusion criteria across the four RCTs (BHV3000-301, -302,-303 and -310) were identical and studies solely in an Asian population had been included for the migraine prevention network meta-analysis (NMA). The EAG also notes that [redacted] of patients in the acute pooled RCTs in the subgroup with at least 2 triptan failures reported severe pain at baseline, which [redacted] the proportion in study BHV3000-310. For these reasons, the EAG maintains that the BHV3000-310 trial should be included in the base case analysis when the mITT population is assumed (triptan failure status not recorded in the BHV3000-310 trial).

2.1.3 *Key Issue 3: Using response to the first migraine attack to inform response to subsequent migraine attacks*

In their report, the EAG highlight that the single attack design of the rimegepant acute RCTs (BHV3000-301, -302, -303 and -310) meant that there are no clinical data indicating how many patients would respond after taking rimegepant to treat a second or third migraine, who did not respond during their first episode. The economic model therefore assumes that patients who do not respond to the first treatment (based on pain relief at two hours) would not respond to a subsequent treatment.

The company, in their TE response, agree with the EAG that this is an unresolvable area of uncertainty as there are currently no long-term data to inform how response to a single attack may predict response to future migraine episodes.

Stakeholder responses on this issue are collated in Table 3; two suggest the company's assumption is plausible based on their own experience.

Table 3. Stakeholder responses to Key Issue 3: Using response to the first migraine attack to inform response to subsequent migraine attacks

Stakeholder	Comment
Association of British Neurologists advisory group on headache and pain	Response to treatment may vary considerably between attacks, placebo effect may vary considerably.
British Association for the Study of Headache	Response to treatment varies from one attack to another. In practice a lack of response to treatment in three attacks means the treatment is ineffective. However, a good response to first treatment means subsequent attacks will respond to

	treatment, although this is based on physician's clinical experience rather than evidence based.
Clinical expert	General recommendation is three attacks. I am also concerned there is no consideration of the addition of a prokinetic (essential) and other formulations of a Triptan (nasal, injection). The Triptan may not work as it is not getting absorbed.
Patient expert	In my own experience, Rimegepant is the only medication that has worked first time and subsequently. I couldn't extrapolate from my own experience to others'. I would agree that trying the drug for two or three episodes seems a fair way of assessing its efficacy in an individual.
Migraine Trust	People with migraine want a treatment that is reliable and effective and will have greater confidence in a treatment that demonstrates effectiveness for more than 1 attack.
Novartis	No comment.
Teva	This assumption leads to a high degree of uncertainty in the economic modelling as there are currently no data to confirm the response to rimegepant beyond a single dose for acute treatment. […]. In analysing this issue, the EAG has considered the case where patients do not respond to an initial dose but do respond to a second or third dose. Teva notes that the inverse is also possible, with a patient showing an initial response (either to one dose or to multiple doses) which then dissipates. Although this effect may be accounted for, to some extent, by the long-term discontinuation rate applied within the modelling (if it is assumed that these patients discontinue treatment), it is not certain that this would fully account for the potential of this effect. This is especially true as this treatment is positioned as a last-line treatment, meaning that patients may be less likely to discontinue (even if efficacy is reduced) as they would have no further treatment options available to them. This would lead to patients remaining on treatment with reduced efficacy to that assumed within the modelling. The uncertainty in this area could, therefore, cause a significant impact on the ICER (in either direction).

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio.

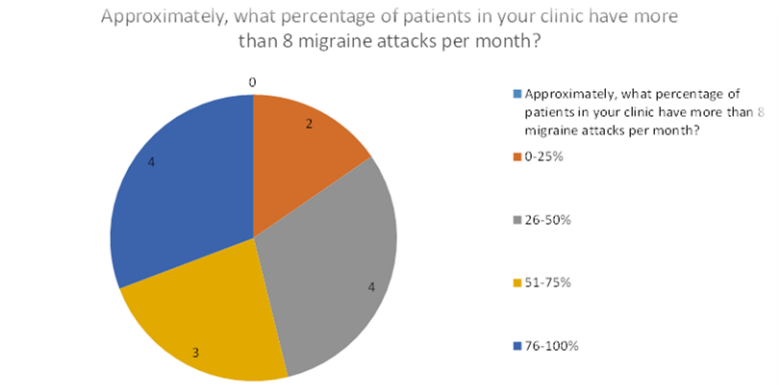
2.1.4 Key Issue 4: Baseline distribution of MMDs

In the company submission (CS), the company preferred the distribution of attacks per month from study BHV3000-201 to the acute RCTs as the acute RCTs restricted inclusion to 2 to 8 migraine attacks per month, which, according to the company, doesn't provide a natural distribution of the full range potentially observed in the UK population for the acute treatment of migraine. In the EAG report, the EAG expressed a preference for the baseline distribution of monthly migraine days (MMDs) (and all baseline patient characteristics) to be informed by the acute pooled RCTs to ensure consistency between sources used for pain relief, pain trajectories and baseline MMDs.

During the TE stage, the company obtained additional feedback from 13 clinicians to determine if study BHV3000-201 is the most appropriate source to inform the baseline distribution of MMDs.

Figure 1 summarises the percentage of patients who have more than 8 migraine attacks per month, seen by these experts in their clinics.

Figure 1. Clinical expert feedback to the company on the percentage of patients having more than 8 migraine attacks per month



The clinicians were asked if patients experiencing more than 8 moderate-to-severe attacks per month would need acute treatment for their migraine (along with other preventative treatment) and 100% of respondents answered “yes”. The clinicians were also asked if there is a relationship between MMD and migraine severity. The clinicians confirmed that there is no relationship and noted that patients can present with low frequency, high severity migraines and vice versa; high frequency, low severity migraines.

Stakeholder responses on this issue were limited. Nevertheless, based on the additional clinical expert responses obtained from the company, the EAG is satisfied that the baseline MMDs observed in study BHV3000-201 are representative of the UK and that pain trajectories are independent of MMDs, meaning they do not need to be informed by the same source.

However, the EAG notes that the company is still using the observed data to model the distribution of MMDs and not a parametric distribution. As noted in the EAG report, the EAG considers the observed data sporadic (

Figure 2) and the Poisson distribution more in line with the distribution observed for migraine prevention and the expected distribution for acute treatment. The EAG therefore implements the Poisson distribution in its base case.

Figure 2. Distribution of migraine events per month for the population with two or more triptan failures in study BHV3000-201 (generated by the EAG, as per Figure 6 of the EAG report)

2.1.5 *Key Issue 5: Assuming rimegepant PRN can result in reductions in MMDs*

The EAG report explains how the long-term reductions in MMD with *pro re nata* (PRN) rimegepant are highly uncertain as they are based on a *post-hoc* analysis of the long-term safety study which may suffer from confounding (including but not limited to a possible placebo effect). In the absence of long-term comparative evidence, the EAG considered it more appropriate to remove reductions in MMD by PRN rimegepant from the base case analysis and include them in scenario analysis.

The EAG also highlighted in their report how assuming reductions in MMD by PRN rimegepant can result in questionable health-related quality of life data. This is because the company derived a baseline utility value by mapping Migraine-Specific Quality of Life Questionnaire Version 2 (MSQv2) values from the BHV3000-201 trial to EQ-5D. The MSQv2 has a 4-week recall period. One of the covariates in the regression model used to predict utility is MMD, which differs between rimegepant and BSC when reductions in MMD by PRN rimegepant are assumed. The utility difference driven by reduced MMDs will be an average over the month, meaning it will not just include improvements in the interictal period but also the improvement from not having those additional migraines. Therefore, including the baseline utility from study BHV3000-201 as the non-migraine utility and then including an additional utility for patients experiencing migraines may result in double counting.

In response to TE, the company explained why rimegepant PRN can result in reductions in MMD and why they disagree with the EAG:

1. MMD reduction among high frequency rimegepant PRN users has been observed in the 201 study and described by three peer reviewed publications (Johnston *et al.* 2021, Johnston *et al.* 2022 and L'Italien *et al*. 2022);[3-5]
2. Given rimegepant has a dual indication, it is biologically plausible that patients will benefit from the prevention properties of acute rimegepant PRN, albeit at a lesser extent than if taking every other day;
3. The concept was also presented and unanimously accepted by all the UK clinicians consulted during The National Institute for Health and Care Excellence (NICE) advisory boards held in May 2022 (the EAG assumes the NICE advisory boards were part of NICE Scientific Advice). It is also seen as significant advantage of rimegepant for these patients by the clinical experts.

For stakeholder comments on this issue, see Table 4. All note the lack of evidence to support the assumption that rimegepant PRN can results in reductions in MMD but some still consider the assumption to be plausible.

Overall, the EAG maintains that it is more appropriate to remove reductions in MMD by PRN rimegepant from the base case analysis and include them in a scenario analysis.

Table 4. Stakeholder responses to Key Issue 5: Assuming rimegepant PRN can result in reductions in MMDs

Stakeholder	Comment
Association of British Neurologists advisory group on headache and pain	This assumption is not based on robust long term data and is uncertain.
British Association for the Study of Headache	The data has shown that use of Rimegepant every other day reduced the total number of mean monthly migraine days. It is, therefore, reasonable to assume that if one uses frequent Rimegepant for acute treatment it will have some preventive effect and will reduce the monthly migraine days, although this is not based on a robust long term data.
Clinical expert	It is reasonable to assume MMD's reduced but this mixed approach really murkies the water.
Migraine Trust	While we do not have evidence of use of this medicine in the UK from people who contact us, we feel that if the treatment can be safely used PRN, potential greater benefit may be derived, as the likelihood of side effects from using different types of treatments, is minimised.
Novartis	No comment.

Teva	Teva believes that the assumption of an overall reduction in MMDs with PRN dosing of rimegepant cannot be justified given the currently available evidence. The evidence presented is based on exploratory efficacy analyses of data from an open-label, uncontrolled trial. In addition, only minimal data and details are provided on these data within the company submission (CS), making any meaningful review of these data challenging. Overall, Teva does not feel that the data presented are compelling enough for this effect to be included within the economic modelling. Furthermore, Teva has some concerns with the analyses conducted to demonstrate these effects and their applicability to higher MMD/migraine attack health states. As mentioned by the company within their submissions, rimegepant has no restrictions on MMDs or migraine attacks within its licensed indication. However, the data presented to justify this effect come from Study BHV3000-201. In this study, there were two PRN dosing groups, a group with 2-8 migraine attacks per month and a group with 9-14 migraine attacks per month (the third group in this trial utilised a combined EOD + PRN dosing schedule). Therefore, the groups included in this analysis do not cover the full range of migraine patients in clinical practice and excludes the most severely affected patients. The analysis presented relies on a regression analysis, which is utilised to extend the results from the studied group across all patients. This adds further uncertainty to this analysis in the most severely affected patient group, where the evidence is based only upon an extrapolation of an effect seen in an open-label, uncontrolled study of less severely affected patients. This again feeds back to Issue 1 and highlights how the exclusion of patients with CM from RCTs, and severely affected patients from Study BHV3000-201, applies limitations to many analyses conducted across this appraisal.

Abbreviations: CM, chronic migraine; EOD, every other day; MMDs, monthly migraine days; PRN, *pro re nata* (as needed); RCTs, randomised controlled trials.

The EAG considers the inclusion or exclusion of reductions in MMDs by PRN rimegepant to impact the appropriate time horizon. As noted in the EAG report, a 20-year time horizon is appropriate to capture the costs and consequences associated with reductions in MMD. However, the modelled reductions in MMD are based on weak evidence and therefore a shorter time horizon could be appropriate when these reductions are removed. Teva and the ICER evidence report concur with the EAG (Table 5).

Table 5. Comments on the time horizon for acute migraine treatment

Stakeholder	Comment
Stakeholder comment from Teva	For the acute modelling, Teva feels that the precedence of previously published analysis provides strong evidence for consideration of a two-year horizon. This is particularly relevant for the acute indication where the costs and benefits are immediate and related to each individual administration of treatment (there are no long-term effects). Also, given the weakness in the RCT data, which is based on response to a single attack only, it would seem prudent to limit the time horizon to reduce long-term uncertainties. In addition, the relatively small changes in ICER when lengthening the time horizon suggests that most benefits are within two years and are captured under this shorter duration horizon.

ICER evidence report (Table 4.2)	Compared with many other chronic conditions modeled using Markov models, migraine onset is rapid, and resolution occurs quickly. Since costs are incurred with each treatment and benefits are observed immediately, we believe that a two-year time horizon will be sufficient to estimate a stable incremental cost-effectiveness ratio for the acute treatment of migraine

Abbreviations: ICER, incremental cost-effectiveness ratio; RCT, randomised controlled trial.

2.1.6 *Additional Issue: Subgroup with at least 2 triptan failures vs mITT*

Section 2.3.1.1 of the EAG report describes in detail why the EAG considers the full trial population to be more relevant and more robust than the subgroup of patients who previously failed 2 triptans in the trials. Throughout the remainder of the EAG report, inputs and results were focussed on the mITT population. In response to TE, the company maintained the subgroup of patients with at least 2 triptan failures as their base case and did not comment on the EAG's preference for the mITT population.

2.1.7 *Additional Issue: Trajectories of rimegepant responders after discontinuation in the acute model*

The EAG's clinical experts disagreed with the company's assumption that all patients who initially respond to rimegepant, then discontinue rimegepant, would respond to best supportive care (BSC) for 12-months. During the clarification stage, the company provided a scenario where rimegepant responder discontinuers were allocated the pain trajectory of BSC all-comers for 12 months, to reflect a mix of responders and non-responders to BSC. As noted in the EAG report, the EAG considered this scenario to be a more realistic representation of response to BSC following rimegepant and included it in the EAG's preferred base case.

In response to TE, the company maintained their base case assumption. One stakeholder (Teva) expressed a strong disagreement with this. They believed the application of BSC non-responder pain trajectories to be the only logical option to ensure that an erroneous placebo benefit is not included within the modelling of rimegepant.

Given that clinical experts to the EAG have advised that a small proportion of patients will respond to BSC when they discontinue rimegepant, the suggestion by the stakeholder is extreme. The EAG also considers it conservative of the company to apply their assumption rimegepant responders only as some rimegepant non-responders may also respond to BSC.

For completeness, the EAG has explored the stakeholder's suggestion in scenario analysis, but maintains its preferred assumption that discontinuers are allocated the pain trajectories off BSC all-comers for 12 months. As shown in Section 4, both scenarios led to similar ICERs (£18,155 vs £18,545).

2.2 Migraine prevention

2.2.1 Key Issue 6: 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)

In the EAG report, the EAG requested clarification on the definition of the population in the decision problem in terms of migraine burden. Originally, the definition specified EM patients with ≥4 MMDs; however, the EAG noted that, as individual migraine attacks can last >24 h, this may represent a slightly broader population than specified in the marketing authorisation for rimegepant in migraine prevention, where it is indicated for those with EM and ≥4 migraine attacks per month.

In their response to TE, the company confirm that the population covered in the decision problem should be in line with the SmPC[6] and key trial (BHV3000-305)[7, 8] in terms of migraine burden, meaning it should read as follows: patients with EM who have ≥4 migraine attacks per month but <15 headache days a month and have failed at least three preventive drug therapies. The EAG agrees with this amendment as using ≥4 MMDs may represent a slightly broader population than specified in the marketing authorisation, although the EAG acknowledges comments from some stakeholders (Table 6) that ≥4 MMDs is in line with existing NICE recommendations for monoclonal antibodies (mAbs) in migraine prevention.[9-11]

In the company's economic analysis, the baseline distribution of MMDs were obtained from study BHV3000-305 and modelled using a normal distribution (see Figure 7 in the EAG report and Figure 22 in the CS). In the base case, [redacted] of MMDs had a duration less than 4 days, which suggests the alternative definition would have a minimal impact on the cost-effectiveness results.

Table 6. Stakeholder responses to Key Issue 6: 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)

Stakeholder	Comment
Association of British Neurologists advisory	Recommend that the number of migraine days per month, rather than number of migraine attacks per month, is used in the analysis as this reflects the burden of

group on headache and pain	migraine for the patient better and keeps the guidance in line with other NICE appraisals for migraine treatments (e.g., mABs and botulinum toxin).
British Association for the Study of Headache	Migraine attacks may go on for longer than a day and hence reduction in the number of migraine attacks should not be used. A reduction in monthly migraine days is along the lines taken by NICE in other appraisals for CGRP MAB and Botox.
Clinical expert	No comment.
Patient expert	No comment.
Migraine Trust	In practice, due to the variation in migraine attack duration, MMDs offer a more meaningful measure of the migraine impact.
Novartis	Novartis agrees with the EAG that a migraine attack can last for >24 hours and that "at least four migraine attacks per month" and "at least four migraine days per month" describe populations that are overlapping but not the same. More specifically, the population with "at least four migraine days per month" specified by the company in their decision problem may be broader than the population defined by "at least four migraine attacks per month" specified in the marketing authorisation for rimegepant. Novartis agrees with the EAG request for clarification on this point. If the NICE recommendation wording were based on "at least four migraine days per month" this would constitute a recommendation for use of rimegepant outside of the licensed population.
Teva	Teva notes that the guide for Technology Appraisals limits appraisals to be within the Marketing Authorisation of a product ("unless the Department of Health and Social Care specifically indicates otherwise"). Therefore, as the licensed indication of rimegepant is for use in "preventive treatment of episodic migraine in adults who have at least 4 migraine attacks per month", this is where the appraisal must be conducted. Teva agrees with the EAG's assessment that migraine days and migraine attacks are not interchangeable concepts. Migraine attacks can last longer than 24 hours, and up to 72 hours (https://www.nhs.uk/conditions/migraine/symptoms/; ICHD-3); whereas a migraine day is any day where migraine symptoms are present. Therefore, there is a difference in disease burden and disability associated with a migraine attack and a migraine day, with a migraine attack having a substantially greater impact on a patient. In addition, Teva notes that the RCT used to inform the preventive side of this appraisal (Study BHV3000-305) included patients with 4 to 18 migraine attacks of moderate to severe intensity per month and not patients with four or more migraine days per month. Given all of these facts, Teva believes the decision problem can only include a population of at least four migraine attacks per month. […]

Abbreviations: CGRP, calcitonin gene-related peptide; EAG, External Assessment Group; ICHD-3, The International Classification of Headache Disorders-3; mAB/MAB, monoclonal antibodies; MMDs, monthly migraine days; NICE, The National Institute for Health and Care Excellence; RCT, randomised controlled trial.

2.2.2 *Key Issue 7: 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 EAG highlights in the EAG report that despite the decision problem for rimegepant use in the preventive setting focusing on those with at least three prior preventive drug treatment failures, the population in the key rimegepant prevention trial (BHV3000-305)[7, 8] is not well aligned with this group, as those with non-response to more than two classes of preventive medications are excluded from the trial. As the EAG's clinical experts noted, those with a higher number of prior failures may have migraines that are more refractory that may be more difficult to treat even with a new drug class such as rimegepant. The EAG considers there to be uncertainty as to how applicable the results from the BHV3000-305 trial are to the refractory population described in the decision problem and the effect this may have on the ICER. The ICER may be expected to increase if the group with a higher number of treatment failures do experience reduced efficacy with rimegepant.

In their response at TE, the company confirm that data were not collected to allow assessment of how prior treatment failures may affect rimegepant efficacy in the BHV3000-305 trial (i.e. comparing groups with one, two or no prior treatment class failures). They also highlight their original argument that for the comparator trials of monoclonal antibodies (mAbs) vs placebo included in the NMA, odds ratios (ORs) for studies that focused on more refractory populations (LIBERTY,[13] FOCUS[14] and CONQUER[15] for erenumab, fremanezumab and galcanezumab, respectively) tended to be numerically larger compared to studies with a broader population. They use this observation to suggest that results from the BHV3000-305 trial may represent a conservative estimate of what would be observed for rimegepant in a group with at least three prior treatment failures. The EAG's views of this argument were noted in the EAG report and remain the same (Section 2.3.2.1); the EAG does not consider differences between studies in refractory and non-refractory populations for each mAb to be substantial and the confidence intervals of the ORs for each study, when calculated by the EAG, overlap within each comparison. Based on this and the expectation (based on feedback from the EAG's clinical experts) that it would be more difficult to achieve a response in those that have a history of non-response to a higher number of treatments, the EAG does not agree with the company's conclusion and considers there to be a lack of robust evidence to inform this conclusion.

The EAG notes that most stakeholders commenting on this issue (four of five) at TE share the EAG's concerns, as indicated in Table 7.

Table 7. Stakeholder response to Key issue 7: 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)

Stakeholder	Comment
Association of British Neurologists advisory group on headache and pain	Patients who have at least 3 prior treatment failure may represent a more difficult cohort to treat but extrapolating from the comparator mAb trials in refractory population is unlikely to provide accurate data (not least the variation in placebo response with variation in method of administration). The magnitude of this effect is uncertain but is likely to increase, rather than decrease, ICER.
British Association for the Study of Headache	Rimegepant trials excluded patients with failure of two or more preventive treatments and hence the results from this trial cannot be applied to those with failure of three prior treatments.
Clinical expert	*When asked whether the rimegepant trial is generalisable to the group with at least three prior preventative drug treatment failures:* this is always tricky as invariably, particularly in the UK people are not treated with a high enough dose for a long enough period. *When asked whether they would expect people with higher numbers of prior treatment failures to indicate refractory migraines:* a reasonable first approximation. *When asked whether, in their opinion, refractory migraines are more difficult to treat with new drug classes:* no. But this may be in part due to the fact that preventers have not been used appropriately.
Patient expert	No comment.
Migraine Trust	We do not have evidence to comment on the generalisability of the trial.
Novartis	[…] the rimegepant BHV3000-305 trial did not provide data for the subgroup of patients for whom three or more prior preventive drug treatments have failed, as the trial excluded patients with non-response to more than two classes of preventive medicines. Therefore, the submitting company have not presented clinical trial data to support the positioning they are pursuing. In contrast, the NICE recommendations for all three of the monoclonal antibodies (erenumab, fremanezumab, galcanezumab) as preventive migraine treatment in patients for whom at least three preventive drug treatments have failed were based on an assessment of clinical and cost effectiveness in this subgroup of patients. The clinical trial subgroup analyses provided as part of the appraisals of the three monoclonal antibodies were not without limitations with regards to their post-hoc nature and/or limited sample size. Nevertheless, the decisions of the NICE Committee in all three appraisals were informed by clinical trial subgroup data that corresponded to the specific population of interest for the decision problem. In contrast, whilst the rimegepant manufacturer is seeking the same positioning as the monoclonal antibodies with regards to the requirement for three prior preventive treatment failures, the rimegepant clinical trials do not provide data in this population.
Teva	[…] This means there is no direct evidence available for rimegepant in the key population of interest, which contrasts with previous appraisals of migraine preventive therapies, where additional trials have been conducted to investigate efficacy in this patient population (e.g., FOCUS, LIBERTY and CONQUER). It is clearly recognised that migraine patients who have failed multiple previous preventive therapies tend to have higher burden of headache- and migraine-related disability, are more likely to experience disease worsening, compared with those that have not failed multiple previous therapies; this is potentially as a consequence

	of longer periods of exposure to pain. Therefore, there are high levels of uncertainty as to whether the effects of rimegepant treatment from the RCT for rimegepant can be generalised to the at least 3 failure population due to clear clinical differences between these populations. […] The multiple failure population group has noticeable differences in patient characteristics (as can be seen within Table 32, p106 of the CS). The three trials focussed on the difficult-to-treat patient group (FOCUS, LIBERTY and CONQUER) can be seen to have older average patients who have had migraine for a longer time. This demonstrates that there is a distinction in this patient group and underlines the necessity for RCT data within the difficult-to-treat patient group (as has been gathered for fremanezumab, erenumab and galcanezumab, and Teva notes is planned for rimegepant in trial NCT05518123 [due for completion in Q3 2024]). Without such available data, it is very challenging to have any confidence in the generalisability of RCT evidence available for rimegepant in this distinct patient group.

Abbreviations: CS, company submission; ICER, incremental cost-effectiveness ratio; mAb, monoclonal antibodies; NICE, The National Institute for Health and Care Excellence; RCT, randomised controlled trial.

2.2.3 *Key Issue 8: Uncertainty concerning the efficacy of rimegepant vs mAbs due to a lack of direct evidence and limitations of the NMA*

In the EAG report, the EAG highlight that although they consider the random effects NMA adjusted for baseline risk to be the best available evidence to inform the relative efficacy of rimegepant compared to mAbs in the economic model, there are limitations associated with the NMA that remain but that are unresolvable particularly due to the limitations associated with the rimegepant trial (BHV3000-305) itself.

In their TE response, the company state that they agree with the EAG's decision to focus on the random effects NMAs with adjustment for baseline risk. However, in the revised economic analysis, the company maintained the results from the fixed effects NMA. No further comment was made by the company on any of the limitations highlighted by the EAG. The EAG therefore notes that uncertainty in the results of the NMA remains due to limitations such as differing treatment histories, inclusion of CM patients in some studies and differences in analysis populations and missing data handling. These limitations are likely to be unresolvable, particularly as the only rimegepant trial is limited in terms of how well the population reflects the decision problem and that the availability of data for comparator trials is likely to be too limited to better address any remaining concerns.

These concerns are shared by those stakeholders that commented on this issue at TE, as indicated in Table 8.

In addition, the EAG notes that Teva highlighted some additional concerns about the NMA not explicitly mentioned by the EAG in their report and also provided some data for the EM subgroup of the FOCUS trial, which was not available to the company when performing the NMA. These are summarised and discussed by the EAG in Table 9.

For cost-effectiveness results employing the EAG and company preferred NMA (random effects NMAs with adjustment for baseline risk, Table 10), see Section 4.

Table 8. Stakeholder comments to Key Issue 8: Uncertainty concerning the efficacy of rimegepant vs mAbs due to a lack of direct evidence and limitations of the NMA

Stakeholder	Comment
Association of British Neurologists advisory group on headache and pain	Agreed that there is considerable uncertainty about comparison of efficacy measures between rimegepant and mABs – direct comparisons between trials cannot be made due to variability in study design and variation in placebo response.
British Association for the Study of Headache	There is no direct trial between Rimegepant and CGRP mAbs hence the efficacy of the two cannot be compared due to variability in study design and variation in placebo response.
Clinical expert	No comment.
Patient expert	No comment.
Migraine Trust	We do not have new evidence to add.
Novartis	Novartis agrees that the lack of direct evidence and the limitations of the NMA create uncertainty in the relative effectiveness comparison of rimegepant and the monoclonal antibodies. We also agree with the EAG's preference for the random effects model. Although baseline risk has been adjusted for by the submitting company, and efforts have been made to remove differences in outcome measures across trials, important sources of heterogeneity between the studies included in the NMA remain […] and therefore a random effects NMA is more appropriate. Finally, it should be noted that the erenumab, fremanezumab and galcanezumab appraisals all presented NMAs based on data for the subgroup of patients with ≥3 prior treatment failures, i.e. for the population that aligned to that of the decision problem. In contrast, because of the lack of data for rimegepant in this population, the submitting company has conducted an NMA based on only the full trial populations of included studies. There is therefore an inconsistency with other migraine appraisals in terms of the indirect evidence of comparative efficacy that is available to the NICE Committee to inform their decision-making, due to the lack of rimegepant data in the relevant subgroup.
Teva	Teva acknowledges that many of the issues associated with the NMA stem from a lack of direct comparative evidence and the heterogeneity between studies (influenced by placebo type, placebo response, endpoint definitions, patient populations [including disease state EM/CM, and number of previous failures]). Combined, these factors mean that the results have a very high degree of uncertainty. Teva notes that whilst many of these factors are beyond the control of the company, the data included for rimegepant increases the uncertainty in the analysis as no data in patients with prior treatment failure are included, and some

	CM patients are included. The fact that the RCT for rimegepant excluded the most relevant patient population also limits the NMA and its applicability to this appraisal, as mentioned in the Key Issue response above. The differences between placebos in the RCTs adds a high degree of heterogeneity into the NMA. […] When considering the NMA results, these numerically favour the mAbs and in a number of cases reach statistical significance. This suggests that the mAbs are more efficacious treatments than rimegepant, but the uncertainty in the NMA means that the magnitude of any difference in treatment effect is highly uncertain. Overall, the limitations and uncertainties that the use of this NMA carries forward into the economic analysis must be borne in mind. […]

Abbreviations: CGRP, calcitonin gene-related peptide; CM, chronic migraine; EAG, External Assessment Group; EM, episodic migraine; mAbs/mABs, monoclonal antibodies; NICE, The National Institute for Health and Care Excellence; NMA, network meta-analysis; RCT, randomised controlled trial.

Table 9. Additional comments on the NMA from Teva

Stakeholder comment	EAG comment
[…] differences in placebo type and administration route raise questions about the validity of the comparison through placebo (which is in fact many different placebos) that is undertaken in this NMA. At best, this issue can be seen to lead to a high degree of uncertainty within the NMA results.	The EAG agrees that placebo administration route for rimegepant and mAb trials differs (subcutaneous in mAb trials vs oral in the rimegepant trial). The EAG does not consider this to be something the company can address further, given this is an inherent difference between rimegepant and mAbs.
Whilst the company has standardised the endpoint definitions used to some extent (in terms of timepoint of the analysis), important differences still remain. The definition of what constitutes a migraine day has not been consistent across clinical trials and important differences can be seen in this definition. For example, Study BHV3000-305 (rimegepant) uses a definition that requires a migraine to last ≥30 minutes; whereas FOCUS (fremanezumab) used a definition that required migraine lasting ≥4 consecutive hours (where the latter is aligned with the ICHD-3 criteria for migraine attacks). Teva believes this is an important issue that has not been fully considered thus far. These differences in what constitutes a migraine day impact all outcomes from this NMA as both are based on measurements of migraine days. The heterogeneity in definition makes comparison between trials more challenging and leads to further uncertainty in this analysis.	The EAG acknowledges these differences in the definition of how a migraine day has been defined in the rimegepant trial compared to the FOCUS trial.[6] However, the EAG highlights the difference between a migraine day and a migraine attack; a migraine attack could start on one day with symptoms continuing into the following day, meaning (if the duration was at least 30 mins on the second day) that the attack involved two migraine days. The definition of a migraine day in the CS also required ICHD-3 criteria to be met. The EAG also notes that most of the other mAb trials (STRIVE, LIBERTY, EMPowER, EVOLVE-1, EVOLVE-2, CONQUER, Sakai *et al.* 2019, CGAB)[7-14] have used a similar definition to the rimegepant CS with a ≥30 min time-point, while others have used other durations (e.g., 2 hours in HALO-EM and Sakai *et al.* 2021).[15, 16] The EAG notes this is a further area of heterogeneity between the trials but does not consider it to be something the company can address further given there is variation even within the mAb trials.
[…] it must be noted when considering the economic analysis that this is based on a difference in response rate only, with any difference in MMD reduction not	The EAG acknowledges that the point estimates from the random effects adjusted NMA for change from baseline in MMDs are numerically better for mAbs

included. As the NMA shows that it is likely that the mAbs are also superior in terms of MMD reductions compared to rimegepant, the fact that this effect was not included within the economic analyses must be considered. This additional benefit for the mAbs has the potential to substantially shift the balance of cost-effectiveness towards the mAbs, as it would lead to reduced overall MMDs for mAbs, leading to greater QALYs and lower health-related costs for these treatments compared with rimegepant.	compared to rimegepant in terms of the point estimates. However, the results across all mAbs vs rimegepant were consistently non-significant. Given the lack of direct evidence to suggest otherwise, the EAG does not consider there to be sufficient evidence to include continuous reductions in MMD in the economic model on top of response rate. The following was also noted in the on page 197 of the CS, "Patient-level data were not available to fit equivalent distributions for the three comparators, and it was not feasible to run the NMA on the mean change from baseline on MMD by response status. Therefore, similar to previous NICE appraisals (erenumab [TA682] and fremanezumab [TA764]),[17, 18] it was assumed that the three mAbs were associated with the same MMD distribution as rimegepant based on their responder status only, i.e. the difference in effectiveness between rimegepant and the comparators was modelled solely as difference in the proportion of patients achieving 50% MMD reduction."
The EAG also makes a comment regarding concerns about the inclusion of CM patients in the FOCUS data, and that the availability of FOCUS data in EM patients would help strengthen the NMA by limiting it to the most relevant patients. Teva notes that some of the relevant ≥50% response data were included within the NICE appraisal of fremanezumab (marked as confidential) and are able to reproduce these data below to assist with this appraisal. Teva has also sourced the required data for change from Baseline in MMDs and these data are also included.	The EAG reviewed the EM subgroup data provided by Teva at the TE stage. Due to time constraints, the new data were not incorporated into the NMAs but a narrative discussion of the possible impact on results is provided here. Although the OR for the 50% reduction in MMDs outcome [redacted] in the EM-specific group compared to the overall population for fremanezumab doses vs placebo, the EAG notes that when pooled with other fremanezumab studies using a fixed effects analysis, the overall OR of fremanezumab vs placebo is [redacted] compared to when the overall population is used. With a random effects analysis, the ORs were [redacted] with the EM subgroup data used compared to the overall population. For the change from baseline in MMDs outcome, fixed and random effects analyses both demonstrated [redacted]*when the EM subgroup was used compared to the overall population. There was also [redacted] when the EM subgroup was used. This [redacted] the EAG raised about the inclusion of the FOCUS trial (Section 3.2.4.3.1 of the EAG report), which consists mostly of CM rather than EM patients. As the results for the pooled fremanezumab studies [redacted] when the EM subgroup of FOCUS is used, compared to when the whole population is used, the EAG considers that there is unlikely to be a large effect on NMA results.

Abbreviations: CM, chronic migraine; CS, company submission; EAG, External Assessment Group; EM, episodic migraine; ICHD-3, The International Classification of Headache Disorders-3; mAb, monoclonal antibodies; MMDs, monthly migraine days; NICE, The National Institute for Health and Care Excellence; NMA, network meta-analysis; OR, odds ratio; QALYs, quality-adjusted life years; TE, technical engagement.

Table 10. ORs used in company and EAG base cases for 50% reduction in MMDs outcome

Treatment	Fixed-effects baseline risk adjusted model (company base case)	Phase II sensitivity analysis, random-effects baseline risk adjusted NMA (EAG base case)
	OR (95% CrI)	
Rimegepant	1	1
Erenumab 140 mg	[redacted]	[redacted]
Fremanezumab 225 mg	[redacted]	[redacted]
Galcanezumab 120 mg	[redacted]	[redacted]

Abbreviations: CrI, credible interval; EAG, External Assessment Group; OR, odds ratio (treatment vs rimegepant)

2.2.4 *Key Issue 9: Gradual vs immediate reversion to baseline MMD during the assessment period and after the assessment period*

In the company's original base case analysis, assumptions regarding reversions to baseline MMD were inconsistent; during the assessment period, the reversion to baseline took 12 months, but after the assessment period, the reversion to baseline was immediate. This approach favoured the least effective treatment (rimegepant) as these patients will maintain benefits for longer after discontinuation than patients who initially respond then discontinue.

The company provided a scenario in the CS assuming an immediate reversion to baseline in both periods, which the EAG considers to be more appropriate than the company's original base case assumption. The EAG also suggested an alternative approach in the EAG report - to assume the reversion to baseline takes 12 months in both periods. In response to TE, the company implemented this alternative approach in its revised base case analysis using tunnel states.

All stakeholders responding to this issue expressed a preference for the same reversion assumption to be applied in both periods, as per the EAG (Table 11). Additionally, two stakeholders considered gradual reversions to be more plausible than immediate revisions. One stakeholder (Teva) preferred immediate reversions in absence of evidence demonstrating a gradual revision following cessation of rimegepant. They also explained how immediate reversions would promote consistency with TA764

(the EAG notes that in Table 41 of the EAG report, the EAG erroneously referred to gradual reversions rather than immediate revisions when extracting the committee's preferred assumptions on active treatment in TA674).[18]

Overall, the EAG is satisfied with the company's revised approach and notes that gradual reversions and immediate reversions (when applied to both assessment periods) lead to similar ICERs (ICERs [south-west] assuming immediate reversions are around £5,000 higher for rimegepant vs each mAb).

Table 11. Stakeholder responses to Key Issue 9: Gradual vs immediate reversion to baseline MMD during the assessment period and after the assessment period

Stakeholder	Comment
Association of British Neurologists advisory group on headache and pain	Time period of reversion to baseline after discontinuation of treatment is uncertain, but gradual (up to 12 months) is more plausible than immediate reversion to baseline after discontinuing treatment.
British Association for the Study of Headache	A gradual reduction in MMD is more plausible than immediate reduction.
Clinical expert	No comment.
Migraine Trust	We do not have new evidence to comment.
Novartis	Novartis shares the EAG concerns regarding the inconsistent approach applied in the submitting company's model for the timeframe over which MMDs revert to baseline for patients who are non-responders at the end of the assessment period compared to those who initially respond but then discontinue active treatment. As outlined in Table 41 of the EAG report provided for this Technical Engagement, in previous migraine prevention appraisals the Committee-preferred approaches at final Appraisal Committee Meeting have maintained consistency in the handling of these two groups, either both reverting to baseline MMDs immediately or both returning to baseline MMDs gradually over the course of 12 months. We consider that for consistency with prior appraisals, the rimegepant appraisal should treat the two groups of patients in the same manner with regards to the timeframe over which MMDs revert to baseline.
Teva	Teva agrees with the EAG that this is an important issue and notes that this represents a substantial deviation from the approach taken in previous appraisals (most particularly the assumptions applied within TA764). Teva firstly would like to clarify the committee's preferred assumptions as applied in TA764, as these are recorded incorrectly within Table 41 of the EAG report (p136). The assumptions for BSC are correctly recorded, but those for active treatment are incorrect. 'Non-responders to active treatment at 12-weeks' and 'responders to active treatment who discontinue treatment' both immediately reverted to baseline MMDs. […] The only appraisal where a waning back to baseline following the discontinuation of active treatment was applied was that for galcanezumab. This effect in the galcanezumab appraisal was based on washout data from the galcanezumab RCTs showing a gradual return of MMDs after treatment cessation. No such data have been presented to show an equivalent effect in rimegepant, and therefore Teva believes that such an effect should not be included for rimegepant. […]

	Within the appraisals of migraine preventive medications, BSC has been defined as acute migraine treatment only. Acute migraine treatment is continued in patients receiving preventive treatment and so those discontinuing will stop preventive treatment only and remain on the same acute treatment. Therefore, there would be no expectation of any additional placebo response in these patients based on a treatment they are already receiving.

Abbreviations: BSC, best supportive care; EAG, External Assessment Group; MMDs, monthly migraine days.

2.2.5 *Key Issue 10: Response probability for rimegepant*

In their report, the EAG highlights that a different definition has been used to estimate relative effectiveness of rimegepant vs mAbs in the NMA compared to that used to define rimegepant responders in the economic model; the rimegepant response probability is based on the outcome "at 12-weeks", while the NMA is based on the "average over 12-weeks". Similarly, the rimegepant response probability is based on moderate-to-severe MMDs, while the NMA is based on mild-to-severe MMDs (the EAG notes that in Table 11 of the EAG report, the EAG should refer to the severity of MMDs rather than the severity of migraine attacks, for consistency with the CS and the remainder of the EAG report). The EAG considered it inappropriate to use different definitions for rimegepant response probability and the relative effectiveness estimates and requested that the company employ a rimegepant response probability based on the "average over 12-weeks" and reduction in mild-to-severe MMDs (38.5%), rather than "at 12-weeks" and reduction in moderate-to-severe MMDs (49.1%).

In their response to TE, while they note that this option is available in the model as a scenario analysis, the company state that they do not agree with the EAG's suggested approach for this to be part of the base case analysis as:

- the "average over 12-weeks" time-point was only selected in the NMA to broaden the evidence base given data at 12-weeks was not available from 5 studies, which would have completely removed galcanezumab from the NMA;
- in studies where data could be obtained for both the "average over 12-weeks" and "at 12-weeks" time-points, relative effects of mAbs vs placebo were similar (Figure 13 of the CS);
- adopting an "average over 12-weeks" measure would lead to some 12-week responders being treated as non-responders, leading to an underestimation in terms of patients that respond to rimegepant and mAbs;
- an online questionnaire sent to the company's advisers indicated that 85% preferred reporting "at 12-weeks" as opposed to "average over 12-weeks" when presented with the

two options and asked how they assessed clinical outcomes in response to treatment after a 3-month period.

While the EAG understands the company's argument that, in practice, assessment of response may be performed "at 12-weeks", in this case defined as between weeks 9 and 12, this does not mean it is appropriate to use different definitions in the economic model to inform rimegepant response probability and the relative effects of mAbs compared to rimegepant, particularly as it appears to have a considerable impact on the ICER. Although results in Figure 13 of the CS may show similar ORs for mAbs vs placebo regardless of how the time-point is defined in those studies where data were available for both variations, the EAG notes that this does not necessarily mean the same would be true for comparisons between rimegepant and mAbs. In addition, the two definitions also differ in terms of whether the reduction is in moderate-to-severe MMDs or mild-to-severe MMDs, which the company has not commented on in their TE response.

Therefore, the EAG maintains that the definition used to inform rimegepant response probability in the economic model should match that used to calculate the relative effects of mAbs compared to rimegepant in the NMA. This is supported by all stakeholders that had an opinion on this issue, reported in Table 12 below.

Table 12. Stakeholder responses to Key Issue 10: Response probability for rimegepant

Stakeholder	Comment
Association of British Neurologists advisory group on headache and pain	Agree that response probability based on the "average over 12-weeks" in patients with mild-to-severe migraine attacks should be used, rather than response at 12 weeks. 12 week average response is in keeping with analysis of mAb treatment. However, many other preventive treatments for migraine (e.g. betablockers, topiramate) may take 6-8 weeks to show response
British Association for the Study of Headache	The response to Rimegepant over a period of 12 weeks should be used rather than assessment at 12 weeks.
Clinical expert	No comment.
Migraine Trust	Patients/public who contact us, have not yet used this treatment and we therefore cannot speculate about the response probability.
Novartis	Novartis agrees with the EAG that the absolute probability of response to which the odds ratios from the NMA are applied in the cost-effectiveness model should be the absolute response probability that aligns to the definition used for the NMA (i.e. the average response probability over 12 weeks). The odds ratios derived from the NMA represent the relative treatment effect of rimegepant versus other comparators as an average over 12 weeks, and therefore it is logically appropriate to apply this relative effect to a baseline absolute probability that represents the same.
Teva	Teva agrees with the EAG that there is a need for consistency between inputs with regard to the outcome definition for response. Therefore, the at least 50% response

	"average over 12-weeks" including mild-to-severe MMDs would appear to be the most appropriate data for the response of rimegepant. As noted by the EAG, this issue is particularly important when the response rates for the other treatments included within this economic modelling are based on this response rate for rimegepant. In addition, Teva notes that, in clinical practice, MMDs rather than migraine attacks are the most commonly utilised measure. Also, all MMDs are likely to be assessed in clinical practice, rather than only a focus on moderate to severe migraine. Teva also notes some inconsistency in the reporting around this issue between MMDs and migraine attacks. It appears that the CS is consistent in referring to this endpoint as at least 50% reduction in MMDs (see Table 8, p55 CS). However, within the EAG report the wording of migraine attacks is used in relation to this issue. Teva would like to ensure that there is consistency and accuracy in the use of these two distinct terms and notes that the data for other treatments are collected using a definition of at least 50% reduction in MMDs.

Abbreviations: CS, company submission; EAG, External Assessment Group; mAb, monoclonal antibodies; MMDs, monthly migraine days; NMA, network meta-analysis.

2.2.6 *Key Issue 11: Applying the NMA results from Cycle 1 vs Cycle 3*

The EAG highlighted in their report that the BHV3000-305 trial and comparator trials demonstrate a significant reduction in MMDs within the first few weeks of treatment (Section 4.2.7.2 of the EAG report). Also, given that response in the NMA was assessed as the "average over 12-weeks" and not "at 12-weeks", the EAG considers that the results from the NMA could be implemented in the economic analysis from Cycle 1 (Weeks 1 to 4) rather than Cycle 3 (Weeks 9 to 12). This approach would better reflect clinical practice as patients on different treatments would experience different reductions in MMDs before their assessment at Week 12. In the model, this would affect costs (health care resource use estimates depend on MMD, Table 68 of the EAG report) and benefits (MMD is a covariate in the regression to predict utility, Table 63 of the EAG report).

In response to TE, the company agreed early benefits may accrue in some patients prior to 12 weeks. In the revised model, the company split the MMD distributions at Week 4 and Week 8 according to response (Table 13) and enabled the proportion of responders at Week 4 and Week 8 to differ by treatment arm, using the relative effectiveness estimates from the NMA.

The company provided two options in the revised model to do this:

1. the full benefit seen at week 12 in the original analysis is applied from Week 4
2. the actual benefit observed prior to week 12 among week 12 responders is applied from week 4, which is less than that seen at week 12, estimated by an alternative regression.

In either option, the degree of benefit attributed to an individual treatment arm is a function of the probability of response determined through the NMA. The first option was applied in the company's revised base case. The company provided no explanation for preferring option 1 in their TE response. The company also provided no details on the alternative regression used to inform option 2, but this could be found in the economic model (Table 14).

The EAG is concerned that the predicted mean in the original base case is equal to the predicted mean in the revised base case for non-responders (Table 13). The EAG would expect the predicted mean for non-responders in the revised base case to be higher than the original base case, or for the original base case predictions to be somewhere in-between responders and non-responders from the revised base case. The EAG considers this to be a limitation of using the original regression to predict the distribution of MMD.

Table 13. Predicted mean MMD for rimegepant, erenumab, fremanezumab, and galcanezumab observed in the company's base case analysis

Assessment	Original base case		Revised base case (option 1)		Scenario in the revised model (option 2)	
	Responder	Non-responder	Responder	Non-responder	Responder	Non-responder
Baseline (cycle 0)	[redacted]		[redacted]		[redacted]	
Week 4 (cycle 1)	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
Week 8 (cycle 2)	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
Week 12 (cycle 3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 14. Alternative regression used to estimate the distribution of MMD during the 12-week assessment period (zero inflated negative binomial II)

Term	Coef.	Std. Err.	z	P>z	95% Conf. Interval	
[redacted]						

Table 15 provides the cost-effectiveness results generated by the EAG from each option, and the company's original base case assumption (NMA results applied from Cycle 3). As shown in Table 19, the difference between options 1 and 2 is minimal, and the original base case assumption favours rimegepant the most.

Table 15. Results of scenario analysis on Key Issue 11 (generated by the EAG)

Results per patient	Ere (4)	Gal (3)	Fre (2)	Rim (1)	Incremental value		
					(1-4)	(1-2)	(1-3)
Revised base case: NMA applied from Cycle 1 using option 1 (original regression with adjustment of early period)							
Total costs	£23,927	£25,925	£25,105	£19,876	-£4,052	-£6,050	-£5,230
QALYs	9.089	9.108	9.099	9.051	-0.038	-0.057	-0.048
ICER (£/QALY)					£107,789	£105,918	£108,552
NMA applied from Cycle 1 using option 2 (alternative regression with specific coefficients)							
Total costs	£23,939	£25,938	£25,117	£19,886	-£4,052	-£6,051	-£5,231
QALYs	9.084	9.104	9.095	9.047	-0.037	-0.057	-0.048
ICER (£/QALY)					£108,602	£106,718	£109,371
NMA applied from Cycle 3 (original base case assumption)							
Total costs	£23,943	£25,942	£25,122	£19,889	-£4,054	-£6,053	-£5,233
QALYs	9.083	9.102	9.094	9.046	-0.037	-0.056	-0.047
ICER (£/QALY)					£110,065	£108,156	£110,844

Abbreviations: EAG, External Assessment Group; Ere, erenumab; Fre, fremanezumab; Gal, galcanezumab; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; QALY, quality-adjusted life year; Rim, rimegepant

Note: all ICERs are in the south-west quadrant (rimegepant is cheaper and less effective than the comparators)

The EAG also reviewed stakeholder comments on this issue (Table 16). Two stakeholders noted that there could be incremental improvements between Cycles 1 and 3, which would suggest the company's option 2 is most appropriate. A third stakeholder (Teva) noted that TA764 for fremanezumab separately modelled responders and non-responders at all time points (the reduction in migraine frequency was attributed in the model after the first model cycle, and in subsequent cycles until full effect was reached by 12 weeks for fremanezumab and BSC).[18]

Overall, the EAG prefers the company's implementation using option 2 as this aligns better with stakeholders who suggest there are incremental improvements between Cycles 1 and 3, and enables

the distribution of MMDs for non-responders to be predicted as non-responders (as opposed to all patients). However, as noted above, the cost-effectiveness results produced by options 1 and 2 are very similar and therefore choosing between these options is not considered to be a contentious issue.

Table 16. Stakeholder responses to Key Issue 11: Applying the NMA results from Cycle 1 vs Cycle 3

Stakeholder	Comment
Association of British Neurologists advisory group on headache and pain	Although rimegepant effectiveness may be seen within the first few weeks of treatment, there may be some incremental improvement tin response between Cycle 1-3, over 12 weeks, and so applying results from cycle 1 to cycle 3 may not be accurate
British Association for the Study of Headache	Rimegepant may work immediately although there may be incremental response with time and hence applying results from cycle 1 to cycle 3 may not be accurate.
Clinical expert	No comment
Migraine Trust	No comment.
Novartis	No comment.
Teva	Teva believes that the most appropriate approach to this issue depends on the detail of the model structure and how responders and non-responders are modelled […] Teva also notes that in clinical practice the assessment of efficacy will occur at 12 weeks and will be based on the response during the initial treatment period. However, this does not impact how the efficacy of treatment should be modelled during this initial 12-week period, which should occur in the most fair and balanced way possible. […] Teva is therefore unsure whether the issue refers solely to the application of NMA data or whether this issue also covers the modelling of efficacy during this 12-week assessment period. For clarity and to aid committee discussions, Teva wishes to outline the committee's preferred approach in this area within the appraisal of fremanezumab. Firstly, it must be noted that the fremanezumab model separately modelled responders and non-responders at all time points. MMD distributions were applied separately to these responder and non-responder groups (separate distributions were also applied to active treatment versus BSC). These MMD distributions were then adjusted based on mean MMDs taken from RCT data for responders. For non-responders, the committee preferred a scenario where no efficacy for fremanezumab non-responders was assumed […]

Abbreviations: BSC, best supportive care; MMDs, monthly migraine days; NMA, network meta-analysis; RCT, randomised controlled trial.

2.2.7 *Key Issue 12: Comparator treatment acquisition costs*

As suggested in the EAG report, the company amended the regimen for erenumab to reflect the British National Formulary (BNF) and removed the discrepancies between the first cycle and subsequent cycles (with the exception of the loading dose for galcanezumab).[19] This issue is considered resolved.

2.2.8 *Additional Issue: The baseline EQ-5D from the rimegepant and placebo arms of study BHV3000-305*

Study BHV3000-305 collected MSQv2 data at baseline and Week 12. The regression model for utility applied in the company's economic analysis was based on the mapped EQ-5D data at the end of Week 12. Covariates in this regression included MMD and treatment arm ('on treatment'). Given that patients were randomised in this study, the EAG would expect the baseline mapped EQ-5D scores to be similar in both treatment arms. However, if they are dissimilar, this would call into question the appropriateness of the treatment arm covariate in the regression as a difference between the arms at baseline may be persisting at Week 12. This is important as the covariates in the regression had large impacts on the ICER in the company's one-way sensitivity analysis (OWSA). To reduce this uncertainty, the company was asked to provide the baseline mapped EQ-5D scores from study BHV3000-305 according to treatment arm during TE, and to include the data in the regression if any imbalances were observed.

In response to TE, the company provided this data (Table 17). The EAG performed an unpaired T-test on the data provided and obtained a p value of 0.1436. Although this analysis demonstrates no statistically significant difference between the two treatment arms at baseline, the EAG is still concerned that the difference in baseline scores (0.016) is non-trivial and would prefer to see a regression including these data.

Table 17. Baseline EQ-5D from the rimegepant and placebo arms of the study BHV3000-305

Treatment	N	Mean	SD
Placebo	346*	0.5976	0.1447
Rimegepant	348	0.6136	0.1432

Abbreviations: N, number of patients completing the MSQv2; SD, standard deviation
*1 placebo patient was missing data at baseline

3 Company's revised cost-effectiveness results

In response to the TE report, the company presented updated base case analyses. The updates are as follows:

- Acute migraine treatment:
  - The BL_severity coefficient in the QALH regression was applied to the wrong proportion of migraine attacks, this has been corrected.

- Migraine prevention:
    - The reversion to baseline MMD during the assessment period was assumed to take 12 months, while the reversion to baseline MMD after the assessment period was assumed to be immediate, the reversions to baseline MMD during and after the assessment period now take 12 months (see Key Issue 9);
    - Results from the NMA were applied from cycle 3, they are now applied from cycle 1 (see Key Issue 11);
    - Acquisition costs in the initial cycle and subsequent cycles are now equal (with the exception of loading doses) and the regimen for erenumab has been amended from every 30.4 days to every 28 days (see Key Issue 12).

The company's updated base case results for acute migraine treatment are given in Table 18. In the company's updated base case, rimegepant is associated with higher costs and higher quality-adjusted life years (QALYs) compared BSC, resulting in an ICER of £17,521 per QALY gained.

The company's updated base case results for migraine prevention are given in Table 19. As shown in Table 19, the rimegepant is associated with lower costs and lower QALYs than each mAb (i.e., a south-west quadrant ICER). However, the EAG cautions the interpretation of these results as they are based on list prices. The cost-effectiveness results presented in the confidential appendix, which includes the patient access scheme (PAS) discounts for comparator treatments (rimegepant does not have a PAS discount), are more relevant for decision-making.

Only updated deterministic base case results were provided by the company in their TE response. The EAG has been unable to produce probabilistic sensitivity analysis (PSA) results in the company's updated model for acute migraine treatment given that it takes several hours to run (the model also includes a pop-up with this warning, and a note that the previous run took 493.9 minutes). Moreover, the PSA results in this model include a PSA run on 9 June 2022, which is prior to the TE stage. The long running of the PSA was also highlighted as an issue in the EAG report.

As for migraine prevention, the EAG presents deterministic and probabilistic ICERs for the company's updated based case results and the EAG's base case results incorporating all relevant PAS discounts in the confidential appendix.

Table 18. Company's revised base case results (acute migraine treatment)

Results per patient	Rimegepant	BSC	Incremental value
Original company base case			
Total costs	£9,704	£2,396	£7,307
QALYs	8.144	7.718	0.426
ICER (£/QALY)	-	-	£17,160
Revised base case			
Total costs	£9,704	£2,396	£7,307
QALYs	8.343	7.926	0.417
ICER (£/QALY)	-	-	£17,521

Abbreviations: BSC, best supportive care; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; mITT, modified intention-to-treat; QALY, quality adjusted life year

Table 19. Company's revised base case results (migraine prevention)

Results per patient	Ere (4)	Gal (3)	Fre (2)	Rim (1)	Incremental value		
					(1-4)	(1-2)	(1-3)
Original company base case							
Total costs	£23,134	£25,987	£25,201	£19,925	-£3,209	-£6,062	-£5,276
QALYs	9.068	9.086	9.077	9.033	-0.035	-0.053	-0.044
ICER (£/QALY)					£92,671*	£115,211*	£118,883*
Revised base case							
Total costs	£23,927	£25,925	£25,105	£19,876	-£4,052	-£6,050	-£5,230
QALYs	9.089	9.108	9.099	9.051	-0.038	-0.057	-0.048
ICER (£/QALY)					£107,789*	£105,918*	£108,552*

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

*Note: all ICERs are in the south-west quadrant (rimegepant is cheaper and less effective than the comparators)

4 EAG's cost-effectiveness results

In Section 2, the EAG has described several scenarios that warrant further exploration. The scenarios that the EAG has produced are applied to the company's revised base case and include:

- Acute migraine treatment:

- Parametric distribution (Poisson) to model the baseline distribution of MMDs (see Key Issue 4);
- Removing the reductions in MMD associated with rimegepant PRN (see Key Issue 5);
- Removing the reductions in MMD associated with rimegepant PRN and reducing the time horizon to 2 years (see Key Issue 5);
- mITT population (see Additional Issue);
- mITT population including study BHV3000-310 (see Key Issue 2);
- Patients who discontinue rimegepant follow BSC all-comer pain trajectories (see Additional Issue);
- Patients who discontinue rimegepant follow BSC non-responder pain trajectories (see Additional Issue).

- Migraine prevention
  - Phase II sensitivity analysis, random-effects baseline risk adjusted NMA (see Key Issue 8);
  - Immediate reversion to baseline MMDs during the assessment period and after the assessment period (see Key Issue 9);
  - Rimegepant response probability as per the NMA (see Key Issue 10);
  - Alternative applications of the NMA (see Key Issue 11).

Results of the EAG's scenarios for acute migraine treatment are given in Table 20. Scenarios removing the reductions in MMD associated with rimegepant PRN led to the largest increases in the ICER. The only scenario to reduce the ICER involved using the mITT population.

Table 20. Results of EAG scenarios (acute migraine treatment)

Results per patient	Rimegepant	BSC	Incremental value
Revised base case			
Total costs	£9,704	£2,396	£7,307
QALYs	8.343	7.926	0.417
ICER (£/QALY)	-	-	£17,521
Parametric distribution (Poisson) to model the baseline distribution of MMDs			
Total costs	£9,839	£2,392	£7,447
QALYs	8.381	7.968	0.412
ICER (£/QALY)	-	-	£18,061
Removing the reductions in MMD associated with rimegepant PRN			
Total costs	£10,901	£2,396	£8,505
QALYs	8.304	7.926	0.378

ICER (£/QALY)	-	-	£22,529
Removing the reductions in MMD associated with rimegepant PRN (2-year time horizon)			
Total costs	£2,560	£290	£2,271
QALYs	1.205	1.123	0.082
ICER (£/QALY)	-	-	£27,851
mITT population			
Total costs	£6,360	£2,206	£4,154
QALYs	8.797	8.547	0.249
ICER (£/QALY)	-	-	£16,671
mITT population including study BHV3000-310			
Total costs	£6,368	£2,018	£4,350
QALYs	8.896	8.676	0.220
ICER (£/QALY)	-	-	£19,743
Patients who discontinue rimegepant follow BSC all-comer pain trajectories			
Total costs	£9,704	£2,396	£7,307
QALYs	8.329	7.926	0.402
ICER (£/QALY)	-	-	£18,155
Patients who discontinue rimegepant follow BSC non-responder pain trajectories			
Total costs	£9,704	£2,396	£7,307
QALYs	8.320	7.926	0.394
ICER (£/QALY)	-	-	£18,545

Abbreviations: BSC, best supportive care; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; mITT, modified intention-to-treat; MMD, monthly migraine day; PRN, *pro re nata* (when needed); QALY, quality adjusted life year.

Results of the EAG's scenarios for migraine prevention are given in Table 21. All scenarios produce ICERs in the south-west quadrant (i.e. rimegepant is associated with lower costs and lower QALYs than each mAb). Scenarios which favour rimegepant (i.e. higher ICERs) include assuming reversions to baseline are immediate, using the alternative NMA (vs galcanezumab only) and using alternative applications of the NMA. Scenarios which favour the mAbs (i.e. lower ICERs) include using the alternative rimegepant response probability and using the alternative NMA (vs erenumab and fremanezumab). However, the change in the magnitude of the ICERs is relatively small (ICERs range from a minimum of £94,666 to a maximum of £113,245).

Table 21. Results of EAG scenarios (migraine prevention)

Results per patient	Ere (4)	Gal (3)	Fre (2)	Rim (1)	Incremental value		
					(1-4)	(1-2)	(1-3)
Revised base case							

Total costs	£23,927	£25,925	£25,105	£19,876	-£4,052	-£6,050	-£5,230
QALYs	9.089	9.108	9.099	9.051	-0.038	-0.057	-0.048
ICER (£/QALY)					£107,789*	£105,918*	£108,552*
Phase II sensitivity analysis, random-effects baseline risk adjusted NMA							
Total costs	£23,981	£25,895	£25,358	£19,876	-£4,105	-£6,020	-£5,482
QALYs	9.090	9.107	9.106	9.051	-0.039	-0.056	-0.055
ICER (£/QALY)					£104,919*	£106,909*	£99,803*
Immediate reversion to baseline MMDs during the assessment period and after the assessment period							
Total costs	£23,977	£25,978	£25,157	£19,921	-£4,056	-£6,056	-£5,235
QALYs	9.069	9.088	9.079	9.033	-0.036	-0.055	-0.046
ICER (£/QALY)					£112,450*	£110,500*	£113,245*
Rimegepant response probability as per the NMA							
Total costs	£22,171	£24,063	£23,228	£18,660	-£3,512	-£4,568	-£5,403
QALYs	9.038	9.058	9.049	9.001	-0.037	-0.048	0-.057
ICER (£/QALY)					£95,245*	£95,700*	£94,666*
NMA applied from Cycle 1 using option 2 (alternative regression with specific coefficients)							
Total costs	£23,939	£25,938	£25,117	£19,886	-£4,052	-£6,051	-£5,231
QALYs	9.084	9.104	9.095	9.047	-0.037	-0.057	-0.048
ICER (£/QALY)					£108,602*	£106,718*	£109,371*
NMA applied from Cycle 3 (original base case assumption)							
Total costs	£23,943	£25,942	£25,122	£19,889	-£4,054	-£6,053	-£5,233
QALYs	9.083	9.102	9.094	9.046	-0.037	-0.056	-0.047
ICER (£/QALY)					£110,065*	£108,156*	£110,844*

Abbreviations: EAG, Evidence Assessment Group; Ere, erenumab; Fre, fremanezumab; Gal, galcanezumab; ICER, incremental cost-effectiveness ratio; MMD, monthly migraine day; NMA, network meta-analysis; QALY, quality-adjusted life year; Rim, rimegepant

*Note: all ICERs are in the south-west quadrant (rimegepant is cheaper and less effective than the comparators)

In this section of the report, the EAG also presents its preferred base case ICER. The key differences between the company's base case ICER and EAG's preferred base case ICER are given in Table 22.

Table 22. EAG's preferred assumptions

#	Assumptions	Company approach	EAG approach
Acute migraine treatment			
1	Population	Subgroup with at least 2 triptan failures	mITT
2	Study BHV3000-310	Excluded	Included
3	Baseline distribution of MMDs	Observed data	Parametric distribution (Poisson)
4	Trajectories of rimegepant responders after discontinuation	BSC responders	BSC all-comers
5	Assuming rimegepant PRN can result in reductions in MMDs	Included	Excluded from the base case and included in scenario analysis
6	Time horizon	20 years	2 years*
Migraine prevention			
1	NMA	Fixed-effects baseline risk adjusted NMA	Phase II sensitivity analysis, random-effects baseline risk adjusted NMA
2	Rimegepant response probability	At 12-weeks and moderate-to-severe MMDs	As per the NMA: average over 12 weeks and mild-to-severe MMDs
3	Regression used to predict MMD distributions during the assessment period	Option 1 (original regression)	Option 2 (alternative regression with specific coefficients)

Abbreviations: BSC, best supportive care; EAG, External Assessment Group; mITT, modified intention-to-treat; MMD, monthly migraine day; NMA, network meta-analysis; PRN, *pro re nata* (when needed)

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

Table 23 shows the impact of each assumption for acute migraine treatment cumulatively. In the EAG's base case, the ICER is £43,883. However, as discussed in Section 2.1.5, the EAG is aware that some clinical experts and stakeholders are supportive of including reductions in MMD by PRN rimegepant in the economic analysis. When reductions in MMD by PRN rimegepant are included, the ICER is £20,803. Thus, if committee consider the reductions in MMD by PRN rimegepant reasonable, rimegepant could be considered cost-effective as the ICER is under the NICE upper willingness to pay (WTP) threshold of £30,000 per QALY.

Table 23. EAG's base case for acute migraine treatment (cumulative impact)

Results per patient	Rimegepant	BSC	Incremental value
Revised base case			
Total costs	£9,704	£2,396	£7,307
QALYs	8.343	7.926	0.417
ICER (£/QALY)	-	-	£17,521

Assumptions: 1			
Total costs	£6,360	£2,206	£4,154
QALYs	8.797	8.547	0.249
ICER (£/QALY)	-	-	£16,671
Assumptions: 1 + 2			
Total costs	£6,368	£2,018	£4,350
QALYs	8.896	8.676	0.220
ICER (£/QALY)	-	-	£19,743
Assumptions: 1 + 2 + 3			
Total costs	£6,387	£2,017	£4,371
QALYs	8.917	8.697	0.220
ICER (£/QALY)	-	-	£19,857
Assumptions: 1 + 2 + 3 + 4 (scenario around the EAG base case)			
Total costs	£6,387	£2,017	£4,371
QALYs	8.907	8.697	0.210
ICER (£/QALY)	-	-	£20,803
Assumptions: 1 + 2 + 3 + 4 + 5			
Total costs	£7,474	£2,017	£5,458
QALYs	8.876	8.697	0.179
ICER (£/QALY)	-	-	£30,495
Assumptions: 1 + 2 + 3 + 4 + 5 + 6 (EAG base case)			
Total costs	£2,013	£225	£1,788
QALYs	1.266	1.225	0.041
ICER (£/QALY)	-	-	£43,883

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

Table 24 shows the impact of each assumption for acute migraine treatment cumulatively. In the EAG's base case, rimegepant is associated with lower costs and lower QALYs than the mAbs (i.e., a south-west quadrant ICER). Based on WTP thresholds of £20,000 or £30,000 per QALY, rimegepant would be considered cost-effective compared to each mAb as the ICERs are above these WTP thresholds. As noted in Section 3, results including comparator PAS discounts can be found in the confidential appendix.

Table 24. EAG's base case for migraine prevention (cumulative impact)

Results per patient	Ere (4)	Gal (3)	Fre (2)	Rim (1)	Incremental value		
					(1-4)	(1-2)	(1-3)
Revised base case							

Total costs	£23,927	£25,925	£25,105	£19,876	-£4,052	-£6,050	-£5,230
QALYs	9.089	9.108	9.099	9.051	-0.038	-0.057	-0.048
ICER (£/QALY)					£107,789*	£105,918*	£108,552*
Assumptions: 1							
Total costs	£23,981	£25,895	£25,358	£19,876	-£4,105	-£6,020	-£5,482
QALYs	9.090	9.107	9.106	9.051	0.039	-0.056	-0.055
ICER (£/QALY)					£104,919*	£106,909*	£99,802*
Assumptions: 1 + 2							
Total costs	£22,226	£24,031	£23,491	£18,660	-£3,566	-£5,371	-£4,831
QALYs	9.040	9.057	9.056	9.001	-0.038	-0.056	-0.055
ICER (£/QALY)					£92,784*	£95,540*	£88,202*
Assumptions: 1 + 2 + 3							
Total costs	£22,237	£24,042	£23,502	£18,670	-£3,567	-£5,373	-£4,832
QALYs	9.036	9.053	9.052	8.997	-0.038	-0.056	-0.054
ICER (£/QALY)					£93,488*	£96,263*	£88,871*

Abbreviations: EAG, Evidence Assessment Group; Ere, erenumab; Fre, fremanezumab; Gal, galcanezumab; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; Rim, rimegepant

*Note: all ICERs are in the south-west quadrant (rimegepant is cheaper and less effective than the comparators)

5 References

1. Yi X, Fisher KM, Lai M, Mansoor K, Bicker R, Baker SN. Differences between Han Chinese and Caucasians in transcranial magnetic stimulation parameters. *Exp Brain Res* 2014; **232**: 545-53.
2. Houghton IT, Aun CS, Gin T, Lau JT. Inter-ethnic differences in postoperative pethidine requirements. *Anaesth Intensive Care* 1992; **20**: 52-5.
3. Johnston KM, L'Italien G, Popoff E, Powell L, Croop R, Thiry A, et al. Mapping Migraine-Specific Quality of Life to Health State Utilities in Patients Receiving Rimegepant. *Adv Ther* 2021; **38**: 5209-20.
4. Johnston K, Harris L, Powell L, Popoff E, Coric V, L'Italien G, et al. Monthly migraine days, tablet utilization, and quality of life associated with Rimegepant – post hoc results from an open label safety study (BHV3000–201). *The Journal of Headache and Pain* 2022; **23**: 10.
5. L'Italien G, Popoff E, Johnston K, McGrath D, Conway CM, Powell L, et al. Rimegepant 75 mg for acute treatment of migraine is associated with significant reduction in monthly migraine days: Results from a long-term, open-label study. *Cephalalgia Reports* 2022; **5**: 25158163221075596.
6. Ferrari MD, Diener HC, Ning X, Galic M, Cohen JM, Yang R, et al. Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive

medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial. *The Lancet* 2019; **394**: 1030-40.
7. Goadsby PJ, Reuter U, Hallström Y, Broessner G, Bonner JH, Zhang F, et al. A Controlled Trial of Erenumab for Episodic Migraine. *New England journal of medicine* 2017; **377**: 2123-32.
8. Reuter U, Goadsby PJ, Lanteri-Minet M, Wen S, Hours-Zesiger P, Ferrari MD, et al. Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study. *The Lancet* 2018; **392**: 2280-7.
9. Wang SJ, Roxas AA, Saravia B, Kim BK, Chowdhury D, Riachi N, et al. Randomised, controlled trial of erenumab for the prevention of episodic migraine in patients from Asia, the Middle East, and Latin America: the EMPOwER study. *Cephalalgia* 2021.
10. Stauffer VL, Dodick DW, Zhang Q, Carter JN, Ailani J, Conley RR. Evaluation of Galcanezumab for the Prevention of Episodic Migraine: The EVOLVE-1 Randomized Clinical Trial. *JAMA Neurol* 2018; **75**: 1080-8.
11. Skljarevski V, Matharu M, Millen BA, Ossipov MH, Kim BK, Yang JY. Efficacy and safety of galcanezumab for the prevention of episodic migraine: results of the EVOLVE-2 Phase 3 randomized controlled clinical trial. *Cephalalgia* 2018; **38**: 1442-54.
12. Mulleners WM, Kim BK, Lainez MJA, Lanteri-Minet M, Pozo-Rosich P, Wang S, et al. Safety and efficacy of galcanezumab in patients for whom previous migraine preventive medication from two to four categories had failed (CONQUER): a multicentre, randomised, double-blind, placebo-controlled, phase 3b trial. *The Lancet Neurology* 2020; **19(10)**: 814-25.
13. Sakai F, Takeshima T, Tatsuoka Y, Hirata K, Lenz R, Wang Y, et al. A Randomized Phase 2 Study of Erenumab for the Prevention of Episodic Migraine in Japanese Adults. *Headache* 2019; **59**: 1731-42.
14. Skljarevski V, Oakes TM, Zhang Q, Ferguson MB, Martinez J, Camporeale A, et al. Effect of Different Doses of Galcanezumab vs Placebo for Episodic Migraine Prevention: A Randomized Clinical Trial. *JAMA Neurol* 2018; **75**: 187-93.
15. Dodick DW, Silberstein SD, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Effect of Fremanezumab Compared With Placebo for Prevention of Episodic Migraine: a Randomized Clinical Trial. *Jama* 2018; **319**: 1999-2008.
16. Sakai F, Suzuki N, Kim BK, Tatsuoka Y, Imai N, Ning X, et al. Efficacy and safety of fremanezumab for episodic migraine prevention: multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in Japanese and Korean patients. *Headache* 2021; **61**: 1102-11.
17. National Institute for Health and Care Excellence (NICE). Erenumab for preventing migraine: Technology appraisal guidance [TA682], 2021. Available from: **********. Date accessed: Aug 2022.
18. National Institute for Health and Care Excellence (NICE). Fremanezumab for preventing migraine: Technology appraisal guidance [TA764], 2022. Available from: **********. Date accessed: Aug 2022.
19. Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press, 2022. Available from: **********. Date accessed: July 2022.